Saturday 27 August 2016

IMPROVING DIABETES OUTCOMES: BEYOND GLUCOCENTRICITY

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Excess risk of heart failure among persons with type 2 diabetes

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Background/Introduction: Type 2 diabetes is an established risk factor for heart failure but because nearly all events of heart failure occurs in older persons, there is a lack of data in younger individuals. The excess risk and risk factors for heart failure in individuals with type 2 diabetes in relation to glycemic control, age and renal complications remains unresolved.
Purpose and methods: All individuals with type 2 diabetes (n=352315, mean age at baseline 62.9 years, 45.8% women, mean diabetes duration 5.1 years) registered in the Swedish National Diabetes Registry 1998–2012 and five controls randomly selected from the general population (n=1749908), matched according to age, sex, and county were compared. Adjustments were made for age, sex, socioeconomic variables and coexisting conditions.
Results: Over a median follow-up of 5.7 years, until the end of 2013, 29614/352315 (8.4%) of patients and 75716/1749908 (4.3%) of controls were hospitalized with a diagnosis of heart failure as a principal or contributory diagnosis, corresponding to a hazard ratio (HR) of 2.10 (2.07–2.12). Across the entire age range, worse glycaemic control was associated with increased risk of heart failure in a graded fashion, and so was the presence of albuminuria. The risk of heart failure was elevated also among those with well-controlled diabetes (HR ranged from 1.23 [95% CI 1.19–1.27] to 2.30 [95% CI 2.06–2.57], depending on age category). Hazard ratio for young patients with poor glycemic control was 5.77 (95% CI 4.91–6.77). The risk of heart failure was elevated also among patients with normoalbuminuria (HR 1.44 [95% CI 1.41–1.47]) as well as in the subgroup of persons who had both good glycaemic control and with normoalbuminuria (HR ranged from 1.13 [95% CI 1.08–1.19] to 2.11 [95% CI 1.83–2.44], depending on age category). Hazard ratio for young patients with normoalbuminuria and poor glycemic control was 7.94 (95% CI 6.37–9.88). Figure 1 shows hazard ratios (patients with diabetes versus controls) in relation to age and glycemic control.

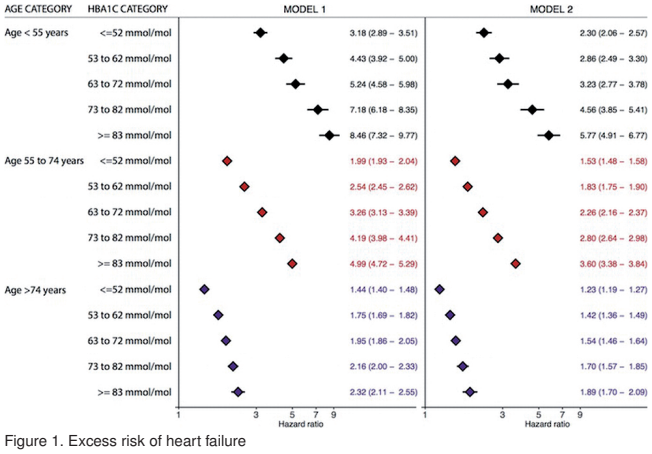

Figure 1. Excess risk of heart failure

Conclusion: Overall, individuals with type 2 diabetes experienced a doubled risk of being hospitalized with HF, compared with population-based controls. Poor glycemic control, young age and renal complications markedly increased the excess risk of heart failure.
Acknowledgement/Funding: Funded by the Swedish Heart and Lung Foundation, and Diabetes Wellness and grants (2013-5187 and 2013-4236) from the Swedish Research Council.

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Efficacy and safety of didpeptidyl peptidase 4 inhibitors and sodium-glucose linked cotransporter-2 inhibitors in patients with type 2 diabetes mellitus: a meta-analysis

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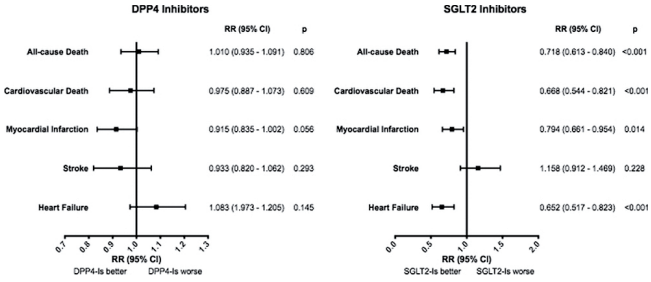
Background: Didpeptidyl Peptidase 4 Inhibitors (DPP4-I) and Sodium-Glucose Linked coTransporter-2 Inhibitors (SGLT2-I) have been demonstrated to improve glycemic control in several studies enrolling type 2 diabetes mellitus (DM) patients. However, only few studies were designed to assess the efficacy of these drugs on cardiovascular (CV) events and mortality. The purpose of the current study was to evaluate the effects of DPP4-I and SGLT2-I on CV events and mortality by a meta-analysis.
Methods: MEDLINE, Cochrane, ISI Web of Science and SCOPUS databases were searched for articles about DPP4-I and SGLT2-I treatments in type 2 DM patients until February 2016. Randomized trials enrolling more than 200 patients, comparing DPP-4-I or SGLT2-I versus placebo or active treatments in patients with DM and reporting at least one event among all-cause and CV mortality, stroke, myocardial infarction (MI) and new onset of heart failure (HF) were included in the analysis. Meta-analysis was performed to assess the influence of treatments on outcomes.
Results: See figure. 157 randomized trials (114 on DPP4-I and 43 on SGLT2-I) enrolling 140,470 patients (107,100 in DPP4-I and 33,370 in SGLT2-I studies), with a follow-up ranging from 4 to 209 weeks, were included in the analysis. Compared to control, treatment with DPP4-I did not affect all-cause (RR:1.010; 95% CI:0.935–1.091) and CV (RR:0.975; CI: 0.887–1.073) mortality as well as risk stroke (RR:0.933; CI:0.820–1.062) and HF (RR:1.083; CI:0.973–1.205), whereas the 8.5% reduction in risk of MI approximated statistical significance (RR:0.915; CI:0.835–1.002). Compared to control, treatment with SGLT2-I significantly reduced the risk of all-cause death by 28% (RR:0.718; CI:0.613–0.840), CV death by 33% (RR:0.668; CI:0.544–0.821), MI by 21% (RR:0.794; CI:0.661–0.954), HF by 35% (RR:0.652; CI:0.517–0.823) without any effect on risk of stroke (RR:1.158; CI: 0.912–1.469).



Conclusions: DPP4-I do not significantly affect mortality and CV events, whereas treatment with SGLT2-I is associated with improved mortality and reduced risk of MI and new onset of HF in patients with type 2 DM.

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Impact of pioglitazone on cardiovascular events in patients with type-II diabetes mellitus after drug-eluting stent implantation

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Background: It is known that outcome of patients after drug-eluting stent (DES) implantation with diabetes mellitus (DM) is worse than that of patients without DM. It was reported that Pioglitazone decreased cardio vascular events via anti-atherosclerotic effect as well as blood glucose lowering effect in patients with DM.
Objective: The aim of this study is to evaluate the effect of Pioglitazone on cardiovascular events in patients with DM after DES implantation from 3-year follow-up results of the Japan-Drug Eluting Stents Evaluation; a Randomized Trial (J-DESsERT).
Methods: In the J-DESsERT trail, a prospective multicenter randomized controlled trial, 3533 patients were randomized 1:1 to coronary stenting with either sirolimus-eluting stent or paclitaxel-eluting stent and followed for 3 years. The criteria of lesion length was $<$46mm with vessel diameters from $\geq$2.5mm to $<$3.75 mm. Definitions for DM of this trial were 1. previous DM diagnosis; 2. currently on diabetic medication (oral hypoglycemic drugs or injection of insulin preparation); 3. HbA1c $\geq$6.9% within 30 days before the procedure.
Results: The number of patients with DM was 1705 (48%) in this trail. Among them, 357 patients had been medicated Pioglitazone before PCI. The rate of cardiovascular events (death/ myocardial infarction/stroke/target vessel revascularization) 3-year after DES implantation in Pioglitazone treated group significantly decreased (11.5%) compared to that in other therapy group without Pioglitazone (17.7%) (P=0.003). There were no significant between group differences in the rates of myocardial infarction (1.6% and 2.2% in the other therapy group), but in the Pioglitazone group there were significantly lower rates of death from any causes (2.4%, vs. 5.6% in the other therapy group; 57% relative risk reduction), stroke (1.9% and 3.8%, respectively; 59% relative risk reduction), and target vessel revascularization (7.9% and 14.2%, respectively; 45% relative risk reduction).
Conclusion: Pioglitazone significantly decreased cardiovascular events of patients with Type-II DM after DES implantation according to the 3-year follow-up results.

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The impact of high intensity burst exercise on the cardiometabolic status of newly diagnosed type 2 diabetic patients

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Background: For newly diagnosed type 2 diabetics, lifestyle interventions are crucial for disease management. Current guidelines recommend extended exercise of low to moderate intensity multiple times per week. Recent studies in

healthy volunteers, however, have demonstrated potential cardio-metabolic benefits of short bursts of intense physical activity. The impact of these exercise regimen in diabetics has yet to be adequately assessed.
Methods: In this randomized control trial, forty newly diagnosed type two diabetic patients were randomized to a regimen of high impact, burst exercise (ten minutes at 85% of peak heart rate three times per day) or sustained exercise (30 minutes at 60% of peak heart rate once a day). Aerobic fitness and Hemoglobin A1C (HbA1C), BMI, exercise adherence, and lipid profiles were assessed over a three month follow-up.
Results: Forty patients on average 67 years old and 70% were recruited within 3 months of their diagnosis of type 2 diabetes. Patients prescribed burst exercise were found to adhere to exercise regimens compared to the sustained exercise group (362 vs 460 minutes per month, $p<0.01$). The burst exercise group also showed a 2.3 fold greater improvement in HbA1C (-0.82 vs -0.25%, $p<0.01$), and a 5.3 fold greater improvement in aerobic fitness ($p<0.01$). There was a 2.3 fold greater improvement in LDL (-0.37 vs -0.16 mmol/mol, $p<0.01$), a 6.7 fold greater improvement in HDL (0.14 vs 0.021 mmol/mol, $p<0.01$), and a 5.1 fold greater reduction in triglycerides (-0.86, -0.17 mmol/mol, $p<0.01$) with burst exercise. Greater relative improvements per minute of exercise in HbA1C were noted with linear regression analysis.
Conclusions: The burst exercise regimen investigated in this study appeared to significantly improve cardiometabolic status of newly diagnosed diabetic patients. It appears to represent a viable alternative to the current standard of low-moderate intensity exercise for diabetes rehabilitation. Further research is required to validate this regimen in larger and more diverse patient populations over longer follow-up.

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Nephro-protective effects of Dapagliflozin in patients with type 2 diabetes

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Background: Proximal tubule is thought to have potential roles in the pathophysiology of diabetic nephropathy, and therefore nephron-protective effects of sodium/glucose cotransporter 2 (SGLT2) has been much focused.
Purpose: The present study was conducted to examine the change in eGFR calculated using cystatin C (eGFRcys) and sodium excretion in urine when Dapagliflozin was added to a conventional diabetes therapeutic medicine.
Methods: In 30 patients with type 2 diabetes (age 53±8 years, 66.6% were male), Dapagliflozin was added for the improvement of the blood sugar control. The blood and urine test measured before, 6 months and 12 months after administration of the Dapagliflozin. The 24 hour sodium excretion was estimated by the Kawasaki formula using the second morning urine sample.
Results: eGFRcys did not change in comparison with before start 6 months later, but was significantly increased from 92.8±18.5 to 101.9±20.5 mL/min/1.73m^2 after 12 months. ($P<0.001$) The systolic and diastolic blood pressure decrease significantly at a medical examination. (P=0.005 and 0.006 at 6 months, respectively) The estimated 24 hour sodium excretion significantly increased from 6 months (6 months $P<0.001$, 12 months P=0.002).

Table 1

	Baseline	6 months	12 months	P value	
				6 months	1 2months
BW (kg)	78.2±14.1	74.9±14.0	73.7±13.5	<0.001	<0.001
HbA1c (%)	7.59±1.09	7.17±0.64	6.98±0.67	0.031	<0.001
eGFRcys (mL/min/1.73m^2)	92.8±18.5	90.0±20.7	101.9±20.5	0.125	<0.001
Urine albumin (mg/gCr)	71.1±119.1	49.2±78.2	56.4±92.5	0.055	0.304
24 hour sodium excretion (mmol/day)	231±62	290±62	284±96	<0.001	0.002
Systolic BP (mmHg)	138.7±18.6	130.3±15.6	131.2±15.5	0.005	0.024
Diastolic BP (mmHg)	85.6±11.2	79.3±10.1	82.5±7.8	0.006	0.061

Conclusions: The add-on therapy of Dapagliflozin increased urinary sodium excretion and reduced blood pressure even in early phase of this therapy. Then, following these beneficial effects, this add-on therapy might provide nephron-protective effects.

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Impact of the presence and treatment status of diabetes on long-term mortality following coronary angiography

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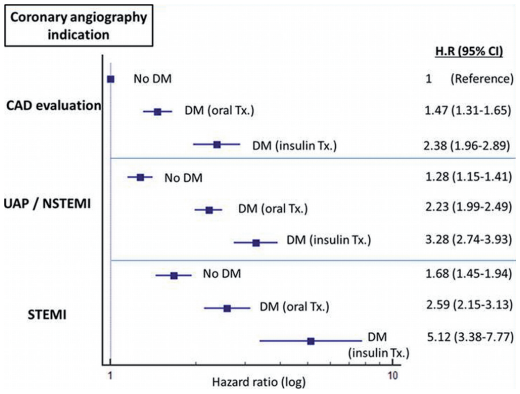
Background: Diabetes mellitus confers increased risk for coronary artery disease (CAD) and mortality. We aimed to determine the impact of diabetes and its treatment, on long-term mortality following coronary angiography for evaluation or therapy of CAD.
Methods: Retrospective analysis was performed of 14,337 consecutive patients, undergoing coronary angiography for stable or acute coronary syndromes (ACS) between the years 2000 and 06/2015. Patient characteristics and long-term mortality were evaluated by Cox regression analysis according to diabetes status (no-diabetes versus diet only, oral-hypoglycemics or insulin treated diabetes) and indication for coronary angiography.
Results: Diabetes was documented in 5,279 (37%) patients, of whom 304 were treated by diet only, 4,002 with oral hypoglycemics and 973 by insulin. The presence and treatment status of diabetes was associated with hypertension, hyperlipidemia, renal failure, higher BMI and female gender, as well as previous percutaneous coronary interventions. In comparison to lack of diabetes (reference), the adjusted hazard ratio (HR) for long-term mortality during a median follow-up period of 78 months (IQR 40–119) for diet only diabetes was 1.41 (95% C.I, 1.11–1.80), p=0.006, for oral hypoglycemic treated 1.63 (1.51–1.77), $p<0.001$, and for insulin treated diabetes 2.50 (2.20–2.85), $p<0.001$. The stepwise increase in long-term mortality in diabetics was noted in both ACS and non-ACS patients (Figure 1) and remained significant after further adjustment for cardiac catheterization indication. Diabetes was a stronger predictor of long-term mortality than ACS so that the relative risk for mortality was higher in medically treated diabetics without ACS, compared to ACS patients without diabetes (HR 1.21, 95% C.I 1.08–1.35, p=0.001).



Relative risk of long-term mortality

Conclusions: In patients referred for coronary angiography diabetes was an independent predictor of long-term mortality, regardless of the clinical syndrome, and mortality was directly related to treatment status/intensity.

50 | BENCH
Dipeptidyl peptidase-4 Inhibitor ameliorates stress-induced glucose metabolism disorder and prothrombotic state

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hdAims/hypothesis: Psychological stress evokes lipolytic release of free fatty acid (FFA) and low-grade inflammation in visceral adipose tissue, mediated by increased adipokine secretion, and contributes to glucose metabolism disorder and prothrombotic state via production of coagulation factors (plasminogen activation inhibitor-1 [PAI-1] and tissue factor [TF]) in white adipose tissue (WAT).
Methods: As accumulating evidence suggests anti-inflammatory potential of dipeptidyl peptidase-4 (DPP4) inhibitors, we investigated the effects of alogliptin on stress-induced adipose tissue inflammation, insulin resistance and prothrombotic state. C57BL/6J mice were subjected to 2-week intermittent restraint stress and orally treated with vehicle, 15 or 45 mg/kg/day alogliptin. Plasma lipids, expression of glucagon-like peptide-1 (GLP-1), DPP4 activity, 8-hydroxydeoxyguanosine (8OHdG; an oxidant stress marker), monocyte/macrophage markers (CD11b, CD68, and F4/80), proinflammatory cytokines (monocyte chemoattractant protein-1, tumor necrosis factor-α, and interleukin-6), adiponectin, and coagulation factors (PAI-1 and TF) in blood and inguinal WAT was determined using immunohistochemistry, enzyme-linked immunosorbent assay, and RT-PCR, respectively. Glucose metabolism was assessed by glucose tolerance tests (GTTs) and insulin tolerance tests (ITT), and expression of insulin receptor substrate-1 (IRS-1) and glucose transporter 4 (GLUT4) in WAT.
Results: The stress procedure increased FFA release, 8OHdG-positive cells and monocyte accumulation in WAT, proinflammatory cytokine, and reduced adiponectin and GLP-1, followed by DPP4 activation in plasma. The stress-induced adipose inflammation increased PAI-1 and TF, and worsened insulin sensitivity and decreased IRS-1 and GLUT4 in WAT. The alogliptin administration suppressed stress-induced FFA release, oxidant stress production, adipose inflammation, procoagulant state in a dose dependent manner, and restored glucose metabolism in GTT and ITT.
Conclusions/Interpretation: The results indicate that alogliptin improves stress-induced prothrombotic state, and glucose metabolism disorder. Our result suggests that alogliptin exerts additive benefits for cardiovascular complication in diabetes patients with mental stress.

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Nephroprotective properties of metformin in randomized, comparative, prospective clinical study

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Background: Prevention of diabetic nephropathy onset and progression could lead to a decrease in concomitant adverse cardiovascular outcomes. Our previous experimental study in rats with type 2 diabetic nephropathy has demonstrated isolated tubuloprotective properties of metformin without any influence on glomerular kidney function, but its renal effects on tubular function in patients with diabetes have still remained unclear.
Purpose: The study aimed to assess the effects of metformin added-on insulin therapy on kidney dysfunction markers (glomerular and tubular separately) in type 2 diabetic patients.
Methods: In a single-center, unblinded, randomized, comparative, prospective clinical study we investigated the dynamic of serum (estimate glomerular filtration rate (GFR) using creatinine (eGFRcr) and cystatin C (eGFRcys)), and twice-measured urinary markers of renal dysfunction expressed per gram of creatinine, based on a first morning urine spot (indicators of glomerular injury – albuminuria, and excretion of collagen type IV; and tubular (neutrophil gelatinase–associated lipocalin (NGAL)) and liver fatty acid–binding protein (L-FABP)) damage markers in forty three well-controlled insulin-treated patients with type 2 diabetes randomized either to continue insulin therapy (insulin-treated group (IG), n=21), or to receive 6-month metformin treatment in daily dose 1500 mg added-on insulin (metformin/insulin-treated group (MIG), n=22). Non-inclusion criteria were severe micro- and macrovascular diabetic complication, uncontrolled hypertension and dyslipidemia, inflammatory and oncological conditions, liver disorders, nephrotoxic drugs usage, and renal disease other than diabetic nephropathy.
Results: Studying groups were comparable on the basis of sex, age (IG = 60,05±6,13; MIG = 60,14±5,95 years), and duration of diabetes (IG = 10,52±4,84; MIG = 9,11±3,95 years). At baseline, in MIG eGFRcr was 77,5±13,32 ml/min/1.73 m^2, eGFRcys 92,34±14,52 ml/min/1.73 m^2, albuminuria 24,6±17,6 mg/g, excretion of collagen type IV 3,78±2,87 μg/g, urinary NGAL 19,28±14,92 μg/g, and urinary L-FABP was 3,36±2,19 μg/g, and these parameters didn't statistically differ compared to IG. Although there were no comparable changes in eGFRcr, eGFRcys, albuminuria, and collagen type IV in both studying groups, NGAL and L-FABP were significantly improved in MIG after 6-month metformin treatment (10,72±11,55 μg/g (p=0,039)), and 2,09±1,81μg/g (p=0,042), respectively. Moreover, these changes were independent from body weight, HOMA-IR, and serum lipid profile.
Conclusion: The results of the study showed that 6-month metformin treatment in daily dose 1500 mg added-on insulin therapy in well-controlled type 2 diabetic patients could result in amelioration of tubular dysfunction observed in patients even during early (normoalbuminuric) stages of diabetic nephropathy.
Acknowledgement/Funding: The research was supported by research resource center "Molecular and cell technologies" of St. Petersburg State University

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Histone 3 lysine 27 trimethylation in type 2 diabetes: a novel potential pharmacological target in diabetic foot ulcer treatment

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Background: Type 2 diabetes (T2D) is a common disease and its prevalence is rapidly increasing, especially in the elderly population. About 15% of diabetic patients develop foot ulceration (DFU) and approximately 40% of them undergo limb amputation. Therefore, new therapeutic strategies are required to face the clinical challenge posed by DFU. Hyperglycemia leads to chromatin remodeling and epigenetic changes. Histone 3 Lysine 27 (H3K27) trimethylation is an epigenetic change involved in wound healing and keratinocyte function during skin repair; it results from the balance of the opposite activities of the histone methyltransferase EZH2 and histone demethylase JMJD3. The role of H3K27 trimethylation in diabetic skin wound healing is unknown.
Purpose: We sought to evaluate H3K27 trimethylation, EZH2 and JMJD3 expression and their relation to the cell functional properties in human keratinocytes from diabetic patients and in the human keratinocyte cell line HaCaT exposed to high glucose.
Methods: Skin samples were obtained from diabetic patients with DFU and non-diabetic patients with critical limb ischemia without diabetes undergoing limb amputation, just below the amputation line. Additional control skin samples were obtained from non-diabetic patients undergoing saphenectomy. Keratinocytes were isolated from skin biopsies; we used HaCaT cells cultured either in 50mM glucose (high glucose; HG) or 25mM glucose (low glucose; LG). H3K27 trimethylation was modulated by EZH2 or JMJD3 inhibition either with newly synthesized drugs or RNAi technology. Gene expression and protein levels were evaluated by real-time PCR and Western blot, respectively. Cell proliferation was evaluated by cell counting and MTT assays; cell migration was evaluated by scratch assay.
Results: H3K27 trimethylation was lower in diabetic skin biopsies than in the skin of normoglycemic subjects. In agreement with this result, HG reduced EZH2 expression and H3K27 trimethylation in HaCaT cells; this effect was associated with impaired HaCaT cell proliferation and migration. EZH2 pharmacological inhibition or silencing down-modulated H3K27 trimethylation and inhibited keratinocyte proliferation and migration. In contrast, JMJD3 pharmacological inhibition or silencing enhanced H3K27 trimethylation and accelerated both cell proliferation and migration. Interestingly, JMJD3 inhibition in HaCaT cells cultured in HG rescued the inhibitory effect of hyperglycemia on cell proliferation and migration. Finally, enhanced H3K27 trimethylation in keratinocytes isolated from diabetic patients, either by JMJD3 pharmacological inhibition or genetic silencing, accelerated wound healing in the scratch assay.
Conclusions: Diabetes and hyperglycemia down-modulate EZH2 expression and H3K27 trimethylation in keratinocytes. JMJD3 inhibition reverts diabetes- and hyperglycemia-induced H3K27 trimethylation reduction, and improves keratinocyte functional impairment.
Acknowledgement/Funding: This work has been supported by grants from the Italian Ministry of Health: Ricerca Corrente and contract 72/RF-2010-2318330.

THE HEART IN HYPERTENSION

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Electrocardiographic left ventricular hypertrophy, obesity and incident cardiovascular events. The MOLI-SANI study

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We aimed at investigating the prevalence and the prognostic significance for fatal and non fatal cardiovascular (CV) events of different electrocardiographic (ECG) criteria for left ventricular hypertrophy (LVH) in normal weight, overweight and obese subjects in an adult Italian population. For this purpose 18330 adults (mean age 54±11 years, 55% women,53% hypertensives) were analyzed from the Molisani cohort. Obesity was defined using the ATPIII criteria. ECG-LVH was defined according to ESH-ESC guidelines The age and sex-adjusted prevalence of ECG-LVH did not differ from normal weight subjects to class 2–3 obesity subjects when the strain or Cornell Voltage (CorVol) criteria were used. In overweight and obese patients, as compared with normal weight subjects, a progressively lower prevalence of ECG-LVH was observed when the Sokolow-Lyon (SL) index was used, while a higher prevalence was shown by using the aVL-R-wave voltage (>11 and >5.7mm) and the Cornell Voltage-QRS duration product (CP). The incidence of CV events was significantly greater in subjects with ECG-LVH diagnosis by the CorVol (HR 1.89; 95% CI: 1.05 to 3.39), the CP (HR 1.87, 95% CI: 1.31 to 2.67),and the presence of strain (HR 1.89; 95% CI: 1.05 to 3.39) .After adjusting for different confounders (age, sex, cigarette, hypertension, hypercholesterolemia, diabetes, income, education, occupational class, physical activity) and for BMI categories, only the CP remained significantly associated to a higher incidence of CV events (HR 4.8; 95% CI: 1.85 to 12.45). The predictive significance of different LVH criteria were assessed across BMI categories; after adjusting for different confounders, LVH identified by a R wave in aVL>11 (HR 4.63; 95% CI: 1.37 to 15.62) and the presence of strain (HR 24.1; 95% CI: 2.85 to 204) were significantly associated with an increased risk of CV events in class 2–3 obesity subjects; CV-LVH remained an independent predictor of events only in class 1 obesity individuals (HR 1.76; 95% CI: 1.16 to 2.67), while CP-LVH predicted an increased risk of CV events only in normal weight or overweight subjects (HR 2.55; 95% CI: 1.53 to 4.26 and HR 2.72; 95% CI: 1.14 to 6.48, respectively). In conclusion, our results confirm that ECG-LVH prevalence may differ according to the criteria used, across BMI categories. The use of different LVH criteria according to BMI categories may improve CV risk stratification in a general population independently of several confounding factors.

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The increase in arterial stiffness may change in left ventricular geometry and lead to heart failure with preserved ejection fraction

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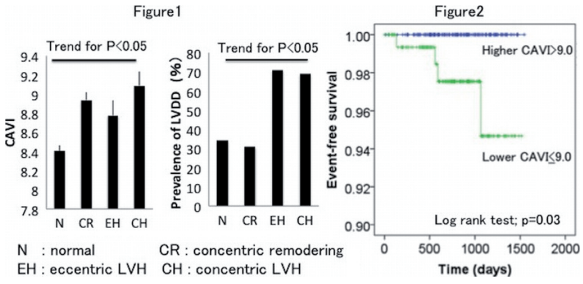
Background: Increased arterial stiffness is reported to be associated with left ventricular hypertrophy (LVH) and LV diastolic dysfunction (LVDD). However, the impact of arterial stiffness on LV geometry and the development of heart failure with preserved ejection fraction have not been fully elucidated.
Purpose: To evaluate the association of cardio-ankle vascular index (CAVI) of LV geometry and the incidence of heart failure with preserved ejection fraction.
Methods: A total of 1273 subjects (mean 65 years, 55% men, 40% diabetes mellitus) were evaluated after exclusion of patients with coronary artery disease, severe valvular disease, cardiomyopathy and LV ejection fraction<50%. Arterial

stiffness was evaluated using the cardio-ankle vascular index (CAVI) based on oscillometric method. LV geometry and the parameters of LV diastolic function were determined using echocardiography. LV geometry was determined by relative wall thickness and LV mass index, and LVDD was defined according to ASE guideline.
Results: When patients were classified based on LV geometry, CAVI and the prevalence of LVDD in patients with concentric LVH were the highest than those in patients with other LV geometry, respectively; however, this association was different in patients with concentric remodeling (Figure 1). There was a significant correlation of CAVI with LV mass index (r=0.08, p<0.01), LAVI (r=0.15, p<0.01), E (r=0.08, p<0.01), e' (r=0.27, p<0.01), and E/e' (r=0.38, P<0.01). When patients were divided into the tertile according to CAVI, multiple logistic analysis revealed that the third tertile of CAVI was independently associated with concentric LVH (OR: 2.00, 95% CI: 1.29 to 3.56, p=0.02) and LVDD (OR: 1.50, 95% CI: 1.08 to 2.09, p<0.01) after adjustment of covariates.
During a median follow-up of 2.2 years, heart failure occurred in 1.2%. When patients were divided into two groups according to CAVI as a cut-off value of 9.0, the incidence of heart failure in the higher CAVI group was significantly greater than that in the lower CAVI group (log-rank test, p=0.03) (Figure 2). After adjustment of confounding factors, increased in CAVI remained associated with heart failure (p=0.022), with a hazard ratio of 2.896 (95% CI: 1.162 to 7.219).



Conclusions: Increased arterial stiffness influence LV geometry leading to heart failure with preserved ejection fraction.

105 | BEDSIDE
Reduction of body weight promotes regression of left ventricular hypertrophy in obese hypertensive outpatients: a real-world analysis from the campania salute network

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Background: Reduction of left ventricular (LV) mass index (LVMi) during antihypertensive treatment is difficult to achieve in obese subjects, despite optimal blood pressure (BP) control. Our analysis investigates probability of reduction of LVMi in treated obese hypertensive patients related to changes of body weight.
Methods: From the Campania Salute Network (CSN) registry, we identified 1754 patients (53±11 years, 46% women) with body mass index (BMI) ≥30 kg/m^2 and ≥12-month follow-up. Echocardiographic LVMi was assessed at baseline and at the last available visit. LV hypertrophy (LVH) was defined as LVMi ≥47 g/m$^{2.7}$ in women or ≥50 g/m$^{2.7}$ in men. We adjudicated significant reduction of LVMi when achieving normal values or reducing LVMi ≥10% of baseline value. Weight reduction was considered as ≥5% reduction in body weight.
Results: LVH was initially present in 1061 patients (46% women, 15% diabetic). At the end of follow-up (median: 49 months, 30–92), LVMi was reduced in 98 patients (6%, RED); 1137 patients had LVH (PERS) and 519 maintained LVMi under the threshold for LVH (NOR). At baseline, RED were younger, less likely to be diabetic and had lower baseline BMI, LVMi and average systolic BP during follow-up, while glomerular filtration rate (GFR, by CKD-EPI) was higher than in PERS (all p<0.05). Significant reduction of LVMi occurred more frequently (8.3% vs 4.6%, p<0.009) in patients losing weight (n=481 or 27%) than in those maintaining initial weight (n=1273). In multinomial logistic regression analysis, comparing RED, PERS and NOR (used as reference), weight reduction increased the chance of LVMi reduction by near 2-fold (Table), independently of age, female sex, average follow-up systolic BP, and baseline GFR, diabetes and LVMi.

Table 1. Independent predictors of reduction of LV Mass index during follow-up

	Reduction of LV mass index		LVH at the end of follow-up	
	OR (95% CI)	p≤	OR (95% CI)	p≤
Age	0.98 (0.95–1.01)	0.15	1.02 (0.99–1.04)	0.15
Female sex	2.63 (1.54–4.50)	0.001	4.57 (3.06–6.84)	0.001
Average follow-up SBP	0.98 (0.96–1.01)	0.17	1.01 (0.99–1.03)	0.17
GFR	1.00 (0.99–1.02)	0.67	1.00 (0.99–1.01)	0.87
Diabetes	0.91 (0.37–2.21)	0.83	1.53 (0.85–2.78)	0.16
LV mass index	1.55 (1.44–1.66)	0.001	1.74 (1.63–1.85)	0.001
≥5% weight loss	1.89 (1.11–3.22)	0.02	0.92 (0.60–1.39)	0.68)

Conclusion: In treated obese hypertensive patients, weight reduction during follow-up promotes significant reduction of LVMi, independent of baseline characteristics and BP control.

DRUG THERAPY OF HEART FAILURE

170 | BEDSIDE
Are beta-blockers needed in patients after primary prevention implantable cardioverter-defibrillator? A multicenter population-based cohort study

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Introduction: Recent large observational studies have indicated that the role of β-blockers for prevention of cardiovascular events in patients with coronary artery disease (CAD) might be reconsidered. Conversely, no real evidence exists from the now relatively old randomized trials in patients with chronic heart failure that β-blockers reduce mortality after prophylactic cardioverter-defibrilllator (ICD) implantation. We examined the impact of beta-blocker use on outcomes after prophylactic ICD implantation.
Methods: All patients, with coronary artery disease or dilated cardiomyopathy, implanted with an ICD in the setting of primary prevention in 12 centers in France between Jan. 2002 and Jan. 2012 were included in this retrospective observational multicentric study. Device therapies and complications were determined at routine clinic visits during a mean follow-up of 3.1±2 years. Risks of events were analyzed with propensity score matching.
Results: Among 3975 ICD recipients, patients not treated with beta-blockers (n=601) were older (65±11 vs 63±11, p<0.0001), had similar rate of CAD (60% vs 58%, p=0.51) and more frequently had lower ejection fraction (32% vs 27%, p=0.009) and cardiac resynchronization therapy (59% vs 54%, p=0.02). Propensity score for beta-blocker use was estimated for the 3984 patients and used to assemble a cohort of 541 pairs of patients receiving and not receiving beta-blocker, who were balanced on 22 baseline characteristics. Among matched patients, risks were higher with lack of beta-blocker use compared to users for all-cause death (Hazard Ratio [HR] 1.34, 95% CI 1.02–1.75, p=0.04) and cardiac death (HR 1.50, 95% CI 1.06–2.13, p=0.02), whilst similar for sudden death (HR 1.15, 95% CI 0.44–2.98, p=0.77), rates of appropriate therapies with primary prevention ICD (HR 1.03, 95% CI 0.79–1.35, p=0.82) and rates of inappropriate therapies (HR 1.24, 95% CI 0.60–2.53, p=0.56).
Conclusions: In a large contemporary cohort of patients with prophylactic ICD implantation, lack of beta-blocker use was associated with similar risks of sudden death, appropriate and inappropriate device therapies but higher rates of mortality and cardiac death. Although the benefit may be lower for the prevention of sudden death, beta-blockers should continue to be widely used as currently recommended for heart failure in the specific setting of patients with prophylactic ICD implantation.

171 | BEDSIDE
Non-withdrawal of beta-blockers in acute decompensated chronic and de-novo heart failure is associated with lower in-hospital and 3-months mortality: Findings from the GULF-CARE

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Background: Beta-blocker therapy has been demonstrated to reduce mortality in chronic heart failure. Whether it should be temporarily withdrawn during acute decompensating chronic or de-novo heart failure, guidelines are not clear.
Purpose: The aim of this paper is to report on use of beta-blockers in patients admitted with heart failure in the Middle East and to assess short-term and long-term consequences of withdrawal or continuation of beta-blockers in heart failure patients.
Methods: The Gulf CARE (Gulf aCute heArt failuRe rEgistry) is a prospective

multicenter study of 5005 consecutive patients hospitalized with acute heart failure during February-November 2012 in 7 Middle Eastern countries. We studied mortality and re-hospitalization for heart failure in patients with acute decompensated chronic and de-novo heart failure, and a left ventricular ejection <40%, up to one year.
Results: Among the 5005 patients admitted in the GULF-CARE, 2,208 patients were treated with beta-blockers, of whom 1,549 (56.9%) were diagnosed with acute decompensated chronic HF (ADCHF) and 632 (26.6%) with acute de-novo heart failure (ADNHF). In the ADCHF group, 1054 patients (68%) had a LVEF<40%. Among those 16 (1.6%) in-hospital deaths occurred in patients whose beta-blocker therapy was not withdrawn as compared to 37 (40.2%) when beta-blocker was discontinued (OR 0.02, 95% CI [0.01–0.05], p=0.001). In the ADNHF group, 260 patients (24.6%) had a LVEF<40%. Among those, 5 (2.2%) in-hospital deaths occurred in patients whose beta-blocker therapy was not withdrawn as compared to 17 (47.2) when beta-blocker was discontinued (OR 0.02, 95% CI [0.01–0.07], p=0.001). At 3 months, mortality was lower in ADCHF patients in whom beta-blockers were maintained during the acute decompensation (OR = 0.45, 95% CI [0.21–0.98], p=0.02), but not in the ADNHF group. At one year, the earlier benefit of non-withdrawal of beta-blockers was lost in all patients. However, rehospitalization for acute heart failure and length of hospital stay were unaffected by beta-blocker discontinuation at all time intervals.
Conclusions: Non-withdrawal of beta-blockers in acute decompensated chronic heart failure is associated with lower in-hospital and 3-months mortality, and lower in-hospital mortality in patients with de-novo heart failure.

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Beta-blockers, ACE/ARB and MRA at discharge and outcome after hospitalization of heart failure in octogenarians with HFPEF and HFREF: a report from the BIO-HF registry

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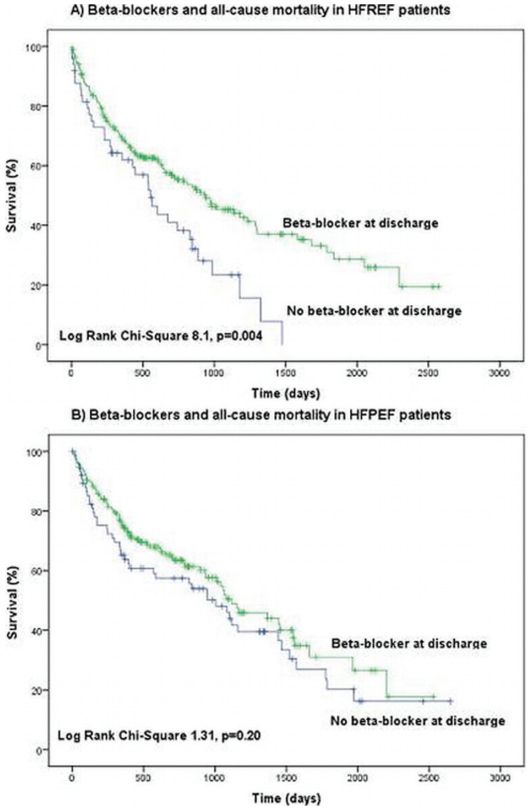
Purpose: We aimed to assess the impact of the use of beta-blockers (BBL), ACE/ARB and mineralocorticoid receptor antagonists (MRA) on all-cause mortality after discharge for hospitalization for heart failure in octogenarians
Methods: We studied 548 octogenarians who were included in the BIO-HF registry in 2 Belgian hospitals for an hospitalization for heart failure between 2010 and 2013. Patients were followed after discharge for all cause-mortality (complete follow-up in 97%) for a mean follow-up of 24 months.
Results: Mean age of the 531 patients with complete follow-up was 85±4 years (55% women). Mean LVEF was 46±16%. HFPEF (LVEF>50%) was present in 50% of patients. At discharge BBL were given in 80% of patients with HFREF and 69% of patients with HFPEF (p=0.005), ACE/ARB in 62% and 48% (p=0.002), and MRA in 39% and 28% respectively (p=0.011)



In total 276 patients (52%) died during follow-up. Independent predictors for mortality in multivariate Cox regression analysis were higher age, absence of beta-blockers at discharge, lower systolic blood pressure on admission, higher creatinine levels on admission and a history of stroke (all p<0.05). The protective effect of BBL was however only seen in patients with HFREF and not in HFPEF (figures A and B for Kaplan-Meier curves). In univariate analysis, but not in multivariate analysis, the use of ACE/ARB was associated with better outcome. Again, this effect was only seen in HFREF patients and not in HFPEF patients. The use of MRA was not associated with better outcome in HFREF and HFPEF patients.
Conclusion: In octogenarians admitted with HFREF, the use of BBL and ACE/ARB at discharge are associated with a better outcome. This effect was however not seen in HFPEF patients. The use of MRA was not associated with a better outcome in both HFREF and HFPEF patients. These data can help prioritizing heart failure medication in very old patients admitted with heart failure.

173 | BENCH
Fingerprint of the renin-angiotensin-system during ARNI therapy in patients with systolic heart failure

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Objective: Angiotensin-receptor-neprilysin-inhibition (ARNI), which combines angiotensin receptor blockade (ARB) and neprilysin inhibition (NEPi), has been shown to reduce hospitalization and all-cause mortality in patients with heart failure with reduced ejection fraction (HFrEF) compared to angiotensin-converting-enzyme-inhibitor (ACE-I) therapy. NEPi was also hypothesized to exert favorable effects on systemic renin-angiotensin-system (RAS) components, however, the effect of ARNI on the alternate RAS axis has not been studied in details.
Methods: In our exploratory study, we investigated 6 patients with HFrEF eligible for ARNI therapy in line with the PARADIGM enrollment criteria. Blood samples were collected under ACE-I therapy and 4 weeks after switching to ARNI therapy. The full spectrum of circulating plasma angiotensin metabolites were stabilized with protease inhibitors and subsequently quantified by mass spectrometry.
Results: (Figure 1) As expected, ACE-I therapy led to suppressed Ang1–8 (AngII) levels associated with elevated levels of Ang1–10 (AngI). Switching to ARNI therapy resulted in a marked increase of Ang1–8 levels (ACE-I: 4.0pg/ml vs. ARNI: 283.2pg/ml) and lower Ang1–10 levels (ACE-I: 578.5pg/ml vs. ARNI: 459.1pg/ml) due to recovered ACE activity and the onset of the ARB effect. However, the levels of the putatively beneficial Ang1–7, a member of the alternate RAS axis and counter player of Ang1–8, were higher on ACE-I therapy (ACE-I: 24.5pg/ml vs. ARNI: 4.0pg/ml). This could be caused by the concomitant formation of Ang1–7 from excess Ang1–10 by NEP and reduced degradation to Ang1–5 by inhibited ACE. ARNI therapy on the other hand consisting of ARB and NEPi, leaving ACE activity largely unaffected, seems to go along with low Ang1–7 levels as a net effect on the enzymatic interplay.

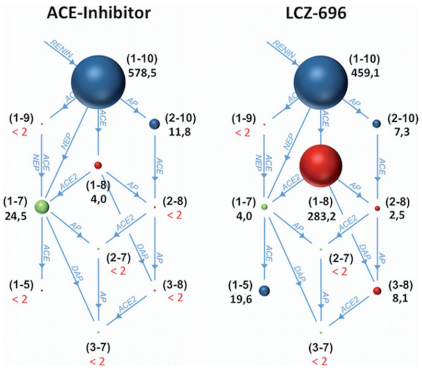

Figure 1

Conclusions: Ang1–7 levels seem to be reduced on ARNI therapy compared to ACE-I. This suggests that the alternate RAS axis may not play an important role in mechanisms responsible for the therapeutical benefits of ARNI.

174 | BENCH
Anti hypertrophic effects of LCZ696 in chronic cardiac pressure overload

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Background/Introduction: LCZ696 is a newly approved drug for treatment of Heart failure with reduced ejection fraction (HFrEF). It combines the effects of angiotensin receptor blockade and neprilysin inhibition, and was in a large clinical trial shown to yield a major reduction in mortality when compared to current standard therapy for HFrEF. The mechanisms mediating this beneficial effect re-

main largely unknown. Furthermore, better understanding of this new molecule's mechanisms of action can potentially open up for other clinical applications.
Purpose: To investigate the effects of LCZ696 on cardiac function and remodeling in a chronic model of increased afterload.
Methods: Thirty male Sprague Dawley rats were randomly assigned to three different groups: vehicle treated sham operated (Sham, n=5); vehicle treated transverse aortic banding (TAC) (vehAB, n=12); LCZ696 treated transverse aortic banding (LCZAB, n=13). Oral gavage was performed once daily in all groups for six weeks. Echocardiography and MRI were performed at six weeks, organ weights were assessed, and tissues were examined using PCR and HPLC. * indicates $p<0.05$ for vehAB vs. LCZAB.
Results: Both LCZAB and vehAB had similar trans-stenosis gradients as assessed by echocardiography at randomization. MRI demonstrated increased left ventricular mass in TAC animals, with LCZ reducing the observed change (Sham; LCZAB; vehAB: 197±8,5; 213±8.46; 248±13.24 mm^3*). Echocardiography indicated a trend towards better diastolic function in LCZ treated animals. MRI showed a trend towards decreased EF in TAC animals, with LCZ yielding improvement (73.8±2.44; 71.42±1.5; 66.55±2.25%). At six weeks, LCZAB had a 11,5% lower left ventricular weight than vehAB (0.85±0.02; 1.0±0.045; 1.1±0.057 g *). Lung weight was lower in LCZAB than vehAB (1.5±0.049; 1.6±0.020; 1.72±0.07 g *), indicating improved cardiac function. There was a trend towards an increase in Myh-7 in TAC, with lower levels in LCZAB than in vehAB, indicating possible favorable effects on cardiac remodeling. At six weeks TAC did not show increased collagen on HPLC for hydroxyproline. Similarly, there were no increases of Col1. There was a trend towards vehAB showing the highest expression of Col3 and lowest expression of MMP9.
Conclusion(s): LCZ696 treatment reduces cardiac hypertrophy in this model of sustained pressure overload, and showed a favorable trend for improved diastolic and systolic function. Our findings support that the beneficial effects observed in recent clinical studies could reflect favorable anti cardiac remodeling properties and that the clinical utility of this novel compound might be extended to patients with diastolic dysfunction secondary to pressure overload. There was no observed fibrosis in this study. Further studies are warranted to investigate the underlying mechanisms responsible for the observed beneficial effect and the possible utility of LCZ696 in other disease states involving cardiac pressure overload.
Acknowledgement/Funding: Drugs were a gift from Novartis Pharma AG

175 | BENCH
Superior actions of chronic peptide therapeutics with Cenderitide on cardiorenal function and remodeling compared to enalapril through reverse activation of gene pathways in experimental heart failure

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Purpose: Targeting the cardiorenal connection is an important therapeutic strategy that may halt the vicious cycle that exists between the heart and kidney in heart failure (HF). The cardiac natriuretic peptides have cardiorenal protective effects, such as natriuresis, inhibition of fibrosis and suppression of the renin-angiotensin-aldosterone system through the GC-A or GC-B receptors. As no dual GC-A/GC-B activator exists in nature, we created a novel dual GC-A/GC-B activator called Cenderitide (CD), which are in clinical trials for HF. However the chronic effects of CD therapy on cardiorenal function and remodeling are undefined. Hence, we sought to compare the actions of chronic administration of CD and the ACE inhibitor, enalapril, on cardiorenal function and remodeling genes in experimental HF. We hypothesized that dual GC-A/GC-B stimulation with CD could reverse the activation of heart and kidney gene pathways that may lead to beneficial effects in HF.
Methods: Experimental HF was induced in canines by rapid ventricular pacing at 240 bpm for 10 days, which mimics human HF. Canines were divided into 3 groups (n=5 of each), untreated, CD with continuous SQ pump (CD-pump, 5 ng/kg/min) or oral enalapril (0.5 mg/kg/day) for 10 days from the beginning of pacing. We measured hemodynamics, echo parameters, circulating neurohumoral factors at day 11. We also examined 182 gene profiles using RT-PCR microarrays related to the NP system, fibrosis, growth factors, and inflammation in left atrium (LA) and kidney cortex (KC). Gene network, pathway, bio-function and comparison analysis were performed using Ingenuity Pathway Analysis (IPA) System.
Results: The CD-pump group, showed significantly less atrial and renal weights, higher cardiac output, glomerular filtration rate, and ejection fraction, and lower systemic vascular resistance and plasma renin activity (all $p<0.05$) without lowering mean arterial pressure (MAP) compared to untreated while the enalapril group lacked these effects and had lower MAP. Gene profile analyses in LA and KC showed significant reverse effects on modulated genes in HF such as TNF-alpha, IL-1 beta, ROCK-2, caspase 7, Fas ligand, C-Myc and TP53 in CD-pump group compared to untreated, which was not observed with enalapril. Network and pathway analysis revealed improvements with CD in the LA and KC with improvements in global gene pathways specifically related to cell survival, cellular movement, and inflammatory/immune response, which were not observed or were less with enalapril.
Conclusions: Continuous SQ infusion of Cenderitide demonstrated superior beneficial effects on cardiorenal function and remodeling genes compared to ACE inhibition by reducing activated deleterious gene profiles in HF. Our findings suggest that chronic peptide therapeutics with Cenderitide therapy provides key cardiorenal protective actions in the setting of HF, which go beyond ACE inhibition and support further investigations.

176 | BEDSIDE
Mineralocorticoid receptor antagonists on admission and in-hospital outcome of patients hospitalized for acute heart failure

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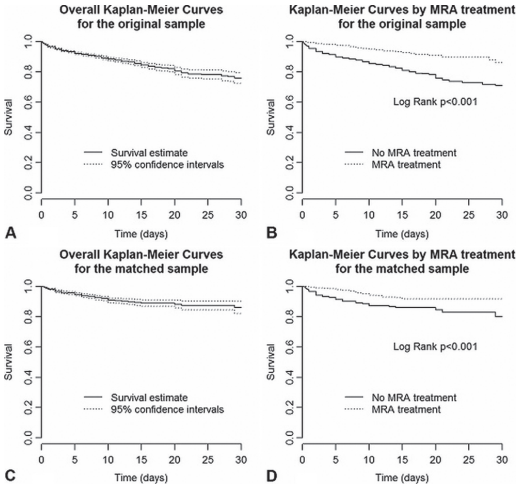
Background: Mineralocorticoid receptor antagonists (MRAs) constitute a beneficial therapy in chronic heart failure, but their use in the acute heart failure (AHF) setting remains rather unexplored. We assessed short-term outcome in AHF patients receiving or not MRAs in a large AHF cohort.
Methods: The Acute Heart Failure Global Registry of Standard Treatment (ALARM-HF) was conducted during 2006–2007 and included a total of 4953 patients hospitalized for AHF in 9 countries in Europe, Latin America and Australia. We compared in-hospital mortality between patients receiving or not MRAs. Nearest-neighbor matching with 1:1 ratio by propensity score was applied to produce a balanced subsample consisting of pairs of treated and untreated patients. Mortality was assessed by Mantel-Cox test and Cox regression with adjustment for age category (≤75y vs >75y), sex, systolic blood pressure (SBP), heart rate (HR), atrial fibrillation (AF), NYHA class, left ventricular ejection fraction (LVEF), acute coronary syndrome (ACS), renal dysfunction and cardiogenic shock at presentation.
Results: From the original cohort of 4953 patients (1439 treated with MRAs and 3514 not treated) in which 39 baseline variables differed significantly between treatment groups, a subsample of 2006 patients was derived using propensity score matching (1003 in each treatment group) in which all baseline variables were balanced as assessed by standardized mean differences. Overall, MRA therapy led to a reduced in-hospital mortality both in the original [HR:0.311, 95% CI (0.239, 0.405), $p<0.001$] and in the matched sample [HR:0.371, 95% CI (0.260, 0.530)] (Figure). The beneficial effect on mortality persisted after adjustment for potential confounders before and after propensity-score matching [HR:0.297, 95% CI (0.204, 0.433), $p<0.001$ and HR:0.392, 95% CI (0.253, 0.607), $p<0.001$, respectively]. In the subgroup analysis after matching, MRA therapy exerted a beneficial effect on mortality irrespective of age category (≤75y vs >75y), sex, cardiogenic shock, ACS, cardiac rhythm (sinus rhythm vs atrial fibrillation) at presentation both before and after matching. However, although MRAs reduced mortality on patients who presented with oliguria or anuria (log-rank $p<0.001$), they did not affect mortality in patients with normal diuresis at presentation (log-rank p=0.13). Moreover, MRAs had no effect on mortality in patients with LVEF ≥30%.



Conclusion: In AHF, MRA therapy prescribed in-hospital is associated with a significantly lower short-term mortality.

177 | BEDSIDE
The effect of metformin on mortality rates and exercise tolerance in patients with heart failure and type 2 diabetes

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Background: Type 2 Diabetes mellitus is a frequent cause of heart failure. Impaired glucose management, hyperinsulinemia and insulin resistance present in T2DM, resulting in abnormal biochemical processes, that worsen the course of heart failure. Similarly, increased oxidative stress, chronic activation of the renin-angiotensin-aldosterone system and activation of isoform PKCβ2 and RhoA/Rho kinase pathways are suspected of participation in the development of heart failure in type 2 diabetes.
Metformin is a first-line drug in type 2 diabetes. It seems to be the only antidiabetic agent, which can reduce the risk of major cardiovascular events and mortality in type 2 diabetes, however, its implementation in T2DM with HF is still contraindicated.
Purpose: The aim of this post-hoc analysis was to assess whether metformin administration in patients with heart failure and type 2 diabetes affects mortality rates and exercise tolerance in 12-months follow-up.
Methods: The study included 1030 of 1126 patients with HF representing Polish population of the prospective observational study Heart Failure Long Term Registry. 350 patients of the study population with a history of antidiabetic medication were identified (112 women, mean age 66.8±10.8 years; BMI 30.3±5.5 kg/m^2; LVEF 34.3±14.1%) and divided into two groups: receiving metformin or not receiving metformin.
Results: 135 of 350 patients were treated with metformin. At 1-year follow-up death occurred in 128 HF patients of the whole population (12.4%), in 53 patients with diabetes (15.3%) compared with 75 patients without diabetes (10.9%) (HR 0.88; 95% CI: 0.86 to 0.90; p=0.045). Metformin treatment was associated with lower mortality rates compared with non-metformin treated group (9,6% vs. 18,6%; HR 0,85; 95% CI: 0,81 to 0,89, p=0,023).
Metformin treatment was associated with lower NYHA class on admission to a hospital in patients with acute HF or worsening compared with not-metformin treated group (2.95 vs. 3.22; p=0.008). On discharge or first visit in outpatient clinic and in 12 months follow-up mean NYHA class was similar in both groups with diabetes (respectively: 2.29 vs. 2.38; p=0.17; 2.31 vs. 2.26; p=0.57). In terms of age, gender, height, systolic and diastolic blood pressure, and last known ejection fraction, both groups with diabetes were similar, however, in group treated with metformin higher weight and body mass index (respectively: 90.2±19.1 vs. 84.0±15.3 kg, p=0.003 and 31.4±6,0 vs. 29.6±5,1 kg/m^2, p=0.003) were observed.
Conclusion: The results of this study suggest that metformin treatment is associated with a reduction in mortality and better clinical condition in diabetics with heart failure. Therefore, we support the other authors suggestion that metformin contraindications should be reconsidered.

178 | BEDSIDE
Novel diuretic response score predicts future cardiac events in acute heart failure patients

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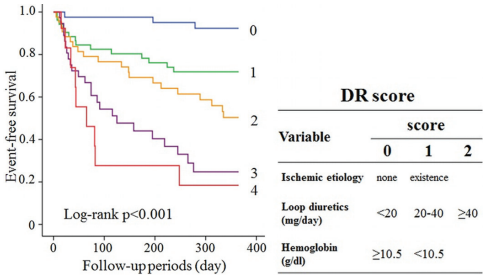
Background: Heart failure (HF) patients are generally treated with diuretics under the monitoring of systemic congestion. Poor diuretic response (DR) is associated with worse prognosis in patients with HF. However, little is known about the predictor of poor DR leading to worse prognosis.
Purpose: The aims of this study were 1) to clarify the clinical characteristics on admission of poor DR in acute HF patients with systemic congestion and 2) to establish a score for predicting future cardiac events.
Methods: We enrolled 186 consecutive acute HF inpatients survived to discharge (mean age of 78 years, 104 females). DR was calculated by the formula; in-hospital Δbody weight (kg)/80 mg oral furosemide or equivalent loop diuretic dose. Systemic congestion on admission was simply evaluated by the presence of leg edema or jugular venous distention. We performed a logistic analysis to clarify the characteristics of poor DR patients and constructed a new scoring system defined by ROC curves of each factors. All patients were followed up to one year after discharge. Cardiac events were defined as cardiac deaths and re-hospitalization for worsening heart failure.
Results: The mean of left ventricular ejection fraction was 44% and plasma brain natriuretic peptide level was 960 pg/mL. The median length of stay was 18 days, the total amount of furosemide was 570 mg, and the Δbody weight was -3.6 kg. Ischemic status, hemoglobin level and pre-hospital loop diuretics dosage independently characterized poor DR (OR: 3.05; 95% CI: 1.32–7.06; p=0.009, OR: 0.81; 95% CI: 0.67–0.98; p=0.027, OR: 1.03; 95% CI: 1.01–1.05; p<0.001, respectively). DR score was calculated as the summation of points awarded for the presence of 3 parameters (ischemic etiology, 1point; hemoglobin <10.5g/dl, 1point; and pre-hospital loop diuretics dosage, 20–40mg, 1point; ≥40mg, 2points). The probability of cardiac events was significantly higher as the DR score was increased (Figure) and adjusted multivariate analysis identified the DR score as an independent predictor of cardiac events (HR: 1.70 per 1 point; 95% CI: 1.33–2.18; p<0.001). In addition, the DR score was associated with worsening renal function in hospital (p=0.001) and needs for loop diuretics at discharge (p<0.001).



Kaplan-Meier analysis for cardiac events with DR score.

Conclusions: Poor DR of acute HF inpatients with systemic congestion is characterized by ischemic etiology, anemia and excessive loop diuretic exposure on admission. DR score is a novel scoring system giving a good prediction for DR, in-hospital worsening renal failure, needs for loop diuretics at discharge and future cardiac events in acute HF patients.

WHAT'S NEW IN HEREDITARY DYSLIPIDAEMIA?

179 | BEDSIDE
Reducing low density lipoprotein cholesterol (LDL-C) in homozygous familial hypercholesterolemia (HoFH) with a microsomal triglyceride transfer protein (MTP) inhibitor may reduce CV events

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Background: HoFH is characterised by increased risk of premature CV events & cardiac death due to cumulative exposure to very high levels of LDL-C. Lomitapide (MTP inhibitor) has been shown to reduce mean LDL-C levels in adult HoFH patients by 50% in a completer population (median 40%); however, impact on CV events is unknown.
Hypothesis: Reduction in LDL-C levels in HoFH patients treated with lomitapide may lead to reduced numbers of CV events.
Methods: There are little data to estimate the expected CV event rate in HoFH patients. We used data on major CV events (MACE) reported in patients with FH (both HoFH [49%] & heterozygous FH [HeFH]) in the 2 years prior to taking mipomersen as the best available source to estimate event rate (Duell, AHA 2014). This is likely to be a conservative estimate as HeFH patients tend to have a lower CV risk than HoFH patients. During the 24 months prior to mipomersen treatment, 64 FH patients (62%) had 146 events in 207 patient years of exposure (25.7 patients had a MACE/1000 months observed, 58.8 events/1000 months observed). These data were transformed to give an expected event rate of 69 for the same patient-years exposure as in the lomitapide studies (98 patient-years). The expected event rate was compared to actual MACE recorded in the lomitapide clinical studies.
Lomitapide was added to standard of care in 29 adult HoFH patients with mean baseline LDL-C 8.7mmol/L in a single arm 78-week phase 3 trial & extension study (up to 246 weeks; Cuchel, Lancet 2013; Cuchel, Circulation, 2015). 12 patients dropped out of the phase 3 study and/or did not enter the long-term extension & therefore were not followed up. As these patients may have unreported CV events, we performed a "worst-case analysis" where each patient was assumed to have had 1 MACE.
A chi-square test was performed & the number needed to treat (NNT) to prevent a MACE was calculated for the observed number of events & worse case scenarios.
Results: Only two MACE were reported in the lomitapide trials, both occurring in the long term extension study; 1 cardiac death & 1 CABG (equivalent to 1.7 events/1000 patient months of treatment). In the worst-case analysis, 14 CV events may have occurred in patients who had received lomitapide (equivalent to 11.9 events/1000 patient months of treatment). This compares to an estimated number of expected MACE of 69 in the FH patients not on lomitapide (chi2=220; p<0.001 for observed events & chi2=148; p<0.001 for worst case scenario). The likely NNT to prevent a MACE in 1 year of lomitapide treatment is estimated between 1 & 2 (both observed & worst case scenario).
Conclusions: There were significantly fewer MACE in patients taking lomitapide than would be expected based on a model of expected event rate. The NNT with lomitapide to achieve the estimated event reduction is very low. The data are

suggestive that lomitapide may reduce CV events in HoFH patients. More data are required to confirm in clinical practice.
Acknowledgement/Funding: The study was funded by Aegerion Pharmaceuticals

180 | BEDSIDE
Antioxidant property of high-density lipoprotein predicts the presence of atherosclerotic cardiovascular disease and corneal arcus in patients with familial hypercholesterolemia

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Background: Familial hypercholesterolemia (FH) is characterized by elevated LDL-cholesterol and increased risk of premature atherosclerotic cardiovascular disease (ASCVD). Although it has been reported that low-density lipoprotein-lowering therapy delays the onset of ASCVD, it still remains difficult to prevent it. Therefore, novel biomarkers and therapeutic targets are necessary to evaluate and prevent atherosclerosis in FH. Recently, we reported that cholesterol efflux capacity was independently and inversely associated with the presence of ASCVD in FH patients. Accordingly, we hypothesized that antioxidant property of high-density lipoprotein (HDL) also involve the development of atherosclerosis, tendon xanthomas, and corneal arcus in patients with FH.
Purpose: The aim of this study was to investigate associations between antioxidant property of HDL and the presence of ASCVD as well as clinical features in patients with heterozygous FH.
Methods: Among patients followed up in the outpatient clinic of our hospital, 225 consecutive patients diagnosed as heterozygous FH were enrolled in this cross-sectional study. All patients had been previously treated with lipid lowering therapy including statins. Oxygen Radical Absorbance Capacity (ORAC) assay was used for the evaluation of the antioxidant activity of apolipoprotein B–depleted serum from the study participants. Achilles tendon thickness was measured using soft X-ray radiography and carotid atherosclerosis was evaluated by high-resolution ultrasonography.
Results: Eighty-one patients (36%) of them were known to have ASCVD. ORAC value was correlated with both serum HDL cholesterol (HDL-C) ($r = 0.27$, $P<0.0001$) and serum apolipoprotein A-I (ApoA-I) ($r = 0.27$, $P=0.0003$) levels. In univariate analyses, ORAC value was lower in patients with ASCVD compared with those without ASCVD. This relationship remained significant after adjustment for cardiovascular risk factors (odds ratio per 1-SD increase, 0.97; 95% confidence interval, 0.95–0.99; P=0.0231). However, subsequent adjustment for HDL-C or ApoA-I levels attenuated this relationship. Decreased ORAC value was associated with the presence of corneal arcus even after adjusting for cardiovascular risk factors and HDL-C (odds ratio per 1-SD increase, 0.97; 95% confidence interval, 0.94–0.99; P=0.0035). Interestingly, there were no correlation between ORAC value and Achilles tendon thickness nor carotid intima-media thickness.
Conclusions: ORAC value, an antioxidant property of HDL, was independently associated with the presence of ASCVD and corneal arcus in heterozygous FH. In view of residual risks after treatment with statins, the antioxidant property of HDL might be a novel biomarker and a therapeutic target for preventing atherosclerosis in patients with FH.

181 | BEDSIDE
Lp(a) levels predict cardiovascular events in patients with Familial Hypercholesterolemia but not in unaffected relatives. SAFEHEART registry results

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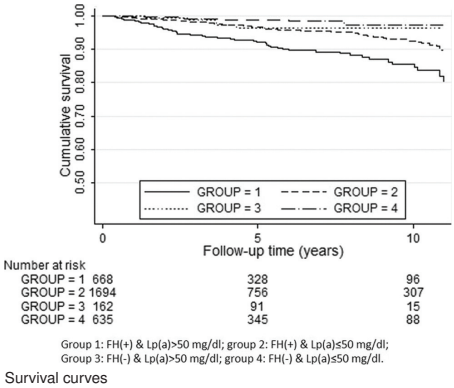
Background: Heterozygous familial hypercholesterolemia (FH) increases the risk of cardiovascular disease. Lp(a) is a predictor of cardiovascular events in patients with FH. Nevertheless, it is not well known its prognostic accuracy in patients without FH.
Aim: To determine the relationship between Lp(a) levels and the development of cardiovascular events in a large cohort of FH patients and unaffected relatives.
Methods: Data from the study, which recruited individuals aged 18 and older between January 2004 and October 2015 were analysed. Out of them, 2362 were genetically diagnosed of FH and followed-up; 797 unaffected relatives were also followed-up. The end-point consisted of fatal or non-fatal new onset myocardial infarction, fatal or non-fatal new onset ischemic stroke, coronary revascularization, aortic valve replacement, peripheral artery revascularization and cardiovascular death. Lp(a) level cut-off point was 50 mg/dl.
Results: Mean age of FH individuals and unaffected relative were 45.5±15.4 and 42.5±15.5 years. 1087 (45.2%) FH patients and 373 (45.9%) relatives were male. Mean follow-up time was 5.5±3.2 years. Figure below shows the survival curves for the combined end-point. Log rank p value was <0.001 and 0.24 for FH patients and unaffected relatives respectively.



Survival curves

Conclusions: Increased Lp(a) levels are related to the development of cardiovascular events in patients with FH. Nevertheless, this association is not found in their relatives without FH.
Acknowledgement/Funding: Grant G03/181 and FIS PI12/01289 from Instituto de Salud Carlos III (ISCIII), Grant 08-2008 Centro Nacional de Investigación Cardiovascular (CNIC).

182 | BEDSIDE
Familial hypercholesterolaemia diagnosis: a case of missed opportunity

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Background/Introduction: Individuals with familial hypercholesterolaemia (FH) have lifelong elevations of LDL-Cholesterol (LDL-C) resulting in an increased risk of severe atherosclerotic disease, such as myocardial infarction and stroke. Its sequelae can be prevented by early diagnosis and treatment. Whilst bespoke studies suggest a prevalence of 1 in 200–250, the "diagnostic" real world prevalence is poorly described.
Purpose: To estimate the prevalence of FH in the UK, from both confirmed and missed diagnoses, in a contemporary real-world primary care database.
Methods: Patient-level data available in the Clinical Practice Research Datalink (CPRD), a UK-based general practice database covering an approximate annual population of 5.2 million patients, were examined. Confirmed FH diagnosis was ascertained via a narrow range of diagnostic codes present in CPRD. For patients with at least one LDL value and no coded diagnosis of FH the possibility of FH was inferred via a score calculated according to either the Dutch Lipid Network Criteria or published EUROASPIRE criteria, or both. Patients without a confirmed FH diagnostic code but achieving a pre-defined "Definite" or "Probable" score were classified as having a missed diagnosis of FH. Prevalence of confirmed and missed FH diagnosis was also estimated separately according to gender and by age range: 19–39, 40–59, ≥60 years. Analyses were restricted to adult patients and all estimates were calculated for the period spanning August 2008 to July 2013.
Results: Diagnoses confirmed by presence of an FH diagnostic code in CPRD indicate a prevalence of 1.3 (95% confidence intervals (CI) 1.3–1.4) per 1,000 persons. This increased approximately ten-fold, to 11.7 (95% CI 11.5–11.8) per 1,000 persons, when missed diagnoses were counted. Prevalence of coded FH increased with age from 0.5 (95% CI 0.5–0.5) to 1.7 (95% CI 1.6–1.8) to 2.1 (95% CI 2.0–2.1) per 1000 individuals in the 19–39, 40–59 and ≥60 years age ranges, respectively. A similar pattern was observed for missed diagnoses; the prevalence being 1.6 (95% CI 1.4–1.8), 8.3 (95% CI 8.1–8.5) and 15.6 (95% CI 15.4–15.8) per 1,000 individuals in the age ranges 19–39, 40–59 and ≥60 years, respectively. Differences in diagnosis by gender were identified, prevalence of coded FH being 1.4 (95% CI 1.4–1.5) per 1,000 in females and 1.2 (95% CI 1.2–1.3) per 1,000 in males, and for missed diagnosis 12.0 (95% CI 11.8–12.2) per 1,000 females and 11.3 (95% CI 11.1–11.5) per 1,000 males respectively.
Conclusion(s): Applying surrogate diagnostic criteria to a real-world primary care dataset the extent of potential under-diagnosis of FH is significant, suggesting that as few as 1 in 10 FH patients may be diagnosed. There appears to be an important need for diagnostic screening and education to identify FH in primary care.
Acknowledgement/Funding: The study was funded by Amgen Ltd

183 | BEDSIDE
Whole exome sequencing in primary severe hypertriglyceridemia

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Background: Few data exist regarding clinical application of whole exome sequencing (WES) for the molecular diagnosis of severe hypertriglyceridemia (HTG).
Methods: WES was performed on 28 individuals exhibiting severe HTG (≥1,000 mg/dl) without any transient causes (15 men, mean age 42±20 yr, median triglyceride 1,756 mg/dl [interquartile range 1,288–2,443]) followed by recessive and dominant inheritance modeling in known monogenic HTG genes and disease-network candidate analysis gene ranking to identify a causative mutation(s), including novel underlying genetic mechanism for severe HTG.
Results: Using our schema, we identified possible causative mutation(s) in 14 individuals (50%). Among them, we identified 2 individuals with lipoprotein lipase (LPL) deficiency with double mutations in LPL gene, and 2 individuals with a heterozygous mutation carrier in LPL gene. Moreover, we identified one individual harboring a double mutations in LPL gene and APOA5 gene. Also we identified one individual with a heterozygous mutation in lipase maturation factor 1 (LMF1) gene, which is rarer form of familial hyperchylomicronemia, and 2 individuals with type 3 hyperlipidemia harboring mutations in APOE gene, including novel ones. Interestingly, we also identified 6 other individuals harboring a deleterious mutation in cyclic AMP-responsive element-binding protein 3-like protein 3 (CREB3L3), MLX Interacting Protein-Like (MLXIPL), SLC25A40 genes, glucokinase regulatory protein (GCKR), possibly associated with this extreme phenotype.
Conclusion: We identified potential causative mutations in 14 among 28 individuals (50%) with severe HTG within the coding region of the genes known to cause rare Mendelian dyslipidemias. Clinical WES is now feasible where molecular diagnoses could be made in such extreme cases, which could potentially provide appropriate therapies.

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Prevalence, clinical features, and prognosis of patients with extremely low high-density lipoprotein cholesterol

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Background: Little data exist on the clinical features of patients with an extremely low level of HDL-C.
Methods: An observational study of 429 patients with an extremely low HDL-C level (<20 mg/dl) among 43,368 subjects whose serum HDL-C was measured for any reason from April 2004 to March 2014. We investigated the potential causes of reduced HDL-C, their prognosis, and the cause of death in patients with extremely low HDL-C levels.
Results: Most patients (n=425, 99%) showed secondary causes, including malignancies (n=157, 37%), inflammatory diseases (n=219, 51%), or other critical situations, such as major bleeding (n=58, 14%). During the median 175 days follow up period, 106 patients died. As many as 80 (75%) of the causes of death were either from malignancies, inflammatory diseases, or major bleeding. Multiple regression analysis showed that the presence of malignancy and HDL-C were independently associated with death. Receiver-operating characteristic curve analyses identified HDL-C <15 mg/dl as the optimal cutoff for predicting a worst-case prognosis. The cumulative survival curve revealed that those patients with HDL-C <15 mg/dl had significantly higher mortality than those whose level was ≥15 mg/dl.

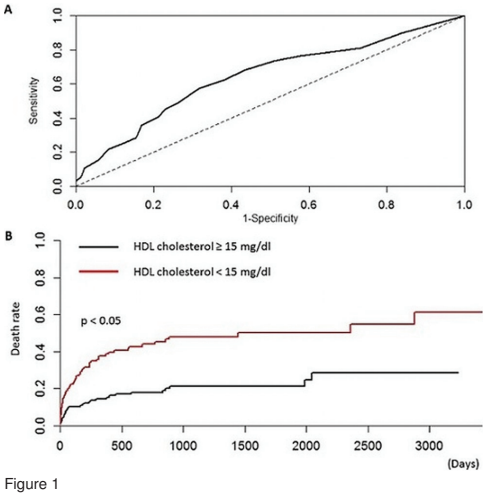

Figure 1

Conclusions: Most patients with an extremely low level of HDL-C displayed secondary causes, including malignancies, inflammatory diseases, and other critical situations. We suggest that secondary causes should be carefully assessed in such patients.

185 | BEDSIDE
Association of genetic variants with dyslipidemia and chronic kidney disease in a longitudinal population-based genetic epidemiological study

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Background: Dyslipidemia, including hypertriglyceridemia, hyper-low density lipoprotein (LDL)-cholesterolemia, and hypo-high density lipoprotein (HDL)-cholesterolemia, is an important risk factor for coronary artery disease. Chronic kidney disease (CKD) increases risk not only for end-stage renal disease but also for a poor cardiovascular outcome. We previously identified nine genes and chromosomal region 3q28 as susceptibility loci for myocardial infarction, ischemic stroke, or CKD in Japanese by genome-wide or candidate gene association studies.
Purpose: The purpose of the present study was to examine the relation of 13 polymorphisms at these 10 loci to the prevalence of hypertriglyceridemia, hyper-LDL-cholesterolemia, hypo-HDL-cholesterolemia, or CKD in community-dwelling Japanese.
Methods: Study subjects comprised 6027 individuals who were recruited to the Inabe Health and Longevity Study, a longitudinal genetic epidemiological study of atherosclerotic, cardiovascular, and metabolic diseases. The subjects were recruited from individuals who visited the health care center at Inabe General Hospital for an annual health checkup, and they are followed up each year (mean follow-up period, 5 years).
Results: Longitudinal analysis with a generalized estimating equation and with adjustment for age, sex, and body mass index (BMI) for the dyslipidemia analysis, or for age, sex, BMI, smoking, hypertension, diabetes mellitus, and dyslipidemia for the CKD analysis revealed that rs6929846 (T→C) of the butyrophilin subfamily 2 member A1 gene (BTN2A1) was significantly associated with hypertriglyceridemia (P=0.0001), hyper-LDL-cholesterolemia (P=0.0004), and CKD (P=0.0007); rs2569512 (G→A) of the interleukin enhancer binding factor 3 gene (ILF3) was associated with hyper-LDL-cholesterolemia (P=0.0029); and rs2074379 (G→A, P=0.0019) and rs2074388 (G→A, P=0.0029) of the alpha kinase 1 gene (ALPK1) were associated with CKD. Longitudinal analysis with a generalized linear mixed-effect model and with adjustment for covariates among all individuals revealed that rs6929846 of BTN2A1 was significantly related to serum concentrations of triglycerides (P=0.0011), LDL-cholesterol (P=3.3 × 10–5), and creatinine (P=0.0006) as well as to estimated glomerular filtration rate (P=0.0004); rs2569512 of ILF3 was related to the serum concentration of LDL-cholesterol (P=0.0221); and rs2074379 (P=0.0302) and rs2074388 (P=0.0336) of ALPK1 were related to the serum concentration of creatinine. Similar analysis among individuals not taking anti-dyslipidemic medication revealed that rs6929846 of BTN2A1 was significantly related to serum concentrations of triglycerides (P=8.3 × 10–5) and LDL-cholesterol (P=0.0004), and that rs2569512 of ILF3 was related to the serum concentration of LDL-cholesterol (P=0.0010).
Conclusion: BTN2A1 may thus be a susceptibility gene for hypertriglyceridemia, hyper-LDL-cholesterolemia, and CKD in Japanese individuals.

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Common polymorphisms in the 5-lipoxygenase pathway confer risk of myocardial infarction - A Danish case-cohort study

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Background: The 5-lipoxygenase pathway is an inflammatory pathway that has been implicated in the development and manifestation of cardiovascular disease. Studies have suggested, that genetic polymorphisms related to key enzymes in this pathway may confer risk of myocardial infarction (MI).
Purpose: This study investigated the association of pre-selected genetic polymorphisms related to four key enzymes in the 5-lipoxygenase pathway (arachidonate 5-lipoxygenase and an activating protein (ALOX-5 and ALOX-5 AP), leukotriene A4 hydroxylase (LTA4-H) and leukotriene C4 synthase (LTC4-S)) with incident MI.
Methods: In a Danish cohort study 57,053 participants, aged 50–64 at enrolment, were recruited from 1993–97. We conducted a case-cohort study including cases

with incident MI and a randomly selected sub cohort of 3,000 participants. Cases were identified from national registries through July 2013. Based on a literature review, a total of 22 SNP's were selected and genotypes were assessed using the commercially available KASP™ genotyping assay. A tandem-repeat polymorphism, located at the promoter region of the ALOX-5 gene, was genotyped by multi-titre plate sequencing. Associations were evaluated using a weighted Cox proportional hazards model adjusting for potential confounders. An additive model of inheritance was assumed unless otherwise stated.
Results: During a median follow-up of 17.0 years we identified 3,089 cases of incident MI. Two SNP's in the gene encoding ALOX-5 AP were associated with incident MI (rs9551963 & rs17222842), suggesting a negative association when comparing homozygotes for the major allele with one or two (rs9551963) and two (rs17222842) copies of the minor allele, respectively. One SNP (rs2247570), located at the genomic region of LTA4-H, was associated with higher risk of MI (HR=1.28, 95% CI: 1.03–1.59) in subjects with two copies of the minor allele compared to homozygotes for the major allele. Furthermore, the promoter polymorphism of ALOX-5 was associated with risk of MI, when assuming a recessive model. For carriers of two variant alleles a HR of 1.43 was observed (95% CI: 1.01–2.02) when compared to carriers of one or two wildtype alleles.
Conclusions: Common polymorphisms in candidate genes of the 5-lipoxygenase pathway was associated with incident MI, suggesting a potential role for this pathway in the development of cardiovascular disease.
Acknowledgement/Funding: The Danish Heart Association, Denmark; Hertha Christensen Foundation; The Danish Cancer Society; Heinrich Kopps Grant

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Big data and lipoproteins: prevalence of dyslipidemias in 100 762 individuals

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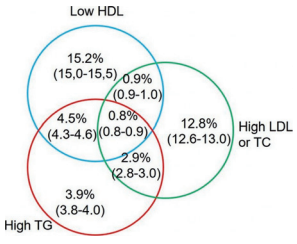
Background: Heterozygous Familial Hypercholesterolemia (HeFH) is a disorder which is under-diagnosed and has a severe long-term cardiovascular risk. This is also the case for other severe dyslipidemias. The prevalence of dyslipidemia has rarely been assessed in large databases.
Methods: Based on a huge sample of lipid panels, we assessed the prevalence of individuals classified with the different Dutch Lipid Clinic Network (DLCN) categories, of isolated high triglycerides (TG) >200 mg/dL, of mixed dyslipidemia [total cholesterol (TC) >240 mg/dL or LDL-cholesterol (LDL-C) >160 mg/dL and TG >200 mg/dL], of isolated low HDL-cholesterol (HDL-C) [TG <200 mg/dL and HDL-C <40 mg/dL] and of high lipoprotein (a) (Lp(a) >50 mg/dL). LDL-C levels were calculated with the Friedewald or the Planella formula if elevated triglycerides.
Results: From 2006 to 2015, 100 762 lipid panels were obtained from subjects higher than 15 years old and of both gender in a large database in a French University Hospital. Mean TC was 195±51 mg/dL; mean TG: 132±116 mg/dL; HDL-C in men 47±14 mg/dL; HDL-C in women 60±18 mg/dL; LDL-C: 115±41 mg/dL and Lp(a): 35±46 mg/dL. The prevalence of LDL-C between 155 and 190 mg/dL was 11.53%; the prevalence of LDL-C between 191 and 250 mg/dL was 2.67%; the prevalence of LDL-C between 251 and 325 mg/dL was 0.30% and the prevalence of LDL-C >325 mg/dL was 0.05%. The prevalence of isolated high TG was 8.75%; the prevalence of mixed dyslipidemia was 4.12%; the prevalence of isolated low HDL-C was 16.07% and the prevalence of high Lp(a) was 25.04%. Different combinations of dyslipidemias (with their confidence intervals) are shown in the figure. The prevalence of hypercholesterolemia and hypertriglyceridemia was 28.1%.



Conclusions: The prevalence of definite or probable HeFH was 1/286 subjects and only 59% of subjects had normal lipid values.

NEW TECHNOLOGIES IN ECHO-VENTRICULAR FUNCTION AND MYOCARDIAL DISEASES

P195 | BEDSIDE
Diastolic dysfunction revisited: a new, feasible and unambigious classification predicts major cardiovascular events

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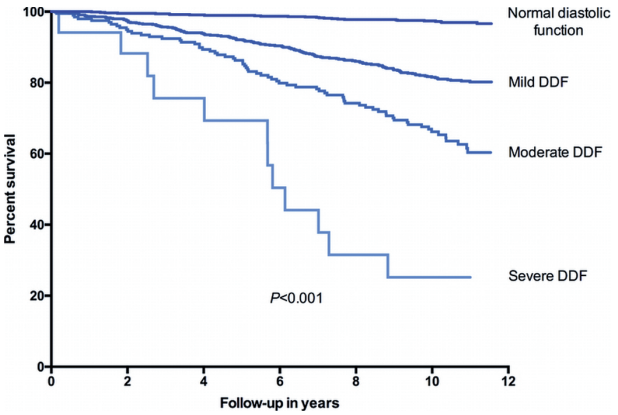
Background: Diastolic dysfunction (DDF) is a significant predictor of major adverse cardiac events (MACE) in the general population and a number of echocardiographic parameters have been shown to reflect DDF. However, current classifications of DDF are ambiguous and subjects often present with non-congruent parameters.
Purpose: The aim of this study was to investigate the independent prognostic value of established echocardiographic parameters in a community-based population and create a new classification of DDF.
Methods: Within a prospective, community-based study, 1851 participants were examined by echocardiography including Tissue Doppler Imaging (TDI) in 2001–2003 and followed (median 10.9 years) with regard to MACE defined as cardiovascular death or admission due to either heart failure or acute myocardial infarction. Follow-up was 100% complete. Risk of MACE associated with different echocardiographic markers of DDF was estimated using Cox proportional hazards regression models.
Results: We found that persons with impaired myocardial relaxation as defined by low peak early diastolic mitral annular velocity e' by TDI had higher incidence of clinical and echocardiographic markers of cardiac dysfunction and increased risk of MACE. Amongst persons with impaired relaxation, only echocardiographic indices of increased filling pressures such as LAVI≥34 mL/m^2 (HR 1.97 (1.13–3.45, p=0.017), E/e'≥17 (HR 1.89 (1.34–2.65), p<0.001), and E/A>2 (HR 5.24 (1.91–14.42), p=0.001) provided additional and independent prognostic information on MACE. Based on these findings, we created a new classification of DDF where all grades were significant predictors of MACE (Figure 1) independently of age, sex, and clinical data (Mild DDF: HR 1.99 (1.23–3.21), p=0.005; Moderate DDF: HR 3.11 (1.81–5.24), p<0.001; Severe DDF: HR 4.20 (1.81–9.73), p<0.001).



Survival according to DDF grades.

Conclusions: In the general population, we found that persons with impaired myocardial relaxation had a higher incidence of clinical and echocardiographic markers of cardiac dysfunction. The presence of echocardiographic markers of elevated filling pressures in persons with impaired relaxation increased the risk of MACE significantly. Based on this, we present a new, feasible, and unambiguous classification of DDF capable of accurate risk prediction in the community.
Acknowledgement/Funding: Grants from the Lundbeck Foundation, the Novo Nordisk Foundation, and the Danish Heart Foundation (07-10-R60-A1698-B132-22413) were received.

P196 | BENCH
Feasibility of noninvasive assessment of myocardial stiffness in the ischemic segment using early systolic lengthening and post-systolic shortening

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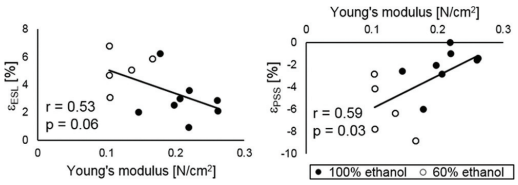
Background: The assessment of myocardial stiffness is important to evaluate cardiac function but it invasively and indirectly assessed by catheter method. Although early systolic lengthening (ESL) and post-systolic shortening (PSS) observed in the ischemic segment could be affected by the myocardial stiffness, there have been no reports to directly prove it. The aim of this study was to eval-

uate the feasibility of noninvasive assessment of myocardial stiffness by speckle tracking echocardiography.
Methods: In 13 open-chest dogs, left ventricular short-axis images were acquired at baseline, during 5-minutes left anterior descending coronary artery (LAD) occlusion and after intramyocardial injection of 100% (n=8) or 60% (n=5) ethanol into the LAD territory to stiffen the myocardium in addition to ischemia. Circumferential strains were analyzed and the peak systolic strain (εS), the amplitude of ESL (εESL) and PSS (εPSS) were measured in each stage. The Young's modulus was measured at the ischemic myocardium from the excised heart with a digital force gauge.
Results: In the group of 60% ethanol injection, εS, εESL and εPSS were almost similar to during LAD occlusion. However, εESL and εPSS significantly decreased in the group of 100% ethanol injection compared to during LAD occlusion (Table). The Young's modulus of the myocardium of 100% ethanol injection was higher than that of the 60% ethanol injection (100%; 0.21±0.04 vs. 60%; 0.12±0.03 N/cm^2, p<0.05). εESL was tended to be correlated to the Young's modulus (r=0.53, p=0.06). εPSS was significantly correlated to Young's modulus (r=0.59, p=0.03).

	100% Ethanol group				60% Ethanol group			
	baseline	occlusion	ethanol	occlusion vs. ethanol	baseline	occlusion	ethanol	occlusion vs. ethanol
ε_{ESL} [%]	2.3±1.2	6.1±3.1	2.9±1.6	P=0.02	2.4±1.9	8.6±2.9	5.1±1.4	P=0.08
ε_{PSS} [%]	−0.3±0.8	−7.7±2.6	−2.2±1.8	P<0.001	−0.3±0.6	−11.1±2.7	−6.0±2.5	P=0.07



Conclusion: ESL and PSS are affected not only by myocardial ischemia but also by myocardial stiffness. The assessment of PSS by speckle tracking echocardiography may be useful for estimating stiffness of the ischemic myocardium.

P197 | BENCH
Increased intraventricular pressure gradient during isovolumic relaxation time is related to dyssynhrony during ischemia. A dog study by the new echocardiographic method of relative pressure imaging

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Background: Velocity information can be converted to pressure information based on fluid momentum equations. We have applied the divergence operation of the Navier-Stokes equation to velocity fields obtained by vector flow mapping and developed a new method, Ultrasonic Relative Pressure Imaging (RPI), to visualize and calculate regional pressure distribution.
Purpose: The purpose was to investigate if RPI can detect regional ischemic dysfunction in the left ventricular (LV) outflow tract in diastole.
Methods: An open-chest dog model (n=7) was applied; LAD was occluded for intervals of 2 minutes. A Millar catheter was introduced into the LV. Echocardiography was recorded from apical 3-chamber views. RPI was created offline; pressure difference (PD) was computed between apex and base of the LV outflow tract. Strain curves were created in 3 anterior and 3 posterior segments of the LV.
Results: The figure shows color-coded RPI during isovolumic relaxation time (IVRT) at baseline and occlusion (upper left & right), red is higher and blue lower pressure relative to reference. Ischemia induced a prominent positive peak in the PD waveform during IVRT as pressure redistributed, increasing from -0.008±0.101 to 0.273±0.043 mmHg (p<0.0001) (lower left). In anterior ischemic segments, postsystolic shortening (PSS) was found. Time delay to peak systolic strain between posterior and anterior segments increased from -1±23 to 69±43 ms (p<0.01) (lower right), and correlated with IVRT PD (r=0.72, p<0.01).
Conclusion: By RPI, an increased positive PD was detected during IVRT in the LV outflow tract during ischemia. This new parameter is related to dyssynchrony and may reflect PSS.

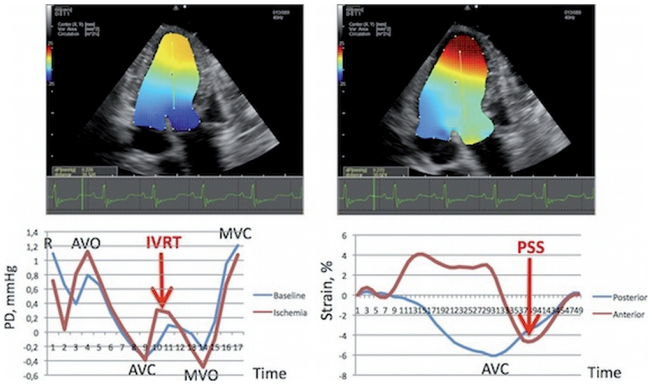

Figure 1

P198 | BEDSIDE
Bidimensional longitudinal systolic strain as predictor of early myocardial toxicity secondary to chemotherapy. A two year follow up

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Introduction: The reduction of ventricular function expressed by the left ventricular ejection fraction (LVEF) is a serious complication of chemotherapy with adverse impact on clinical evolution. Our hypothesis is that minimal changes in myocardial deformation as manifestation of myocardial injury could be detected prior to the reduction of LVEF, with the possibility of the strain alteration persisting in the follow-up despite an improvement in the left ventricle chamber function
Purpose: To evaluate bidimensional strain in the detection of early systolic ventricular dysfunction (≤6 months) in patients treated with cardiotoxic chemotherapy and assess the strain's behavior at 2-years follow-up.
Method: Thirty six patients were prospectively included in the analysis (mean age, 47±16 years). All patient underwent conventional echocardiography, tissue Doppler and speckle-tracking echocardiography. The end point (EP) as a parameter of cardiotoxicity at 6 months was defined as a drop of 5 points in the ejection fraction (EF) with a value <55% in symptomatic patients or a decline of 10 points with a value of EF <55% in asymptomatic patients.
Results:. Seven patients (19.4%) reached the EP. Predictors related to EP were: 3rd month bidimensional longitudinal systolic strain (BLSS) (positive EP (G1) -16.3±2.4% vs negative EP (G2) -19.6% ±2.02%; p<0.01), 4th month bidimensional radial systolic strain (BRSS) (G1 46.4±2.4% vs G2 52±3.4%; p<0.001), 4th month N-terminal prohormone brain natriuretic peptide (NT Pro-BNP) (G1 152±42pg/ml vs. G2 61±38pg/ml; p<0.001). During the follow-up, all patients who had myocardial toxicity at 6 months were treated with enalapril. Significant increment in LVEF and radial strain were observed in G1. The BLSS showed no significant changes during the follow-up period (6th month G1 -15±1% vs G2 -20.3±2%; p=0.0001; 24th month G1 -15.6±1% vs G2 -20,2±2%; p=0.0001). Despite an improvement in EF after enalapril during the follow-up (51±3.5%), EF remained decreased in relation to the baseline value prior to chemotherapy.
Conclusions: The BLSS was the earliest marker of mild ventricular systolic dysfunction in patients treated with chemotherapy. Longitudinal myocardial deformation is not only more sensitive in detecting cardiotoxicity but persists in time despite the improvement in LVEF.

P199 | BEDSIDE
Right ventricular function to predict events in AL-cardiac amyloidosis

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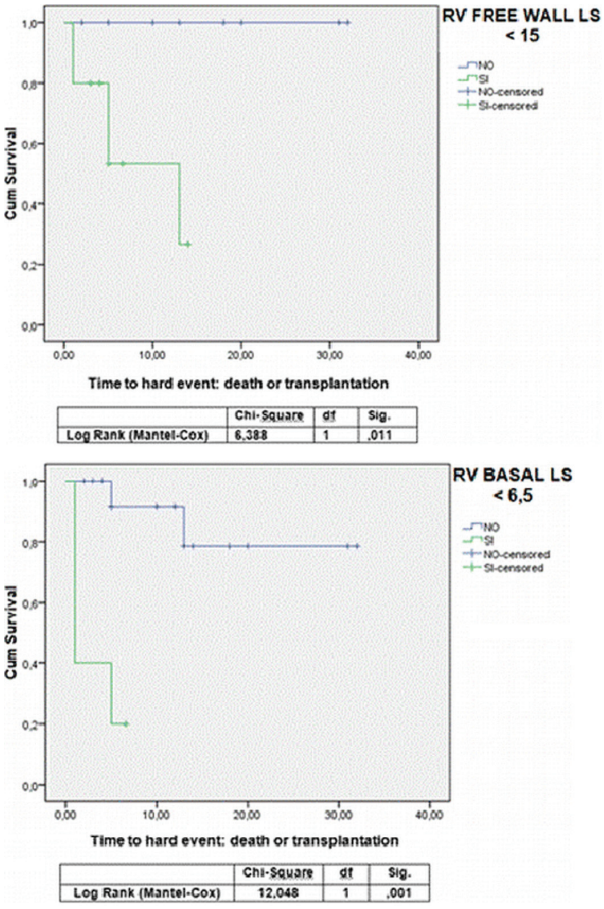
Background: Cardiac amyloidosis (CA) is associated with worse prognosis in systemic light-chain (AL) amyloidosis specially if reduced left ventricular (LV) function and pericardial effusion are present. However, in many occasions they appear late, and therefore it is necessary to identify new parameters to detect patients with worse prognosis at the diagnosis.
Purpose: The aim of the study was to determine whether LV and right ventricular (RV) function, measured by longitudinal strain (LS), provides prognostic information in a cohort of patients with AL-cardiac amyloidosis (AL-CA).
Methods: We retrospectively include 33 patients with AL-CA. Echocardiographic images were obtained at 4 and 2 chamber views. We analyzed LS by speckle tracking in 12 LV and 6 RV segments as well as classic LV and RV function echocardiographic parameters. The primary endpoint was a composite of death or heart transplantation (HTx).
Results: After a median follow-up of 10 months, 14 events (11 deaths and 3 HTx) had occurred. RV free wall LS and RV basal LS were the main predictors of survival (Figure). The cutoff absolute values were <15% for free wall RV LS and <6.5% for RV basal LS. Classic parameters associated with worse prognosis were: presence of pericardial effusion, lower TAPSE and TDI tricuspid annulus systolic velocity (Table).
Conclusions: Among patients with AL-CA, the reduction of RV free wall and RV

Abstract P199 – Table 1. Prognosis parameters

	TAPSE	TDI tricuspid annulus S' velocity	RVGLS	RV free wall LS	RV basal LS	LVGLS	LV basal LS	LVEF	Pericardial effusion
Surv	16.3±3.7	10.5±2.7	−12.4±2.8	−16.5±3.6	−9.4±2.9	−8.3±2.7	−4.7±2.9	57.0±8.1	42.1%
No Surv	13.7±3.2	8.1±1.1	−9.3±3.0	−11.7±3.1	−6.5±2.1	−7.8±3.1	−4.7±2.4	50.1±15.5	78,6%
p	0.04	0.01	0.06	0.02	0.02	NS	NS	NS	0.03



Survival curves

basal LS, as a parameter of RV function, could be important predictors of survival and offer incremental information beyond standard 2-dimensional echocardiographic, clinical and biomarker parameters. Probably it may help to identify patients who will benefit from earlier and more aggressive therapy at the diagnosis.

P200 | BEDSIDE
Noninvasive measurement of myocardial stiffness correlates with severity of diastolic dysfunction

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Background: Noninvasive methods for direct assessment of myocardial stiffness are needed. Herein we test a novel index of myocardial elasticity. Left ventricular (LV) filling following atrial contraction generates intrinsic myocardial stretch that propagates along the LV wall from base-to-apex with a speed proportional to myocardial elasticity. This is conceptually similar to the arterial pulse wave propagation for the assessment of arterial stiffness. Our aim was to test the hypothesis that increasing severity of LV diastolic dysfunction is associated with increasing myocardial stiffness as reflected by a higher wave speed of intrinsic wave propagation (iVP) in the LV myocardium.
Methods: We studied 261 consenting adult patients referred to the echocardiography lab for evaluation of various cardiovascular conditions. All standard echocardiographic measurements were performed according to current echocardiographic guidelines. For iVP measurements, tissue Doppler data (>350 frames/s) were acquired from 6 LV walls in 3 standard apical views. iVP (m/s) was measured in each LV wall as the wave speed of the onset of myocardial stretch from LV base to apex during late diastole.
Results: 66 patients had normal LV diastolic function, 97 patients had grade 1 diastolic dysfunction, 68 patients had grade 2 diastolic dysfunction, and 19 patients had grade 3 diastolic dysfunction; 11 patients had indeterminate diastolic function. There was a clear stepwise increase in iVP with increasing severity of diastolic dysfunction (normal: 1.79±0.06 m/s; grade 1: 1.83±0.05 m/s; grade 2: 1.96±0.06 cm/s; grade 3: 2.96±0.11 m/s; indeterminate group: 2.03±0.15 m/s; ANOVA $p<0.0001$). Parameters related to LV stiffness and filling pressures correlated with iVP (best with mitral E/A ratio: $r=0.42$, $p<0.0001$; weak, but significant correlations with mitral E/e' ratio, left atrial volume index, and E-deceleration time; $p<0.01$ for all), while measures of LV relaxation did not correlate with iVP (mitral annulus e' velocity, $p=0.13$; IVRT, $p=0.25$).
Conclusion: Worsening LV diastolic dysfunction is associated with progressively increasing myocardial stiffness as estimated by the novel index iVP. Further studies are warranted to test the predictive value of elevated iVP and its relation with histopathological changes in the LV tissue.

P201 | BEDSIDE
Recovery in global versus multilayer longitudinal strain following percutaneous revascularization for ST segment elevation myocardial infarction

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Background: Myocardial injury following ST-segment elevation myocardial infarction (STEMI) affects predominantly the sub endocardial layer. Little is known about myocardial recovery following percutaneous coronary intervention (PCI) for STEMI, especially in the endocardial vs mid vs epicardial layers.
Aim: We examined multilayer (endocardial, mid and epicardial layers) global longitudinal strain (GLS), left ventricular ejection fraction (LVEF) from transthoracic echocardiogram (TTE), and cardiac magnetic resonance imaging (CMRI) derived scar size to determine their relationship, and additionally percentage change in various myocardial layers following STEMI.
Methods: Seventy-two consecutive STEMI patients who underwent PCI during their index hospitalization, TTE and CMRI between days 2–7 post STEMI, with repeat follow-up imaging at 8–10 weeks. GLS was measured from apical 4-chamber, 2-chamber, long axis views, and left ventricular multilayer (endocardial, mid, epicardial) data sets were obtained. LVEF was obtained using Simpson's biplane method. Infarct scar size was assessed by late gadolinium enhanced CMRI; a signal intensity threshold of 2 standard deviations (SD) above normal myocardium was used to define the infarct. Pearson correlation was performed to determine the relationship between LVEF, multilayer GLS and CMRI derived scar size. The percentage change in multilayer GLS was also examined.
Results: Patients were aged 55.6±10.6 years, Mean infarct scar size was 36.9±22%. Whilst global strain (all 3 layers) and multilayer GLS correlated with LV scar (epicardial: $r=0.5$, mid: $r=0.5$, endocardial: $r=0.53$; $p<0.001$ for all), TTE LVEF had the best correlation ($r=0.75$; $p<0001$). Endocardial GLS (-17±5%) was > mid GLS (-15±5%) > epicardial GLS (-13±4%). Baseline GLS in all three layers correlated with GLS at follow up. While there were significant increases in GLS in all layers at follow up ($p<0.001$), the greatest increase in GLS was noted in the endocardial layer (mean increase in GLS endo vs mid vs epi: 1.9±4.5% vs 1.7±4% vs 1.6±3.6% respectively).
Conclusion: There is an increase in multilayer GLS over 2 months following STEMI with significant change in strain in all three layers; the greatest increase was noted in endocardial strain. Longer-term follow up in a large patient group is required to confirm these findings and determine its prognostic value.

TARGET ORGAN DAMAGE IN HYPERTENSION

P202 | BEDSIDE
Preventive effect of renin-angiotensin system inhibitors on new-onset atrial fibrillation in hypertensive patients: a propensity score matching analysis

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Background: Several clinical trials have shown that renin-angiotensin system (RAS) inhibitors, i.e., angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers, are associated with lower risk of incident atrial fibrillation (AF) in hypertensive patients. In some recent studies, however, treatment with RAS inhibitors was not effective in reducing AF episodes in patients with paroxysmal AF or after cardioversion. Thus, controversial findings have been shown on whether AF incidence is favorably affected by RAS inhibition.
Purpose: To ascertain whether treatment with RAS inhibitors truly has a beneficial effect on the primary prevention of AF in hypertensives, the present study investigated the various confounder-independent effect, by using a propensity score-matched analysis, of RAS inhibitor use on the new onset of AF in Japanese patients with hypertension.
Methods: From 1,263 consecutive hypertensive patients who underwent echocardiography, 964 subjects (mean age, 63 years) without previous paroxysmal AF, heart failure, myocardial infarction, or valvular disease were enrolled as the overall cohort of this study. New-onset AF as the study endpoint was defined as the first presentation of AF during follow-up.
Results: The mean duration of follow-up was 4.6 years (range, 0.1–9.1 years). During follow-up, 49 cases of new-onset AF were found, indicating the incidence was 1.1% per year. Cumulative AF event rates by the Kaplan-Meier method tended to be lower in patients treated with RAS inhibitors than those without the use of those agents, but the difference between the two groups did not reach significant (log-rank test P=0.057). By univariate Cox regression analysis, age, left atrial dimension (LAD), left ventricular (LV) mass index, and the presence of

chronic kidney disease (CKD) were significantly related to the occurrence of AF. Besides, the use of RAS inhibitors was affected by concomitant diabetes mellitus, CKD, and LV hypertrophy. Thus, a propensity score matching analysis was conducted to minimize the selection bias for RAS inhibitor administration and to adjust several confounding factors influencing the incidence of AF. Between the propensity score-matched two groups treated without and with RAS inhibitors (1:1, n=326, respectively), there were no differences in clinical parameters including age, diabetes mellitus, CKD, LAD, and LV mass index. While, the Kaplan-Meier cumulative AF event rate was significantly lower in the group treated with RAS inhibitors (P=0.013). Univariate and multivariate Cox regression analyses also revealed that the use of RAS inhibitors significantly decreased the occurrence of AF during follow-up.
Conclusion: The present study using a propensity score matching method demonstrated that treatment with RAS inhibitors was associated with a reduced incidence of new-onset AF in hypertensive patients, suggesting that these agents have a beneficial effect on the primary prevention of AF.

P203 | BEDSIDE
Predictors of new-onset atrial fibrillation in essential hypertensives

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Background/Introduction: Evidence suggest that new-onset atrial fibrillation (AF) in hypertensives, is related with organ damage and blood pressure control patterns.
Purpose: To compare the predictive role of hypertension related organ damage and blood pressure control patterns for the incidence of new-onset atrial fibrillation.
Methods: We studied 2.280 hypertensive patients (aged 57.7±11 years, 50% males) without history of AF episodes for a median period of 3.3 years (IQR 2.3–5 years). All subjects had at least one visit annually and at entry underwent complete echocardiographic study and additional workup for exclusion of secondary causes of resistant hypertension (RH). Four groups were identified depending on presence or absence of RH (office-based uncontrolled hypertension under at least 3 drugs including a diuretic or controlled hypertension under 4 or more drugs) at baseline and follow-up: 1.494 patients (65.7%) never having RH, 185 (8.1%) with resolved RH, 230 (10.1%) with incident RH and 365 (16.1%) with persistent RH. Endpoint of interest was new-onset AF.
Results: The incidence rate of new-onset AF over the whole follow-up period was 7.06/1000 persons-years. In the univariate analysis age (HR=1.08, $p<0.001$), office pulse pressure (HR=1.02, p=0.003), duration of hypertension (HR=1.03, p=0.011), left ventricular mass index (HR=1.02, $p<0.001$), left atrium diameter (HR=3.27, $p<0.001$), E/Em (HR=1.09, $p<0.001$), creatinine clearance (HR=0.98, p=0.002), resolved RH (HR=2.65, p=0.009) and persistent RH (HR=1.97, p=0.036) were predictors of new-onset AF. Multivariate Cox regression analysis revealed that age (HR 1.07, $p<0.001$) and LAD (HR 2.67, p=0.001) turned out to be the only independent predictors of new-onset AF while resolved RH just lost statistical significance (HR 2.00, p=0.09). Based on ROC analysis LAD>39 mm predicted new-onset AF with sensitivity 76.5% and specificity 56.7%.
Conclusions: Hypertensives with new-onset AF are characterized by a greater prevalence of cardiorenal adaptations and a longer and unfavorable patent of hypertension control. However, only older age and enlarged LA sizeturned out to predict new-onset AF in the setting of essential hypertension.

P204 | BEDSIDE
Left ventricular torsion and torsional recoil in hypertension assessed by real-time one-beat three-dimensional speckle tracking echocardiography with high volume rates

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Background: Left ventricle (LV) is composed of 3 myocardial layers and inner and outer oblique muscle causes rotation of clockwise direction in base and counterclockwise direction in apex, which makes torsion and contributes a part of LV ejection fraction (EF). LV outer muscle plays a predominant role in torsion, followed by rapid untorsion which contributes to LV filling. LV endocardium is most susceptible to deleterious effects by pressure overload. Although torsion and untorsion have been measured using tagged magnetic resonance, these mechanisms have not been fully examined using one-beat real-time 3-dimensional speckle tracking echocardiography with high volume rate (3D-STE).
Purpose: The aim of this study was to examine LV deformation parameters such as torsion which may reflect LV systolic function and untorsion which may reflect LV relaxation in patients with hypertension (HTN) by 3D-STE and elucidate the feature of torsion and untorsional recoil in HTN and hypertensive heart failure (HHF).
Methods: We studied LV torsion and untorsion by 3D-STE with 70–80vps in 53 controls (age: 67±10), 50 HTN without hypertrophy (LVH) (age: 68±11), 55 HTN with LVH (age: 70±11), 23 HHF with preserved EF (HFpEF, age: 79±12) and 25 HHF with reduced EF (HFrEF, age: 66±16). Time-LV torsion (°/cm) curve was derived from time-twist curve and integrated by long axis length for every instance in time. LV untorsion rate (°/cm/sec) as torsional recoil was measured as tangent of downward slope of torsion curve from top to early diastole 40msec after mitral valve opening. LV radial strain and strain rate at systole (SR-S) that was reported to be closely related to contractility and SR at isovolunic relaxation (SR-IVR) related to relaxation were examined. Tau was estimated as IVR time / (ln 0.9 x systolic blood pressure – ln PCWP). PCWP was calculated as 10.8 – 12.4 × log (left atrial active emptying function/left atrial minimum volume) as we reported.
Results: LVEF reduced in HFrEF (control:65±8, LVH (–): 68±8, LVH (+): 66±16, HFpEF: 60±11 HFrEF: 35±9* %, *$p<0.05$ vs control). LV radial strain decreased in HFpEF and further reduced in HFrEF (35±8, 35±8, 32±8, 28±8*, 18±6*#+$, #$p<0.05$ vs LVH (–), +$p<0.05$ vs LVH (+), $$p<0.05$ vs HFpEF). LV torsion was reduced in HFrEF (1.4±0.2, 1.4±0.3, 1.5±0.3, 1.2±0.2, 1.0±0.2*#+ °/cm), whereas untorsion rate was reduced even in LVH (–) associated with reduction in SR-IVR (untorsion rate; –5.0±3.2, –4.0±1.8, –3.9±1.3*, –3.1±1.2*, –3.1±1.6*# °/cm/s. radial SR-IVR; –0.7±0.4, –0.6±0.4, –0.6±0.4, –0.5±0.2*, –0.5±0.4* s^{-1}). There was a significant correlation between torsion and untorsion rate (r=–0.37, $p<0.01$) or SR-S (r=0.33, $p<0.01$) and between untorsion rate and Tau (r=0.20, $p<0.05$).
Conclusions: We demonstrated that 3D-STE may contribute to measurement of LV torsion and untorsion directly related to LV fiber orientation as a clinical new tool of deformation parameters for detection of myocardial systolic and diastolic function.

P205 | BEDSIDE
Left ventricular concentric geometry, high filling pressures and longitudinal dysfunction are independently associated with late gadolinium enhancement in arterial hypertension

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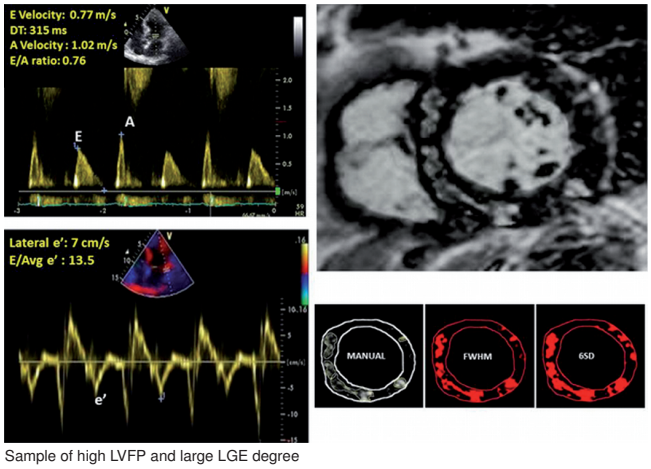
Background: In arterial hypertension elevated left ventricular (LV) filling pressures (LVFP) are closely related with LV longitudinal systolic dysfunction. It is also well known that both LV diastolic and longitudinal dysfunction are widely sustained by myocardial fibrosis.
Purpose: To explore relationships between LVFP and longitudinal dysfunction with myocardial fibrosis in uncomplicated hypertensive patients.
Methods: Forty hypertensive patients (mean age = 65 years) (9 with LV concentric geometry and 31 with normal/eccentric geometry based on a relative wall thickness [RWT] cut-off point of 0.42; 2 patients with clear cut hypertrophy, i.e. LV mass index ≥45 g/$m^{2.7}$ in women and ≥49 g/$m^{2.7}$ in men) underwent echo-Doppler exam (including quantification of global longitudinal strain [GLS]) and cardiac magnetic resonance with late gadolinium enhancement (LGE). LGE volume as a percent of LV myocardium was quantified per slice manually and semi-automatically by mean and 6,5,4,3,2 standard deviation (SD) thresholds and the full width at half maximum (FWHM) threshold.
Results: LGE was identified in 16 patients (40%), it being mainly non-subendocardial and involving always ventricular septum. Regardless the type of LV geometry and diastolic pattern, E/e' was higher ($p<0.0001$) in LGE than in non-LGE patients. All LGE patients had E/e'>8. Elevated LVFP (E/e'≥13 or E/e'>8 + left atrial volume index ≥34 ml/m^2) were found in 44% of LGE and only in 8% of non LGE patients ($p<0.01$). GLS and s' velocity (both $p<0.0002$) were lower in LGE patients. LGE volume - tested in 10 patients - varied substantially with the quantification type but no significant difference of manual, 6SD, 5SD and FWHM was found. Manual quantification showed high intra-observer and inter-observer reproducibility (mean difference and 95% CI = -0.37±0.81 and -0.42±0.82% respectively). 6SD and FWHM were the semi-automated techniques with the highest intra- and inter-observer reproducibility ($p<0.0001$). E/e' cor-



Sample of high LVFP and large LGE degree

related with mean LGE volume quantified manually (r=0.74, p=0.0009), FWHM (r=0.77, p<0.0005) and 6SD (r=0.73, p<0.001). Figure 1 depicts a patient with elevated E/e' and high LGE extent. GLS correlated with LGE quantified manually (r=0.57, p<0.02), by FWHM (r=0.60, p<0.01) and 6SD (r=0.56, p<0.02). s' correlated with LGE quantified manually (r=0.56), by FWHM (r=0.56) and 6SD (r=0.57) (all p<0.02). By adjusting for age and heart rate by a multiple linear regression analysis, E/e' (β=0.46, p<0.001), RWT (β=0.39, p=0.003) and GLS (β=0.33, p<0.01) independently predicted LGE presence (cumulative R^2=0.54, p<0.0001).

Conclusion: In hypertensive patients LVFP, GLS and LV concentric geometry are independently associated with LGE. The extent of LGE is related with the magnitude of both E/e' and GLS (or s'). Increased LVFP, longitudinal dysfunction and LV concentric geometry should be considered as main indicators of myocardial fibrosis induced by pressure overload.

P206 | BEDSIDE
Magnetic resonance imaging as an assessment tool in hypertension

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Background: European guidelines recommend that patients with hypertension (HTN) are assessed for target organ damage. Patients with early onset (<40 years) or drug resistant HTN (office BP ≥140/90 despite ≥3 antihypertensives) should also be investigated for secondary causes. We proposed that a single magnetic resonance imaging (MRI) scan could provide all the imaging required in routine evaluation of patients with HTN.

Methods: Data from 200 consecutive patients investigated as standard with MRI in our Specialist Hypertension Clinic between 2011 and 2015, are presented. Imaging at 1.5T included assessment of cardiac volumetrics and fibrosis (late gadolinium enhancement), and imaging of the kidneys, renal arteries, adrenals, aorta and cerebral vessels. Comparisons were made with other imaging modalities where available; 84 patients had previous echocardiograms, 81 renal ultrasound, and 11 renal CT angiography.

Results: 200 patients (56% male), aged 51.3±1.1 years, office BP 168±2/96±1 mmHg. Indication: 38% drug resistant, 32% young onset, 18% multi-drug intolerant, 12% other difficult to treat HTN.

61% of patients had left ventricular hypertrophy (LVH), 7% had left ventricular remodeling without hypertrophy, and 9% had LV fibrosis. 14% of patients had reduced ejection fraction, 14% impaired diastolic function, and 42% impaired long-axis function. 27% had ≥1 accessory renal artery. We identified 15 prior myocardial infarctions, 6 patients with cerebral or peripheral vascular disease, and 9 with cerebral microaneurysms. Four patients were reclassified with probable hypertrophic cardiomyopathy.

Potential secondary causes: 12 (6%) adrenal masses (including 2 phaeochromocytoma), 10 (5%) renal artery stenoses (RAS), 7 thyroid abnormalities, 1 aortic coarctation, 1 enlarged pituitary gland, 1 polycystic kidney disease, 1 renal coloboma syndrome.

Taking cardiac MRI as gold standard, echocardiography over diagnosed LVH in 15% and missed LVH in 14%. Renal ultrasound reports were normal in 4 cases of adrenal adenoma and 4 of RAS. Renal CT was unable to detect 1 case of adrenal adenoma, as was MRI.

Conclusion: MRI is a safe and effective method of screening for target organ damage and secondary causes of HTN, that can be used alongside standard endocrine testing. It could replace the combination of echocardiography, renal ultrasound and CT imaging used to investigate young onset HTN and resistant HTN. MRI also provides additional information for patients being considered for renal denervation, and gives insight into the pathological changes seen the myocardium in hypertensive heart disease.

Acknowledgement/Funding: Bristol NIHR Biomedical Research Unit for Cardiovascular Disease, University Hospitals Bristol NHS Foundation Trust

P207 | BEDSIDE
Prognostic value of left ventricular remodeling, renal function and 24-h ECG recordings in elderly asymptomatic hypertensive patients

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Backgroun: Predictors of cardiovascular outcome in elderly hypertensive patients have been so far scarcely investigated.

Purpose: We assessed the impact of left ventricular geometry, renal function and 24 hour-Holter electrocardiogram (ECG) recordings and outcome in elderly hypertensive patients.

Methods: We enrolled 251 asymptomatic hypertensive elderly patients (>65 year-old). Left ventricular remodeling was evaluated by 2-D echocardiogram. Kidney function was assessed by serum creatinine and estimated glomerular filtration rate (eGFR) calculated according to the CKD-EPI formula. Lown's class, mean QTc and standard deviation of all normal R-R intervals (SDNN) were assessed by 24-hour Holter-ECG recordings. Data on all-cause and cardiovascular mortality were collected for 2 years.

Results: Mean age was 76.2±11.4 years; 46.6% were male and 32.3% were diabetic. Normal cardiac geometry was found in 14 patients (5.6%), concentric remodeling in 45 patients (17.9%), concentric hypertrophy in 135 patients (53.8%), and eccentric hypertrophy in 57 patients (22.7%). High Lown's classes (> class2) were more frequently observed in the presence of eccentric hypertrophy (66.7%) as compared to other patterns [concentric hypertrophy (53.3%), concentric remodeling (24.4%), normal (21.4%)]. Mean QTc was 444.8±34.8 ms and resulted directly correlated with indexed left ventricular mass (r=0.228; p=0.001). According to renal function, chronic kidney disease (CKD) was observed in 44.6% of patients and was associated with high classes of Lown (57.4% vs. 42.7%; p=0.014).Patients with CKD showed lower SDNN as compared with those with preserved renal function (92.02±36.11 ms vs. 103.84±33.96 ms, respectively; p=0.017); and SDNN was directly correlated with eGFR (r=0.168; p=0.015). At 2 years, all-cause and cardiovascular mortality rates were 38.0% and 21.1%, respectively. Diabetes mellitus (HR: 2.40; 95% C.I.1.16 to 4.99; p=0.019), CKD (HR: 2.22; 95% C.I.1.10 to 4.52; p=0.028), prolonged QTc (HR: 2.18; 95% C.I.1.07 to 4.41; p=0.030) and SDNN<96 ms (HR: 1.98; 95% C.I.1.03 to 4.13; p=0.048) were independent predictors of cardiovascular death at 2 year follow-up.

Conclusions: In elderly hypertensive patients, even in absence of symptoms, an assessment of renal function and LV geometry in addition to a 24-hr Holter ECG (including QTc and SDNN measurements) might represent simple and reproducible tools for the clinicians, able to both categorize the risk of elderly hypertensive patients and predict their outcome.

P208 | BEDSIDE
Carotid intima-media thickness is a noble predictor of the new onset of hypertension in the normotensive general population

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Background: The goal of the management for hypertension is a prevention of hypertensive organ damages leading to cardiovascular events. Although an increased carotid intima-media thickness (IMT) is one of the important markers of crucial hypertensive organ damages, IMT in normotensive subjects has not been intensively discussed in relation with blood pressure.

Purpose: This prospective study was designed to investigate whether carotid IMT predicts new onset of hypertension in the normotensive general population.

Methods: A total of 867 participants (men = 44.4%, 59.1±8.8 year-old), who visited our hospital for a yearly physical checkup from July 2008 to December 2011, were enrolled and their carotid IMT was measured. After baseline examination, they were followed up (median 1091 day) with the endpoint being the development of hypertension. An image of the common carotid artery was obtained by an ultrasound system and the mean IMT was calculated according to the guideline of Carotid Ultrasound Examination (2006).

Results: At baseline, their IMT was 0.75±0.16 mm (male vs. female; 0.77±0.19 vs. 0.74±0.13 mm, p<0.01). During the follow-up, hypertension developed in 184 subjects (76.9 per 1000 person-year), with the incidence being more frequent in male than in female subjects (90.8 vs. 66.1 per 1000 person-year, p<0.05). Carotid IMT at baseline was greater in subjects with than without future hypertension (0.83±0.19 vs. 0.73±0.15 mm, p<0.001) in retrospective analysis. In prospective analysis, non-adjusted hazard ratio (HR) (95% confidence interval [CI]) of IMT for the incident hypertension was 13.38 (6.77–26.43). Multivariate Cox-hazard analysis adjusted for age, gender, body mass index, systolic blood pressure, heart rate, serum creatinine, uric acid, fasting plasma glucose, low-density lipoprotein cholesterol, triglyceride, current smoking habit at baseline and family history of hypertension demonstrated that IMT was a significant predictor of new onset hypertension (HR = 6.88, 95% CI = 3.00–15.82). Univariate and multivariate liner regression analyses indicated the significant correlation between IMT at baseline and yearly increase in systolic blood pressure during the follow-up period (r = 0.176, p<0.001 and r = 0.192, p<0.001, respectively).

Conclusions: Carotid IMT, even in normal range, is significantly associated with the development of hypertension and yearly increases in blood pressure in the normotensive general population. Thus, IMT is important as a predictor of future hypertension as well as a marker of hypertensive organ damage.

OPTIMISING PRIMARY PCI

P209 | BEDSIDE
Radial artery anomalies in STEMI interventions

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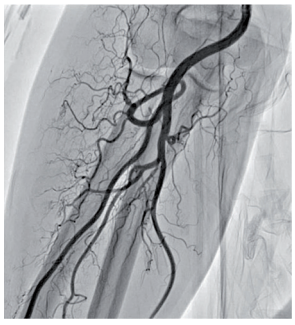
Objective: To access the impact and incidence of radial artery anomalies on the success of STEMI (ST segment elevation miocardial infarction) procedures with primary chosen transradial access site in a large series of patients.
Background: Transradial angiography (TRA) is now the recommended access for PCI in experienced transradial centers, but technically is a more challenging approach mostly due to anatomic anomalies of the radial artery, which may influence the success rate of transradial angiographic procedures. Successful crossing of radial artery anomalies can decrease the number of STEMI patients transferred to Transfemoral approach (TFA) and reduce bleeding complications in primary PCI (percutaneous coronary intervention).
Methods: All consecutive 19292 patients from our center, in the period from March 2011 until December 2014 were examined. Pre-procedural radial artery angiography was performed in all patients. We did a sub analysis of all 2891 STEMI primary PCI patients in that period. 243 STEMI patients with radial artery anomalies were present. Clinical and procedure characteristics, type of radial anatomy variants, failure in TRA site, transfer direction and procedure time were analyzed. Primary end-point of the study was the occurrence of transradial approach failure due to radial anatomical variants and need to crossover to another approach to finish the procedure. Secondary endpoints were presence of access site bleeding complications and radial artery spasm.
Results: Anatomical variants were present in 243 (8,4%) STEMI patients. The most frequent variant was high-bifurcating radial artery origin from the axillary and brachial arteries in 167 (5,7%) patients, 29 (1,0%) had a full radial loop, 45 (1,5%) had extreme radial artery tortuosity, 2 (0,06%) had hypoplastic radial artery. Failure in primarily chosen access site occurred in 13 (5,3%) patients. Successful crossing of anatomical variants was achieved in 230 patients (94, 7%). Highest incidence of cross-over was present in the patients with complex radial artery loop 9/13 (69%), a much higher percentage compared with patients with RA loop without STEMI (21%). Cross-over was done to ipsilateral TUA 6 patients, left RA 5 patients and TFA with 2 patients.



Radial artery loop in STEMI

Conclusion: Failure of transradial procedures in the STEMI setting is associated with radial artery anomalies. Pre-procedural radial artery angiography in STEMI patients gives the operator a roadmap to successfully plan the strategy for crossing the anomaly or transfer to a new approach in the interest of saving time and reducing primary PCI procedure time.

P210 | BEDSIDE
Is there a relationship between operator and center volume with access site related outcomes?

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Background: Transradial access is associated with reduced access site related bleeding complications and mortality following percutaneous coronary intervention (PCI).
Aims: This study aimed to examine the relationship between access site practice and clinical outcomes and how this may be influenced by operator and center experience/expertise.
Methods: Procedures recorded in the from the British Cardiovascular Intervention Society (BCIS) national dataset between 2012 and 2013 in the NHS in England and Wales were used. The association of access site (radial vs femoral) on 30-day mortality was examined over varying levels of operator and center experience using risk-adjusted multiple logistic regression modelling. Operator/center experience/expertise were defined by total volume, transradial volume, and transradial proportion.
Results: A total of 164,395 procedures were available for analysis. After case-mix adjustment, transradial access was associated with an average odds reduction of 39% for 30-day mortality compared with transfemoral access (OR = 0.61, 95% CI 0.55–0.68, $p<0.001$). The magnitude of this risk reduction was modified by increases in total procedural volume and radial proportion at the operator level (OR reduction of 11% per 100 extra procedures, 95% CI 3–19%; OR reduction of 8% per 10%-point increase in radial proportion, 95% CI 3–12%) with no significant impact of operator radial volume, center total volume, center radial volume and center radial proportion.
Conclusions: The lower mortality associated with transradial access adoption relates to both the total procedural volume and the proportion of procedures undertaken radially by operator, with operators undertaking the greatest proportion of their procedures radially having the largest relative reduction in mortality risk.
Acknowledgement/Funding: Work carried out as part of a Medical Research Council funded PhD project

P211 | BEDSIDE
Management and clinical outcome of patients with ST-elevation myocardial infarction and coronary aneurysms

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Background: Coronary arterial aneurysms (CAAs) are dilatations of coronary artery segments exceeding 50% of the reference vessel diameter. The incidence of CAAs ranges from 0.3% to 5.3% according to several angiographic studies. Until now only few case reports have described CAAs in the clinical setting of ST elevation myocardial infarction (STEMI).
Purpose: The aim of the present study is to describe the management and the clinical outcome of a single center STEMI population undergoing primary percutaneous coronary intervention (pPCI) presenting CAAs at angiography.
Methods: From our database including 2300 STEMI in the last ten years (2005–2015), we retrospectively collected data about patients with CAAs as target lesion (Group A) or in at least one non-target vessel (Group B) and patients without CAAs at angiography (Group C). We report the interventional and medical management of group A and the clinical outcome of all the three groups using the composite endpoint death and MI (D-MI) and stent thrombosis (ST).
Results: 43 patients (1.9%) were included in the analysis: mean age 64.9 (SD 11.4 years), 80% male, 19% with diabetes and 49% with anterior MI. Group A included 20 cases (47%) and Group B 23 cases (53%).
In Group A thrombus aspiration was performed in half of the cases (rheolytic in one third); at least one stent was implanted at CAAs site in 70% of cases with a prevalent use of drug eluting stents (DES); in one case the aneurysm was excluded with a covered stent. In most cases (85%) a final TIMI 2–3 flow was obtained. Intraprocedural glycoprotein IIb/IIIa inhibitor was used in 65% of cases. Therapy at discharge included aspirin and a dual antiplatelet therapy (DAPT) in all the cases; vitamin k antagonist oral anticoagulant therapy was prescribed to two patients in association to DAPT.
In Group A ST occurred in 15%, in group B in 8% and in Group C in 2% of the cases. In Group A, at a median follow up of 256 (IQR 9–470) days, D-MI occurred in 30% of the patients. The same rate (30%) occurred in the population of Group B at a median follow up of 385 (IQR 30–1086) days. In both groups D-MI occurred early after the index event (median follow up of 16 days). In Group C the rate of D-MI was 16% at a median follow up of 507 IQR (168–1007) days. In this group the median time to event was 53 days.
Conclusions: In our STEMI population, patients with CAAs as culprit lesions were mainly treated with thrombus aspiration and DES use. The presence of CAAs is associated with a high rate of stent thrombosis, mortality and myocardial infarction occurring early after the index event. Large registries are warranted to best clarify optimal interventional and medical management.

P212 | BEDSIDE
Impact of direct stenting on in-hospital and four-year mortality in patients with acute ST-segment elevation myocardial infarction undergoing primary percutaneous coronary intervention

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Aim: Purpose of this study was to evaluate the impact of direct stenting on long term mortality in patients with ST-segment elevation myocardial infarction (STEMI) treated with primary percutaneous coronary intervention (PCI). In-hospital and long-term mortality were assessed at a median follow-up of 48 months (interquartile range IQR 36–56).
Methods: We identified 4296 consecutive patients undergoing primary PCI with stent implantation from January 2009 to July 2013, from a prospective electronic registry of a high-volume catheterization laboratory. Direct stenting (DS) was defined as stent implantation without balloon predilatation, before or after thrombus aspiration. Conventional stenting (CS) was defined as stent implantation performed after balloon predilatation.

Results: In total, 42.7% of patients (n=1833) were treated with DS and 57.3% (n=2463) with CS. There were no significant differences in baseline characteristics between two groups except: baseline TIMI grade 3 flow rates were more frequent in DS group compared to CS group (17.9% vs. 8.9%; p<0.001); aspiration catheter was used more frequently in DS group (28.8% vs. 17.1%; p<0.001) and glycoprotein IIb/IIIa inhibitors were used more frequently in CS group (34.3% vs. 20.4%; p<0.001).
It patients with DS total stent length was shorter (28.49 mm vs. 31.18 mm; p<0.001) and less contrast was used (163.86 ml vs 194.20 ml; p<0.001), while the levels of peak creatine kinase (CK) were higher in CS group (2115.44 vs. 2002.3 IU/L p=0.003).
In-hospital and 4-year follow-up mortality was lower in patients with DS as compared to CS (2.0% vs. 6.1%; p<0.001 and 10.2% vs. 18.6%, p<0.001, respectively). After adjusting for baseline clinical and angiographic parameters, DS remained an independent predictor of lower 4-year mortality (HR 0.53, 95% CI 0.44 to 0.65, p<0.001).
Conclusion: In unselected real-world population of STEMI patients undergoing primary PCI, direct stenting improved procedural result, reduced peak CK value and was associated with lower in-hospital and 4-year mortality.

P213 | BEDSIDE
Transradial intervention is a strong predictor for all-cause death and does not delay procedure time in routine practice (5-year single center experience)

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Background: Despite of ESC guideline recommendation of transradial intervention (TRI) in patients with ST-segment elevation myocardial infarction (STEMI), the routine practice of TRI is still low in Korea.
Purpose: We evaluated the prognostic value of TRI compared to transfemoral intervention (TFI) for all-cause death and procedure time delay for 5 years in TRI-dedicated single center.
Methods: Among 3788 patients from Jan 2010 to Dec 2014, 2499 patients underwent PCI were enrolled. Chronic total occlusion and intervention for bifurcation were excluded. Patients were divided into 2 groups (TRI vs. TFI). We compared procedure-related factors between 2 groups. Multivariate logistic regression analysis was performed for the prediction of all-cause death and procedure time delay (4th quartile).
Results: TRI was performed in 2269 patients (90.8%). TRI group was younger (65.4±11.3 vs. 68.0±12.3 years, p=0.001). TFI group had more hypertension, diabetes mellitus, chronic kidney disease and ST-segment elevation myocardial infarction (STEMI). TFI group showed lower systolic blood pressure (SBP), lower left ventricular ejection fraction (LVEF), more multi-vessel disease (MVD) and higher Killip classification. There were no differences in use of second generation drug-eluting stent. Total stent number (1.5±0.8 vs. 1.6±0.8, p=0.009) and stent length (35.8 vs. 21.0 vs. 41.6±24.8, p<0.001) were significantly different between TFI and TRI group. TRI group showed faster puncture time (1.5±2.0 vs. 1.9±2.4 mins, p=0.012). But, time for diagnostic coronary angiography, coronary intervention time, total procedure time, contrast volume and fluoroscopic time showed no significant differences (7.9±5.5 vs. 8.2±5.7, p=0.435; 34.3±17.9 vs. 37.4±24.9, p=0.071; 44.8±19.1 vs. 46.4±22.0 mins, p=0.304; 168.1±64.6 vs. 163.0±55.7 mL, p=0.260; 12.3±19.7 vs. 13.9 vs. 15.9 mins, p=0.233) between TRI vs TFI group. In multivariate regression analysis, the predictors of all-cause death were age (odds ratio [OR] 1.05, 95% confidence interval [CI] 1.026–1.074), chronic kidney disease (OR 5.558, 95% CI 2.286–13.509), Killip≥2 (OR 7.179, 95% CI 1.743–4.485), LVEF (OR 0.941, 95% CI 0.919–0.962) and TRI (OR 0.486, 95% CI 0.274–0.861). Moreover, TRI was not a predictor for procedure time delay in univariate logistic regression analysis (OR 0883, 95% CI 0.663–1.174). Predictors for procedure time delay were MVD (OR 2.205, 95% CI 1.830–2.658), Use of intravascular ultrasonography (OR 2.222, 95% CI 1.711–2.886) and STEMI (OR 0.357, 95% CI 0.271–0.471).
Conclusions: In a TRI-dedicated single center experience for 5 years, TRI was a strong predictor for all-cause death in routine practice. Moreover, TRI showed faster puncture time and did not delay procedure time compared to TFI.

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Drug eluting stent vs. bare metal stent in acute myocardial infarction complicated by cardiogenic shock - A substudy of the IABP-SHOCK II-trial

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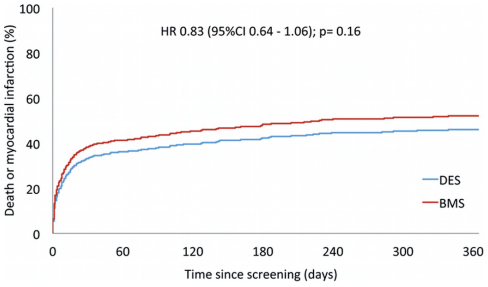
Background: Data comparing the use of drug eluting stents (DES) and bare metal stents (BMS) in acute myocardial infarction (AMI) complicated by cardiogenic shock (CS) are very limited.
Purpose: The present study assesses the outcome of those two stent technologies in the setting of AMI complicated by CS.
Methods: A total of 788 patients with AMI and CS undergoing early revascularization were included in the randomized Intra-aortic Balloon Pump in Cardiogenic Shock II (IABP-SHOCK II) trial and the associated registry. This substudy compares the outcome between DES and BMS. Patients receiving no stent or both DES and BMS were excluded. Primary endpoint was the composite of one-year mortality or re-AMI.
Results: Of the total cohort 652 (83%) patients received either solely DES or BMS and were included in the present analysis. Of these patients 276 (42%) received solely DES and 376 (58%) patients received solely BMS. Among other differences in baseline characteristics patients with DES were younger (66 [54–74] vs. 72 [60–78] years; p<0.001), were less often female (23% vs. 34%; p=0.002), had less often atrial fibrillation at the initial electrocardiogram (8% vs. 16%; p=0.003), had a trend to lower baseline serum lactate (3.4 [1.8–7.0] vs. 3.9 [2.2–7.6] mmol/l; p=0.053) and sustained more frequently an anterior AMI (50% vs. 38%; p=0.003).
The one-year death or re-AMI rate was 45% (124/276) in patients with DES and 60% (226/376) in patients with BMS (HR 0.64 [95% CI 0.51–0.79]; p<0.001). After adjustment for baseline risk factors there was no significant difference between DES and BMS (Figure). There was an independent association of BMS use with age (OR per 10 years increase 1.34 [95% CI 1.15–1.57]; p<0.001), prior known dyslipidemia (OR 0.41 [95% CI 0.28–0.89]; p<0.001), atrial fibrillation (OR 1.99 [95% CI 1.05–3.75]; p=0.03), serum hemoglobin level (OR per 1 mmol/l increase 0.85 [95% CI 0.75–0.97]; p=0.01), treatment at frequently enrolling centers (OR 0.60 [95% CI 0.41–0.89]; p=0.02), coronary single vessel disease (OR 1.61 [95% CI 1.03–2.50]; p=0.04) and anterior AMI (OR 0.55 [95% CI 0.37–0.80]; p=0.006).



Adjusted KM curve for primary endpoint

Conclusion: Despite the frequent use of DES nowadays a substantial number of patients were treated by BMS in the particular setting of AMI complicated by CS. After adjustment for risk factors the one-year outcome of patients treated by DES was similar compared to BMS.
Acknowledgement/Funding: German Research Foundation, the German Heart Research Foundation, DGK, ALKK, University of Leipzig–Heart Center, Maquet Cardiopulmonary and Teleflex Medical.

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Complete revascularization reduces the incidence of acute decompensated heart failure in patients with ST-segment elevation myocardial infarction and multivessel coronary artery disease

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Background/Introduction: Optimal interventional strategy for ST-segment elevation myocardial infarction (STEMI) and multivessel coronary artery disease (MVD) is still controversial. It is also uncertain whether complete revascularization (CR) can reduce the incidence of acute decompensated heart failure (ADHF) compared to incomplete revascularization (IR) in patients with STEMI and MVD.
Purpose: We analyzed the incidence of ADHF and clinical outcomes between CR and IR in patients with STEMI and MVD.
Methods: A total of 575 consecutive patients with STEMI and MVD who admitted at Chonnam National University Hospital between January 2006 and July 2009 were enrolled. By excluding patients with cardiogenic shock, initial cardiac arrest or in-hospital death, a total of 453 patients were analyzed and divided into two groups according to interventional strategy; CR group (n=240) vs. IR group (n=213). Primary endpoint was a readmission due to ADHF during long-term follow-up period (median 6.3 years; interquartile range 3.7 to 7.7 years). We also examined the incidence of major adverse cardiac events (MACE; composite of all-cause mortality, myocardial infarction [MI], and any revascularization), cerebrovascular accident (CVA), and stent thrombosis.
Results: IR group was older (67.4±11.5 vs. 71.5±12.2 years, p<0.001) and had a higher level of NT-proBNP (median 808 [179–1942] vs. 1275 [303–2963] pg/mL, p=0.042). The proportion of gender, prevalence of atherosclerotic risk factors, left ventricular EF, and door-to-balloon time were comparable between two groups. Coronary stenting was done in 447 patients (98.7% in total patients; 99.2 in CR vs. 98.1% in IR group, p=0.427) and peri-procedural complications occurred similarly in both groups (10.0 vs. 11.7%, p=0.650). Among 315 patients who underwent multivessel PCI, 251 patients (79.7%) received staged PCI. During follow-

up period, CR reduced the readmission rate due to ADHF (5.8 vs. 12.2%; HR 0.42, 95% CI 0.22 to 0.81, p=0.009) in multivariate analysis. MACE occurred in 158 patients (34.9%) and 57 patients (12.6%) died. CR also reduced MACE (27.1 vs. 43.7%; hazard ratio [HR] 0.54, 95% confidence interval [CI] 0.39 to 0.74, p<0.001), all-cause mortality (6.7 vs. 19.2%; HR 0.31, 95% CI 0.17 to 0.55, p<0.001), cardiac mortality (3.8 vs. 10.3%; HR 0.33, 95% CI 0.15 to 0.71, p=0.005), and non-target vessel revascularization (TVR) (3.8 vs. 13.6%; HR 0.23, 95% CI 0.11 to 0.48, p<0.001). The incidence of MI, target-lesion revascularization, TVR, and stent thrombosis was comparable between CR and IR group. In subgroup analysis between CR (n=240) and infarct-related artery (IRA) only intervention (n=138) group, CR was also associated with better clinical outcomes compared to IRA only intervention.
Conclusions: CR reduced long-term incidence of ADHF as well as MACE, mortality, cardiac mortality, and non-TVR compared to IR in hemodynamically stable STEMI patients with MVD.

MANAGEMENT OF DEVICE COMPLICATIONS AND LEAD EXTRACTION: ARE WE GETTING BETTER?

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Cardiac implantable electronic device infection: variability in clinical presentation and outcomes in patients with or without previously abandoned leads

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Introduction: Lead abandonment at the time of cardiac implantable electronic device (CIED) system revision or upgrade is widely practiced by remain controversial. We have previously reported on the complexity of extractions in patients with abandoned leads.
Purpose: We sought to assess the clinical profiles and outcomes of CIED infections in patients with or without abandoned leads.
Methods: All consecutive patients undergoing percutaneous extraction of infected CIEDs at our institution (August 1996-September 2012) were enrolled in a prospectively maintained data registry. The clinical profiles and outcomes were compared between patients with (Group 1, n=323) and without (Group 2, n=1063) abandoned leads.
Results: Group 1 patients were older (p=0.04) and more likely to have indications for pacing (p<0.0001). There were otherwise no other significant differences in baseline clinical characteristics between the Groups. Pocket infection was more likely in Group 1 (67.8 vs. 58.0%, p=0.02, endovascular infection 32.2 vs. 42.0%). Nonetheless, Group 1 patients were more likely to have vegetations on transesophageal echocardiograms (30.8 vs. 22.3%, p=0.02, vegetations on lead 27.0 vs. 16.9% in Group 2, p=0.002). When present, vegetations were larger in Group 1 (p=0.0003). All leads were targeted with extraction in all patients. The extraction procedures were more complex in Group 1 with longer procedural and fluoroscopy times, higher likelihood of needing rescue femoral workstations (14.9 vs. 2.9%, p<0.0001) and more procedural complications (11.5 vs. 5.6%, p=0.0007). Extracted lead tips grew positive cultures in 73.7% in Group 1 patients (vs. 61.2%, p=0.003). Lead material retention occurred more commonly in Group 1 (11.5 vs. 2.9%, p<0.0001). Retention of lead material was associated with poor clinical outcomes including higher 1-month mortality (7.4 vs. 3.5%), need for open heart surgery to remove lead remnants (16.2%) and long term suppressive antibiotics (41.2%).
Conclusion: Previously abandoned leads complicate the clinical management of CIED infections.

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Developing an adverse events reporting system to measure real-world outcomes of cardiac implantable electronic devices

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Introduction: Most existing data on complication rates, mortality, morbidity, and costs of cardiac implantable electronic devices (CIED) come from clinical trial samples, which enroll subjects who may not be representative of patients followed in routine practice. Longitudinal and real-world data is needed, but following large groups of patients can present logistical challenges. In order to address these questions, we developed a web-based Adverse Events Reporting System (AERS) to assess longitudinal CIED outcomes, including complications, hospitalization and mortality.
Methods: Prospective multicenter registry of all CIED procedures performed at 9 geographically distributed cardiology centers. Outcome measures were: mortality, major and minor complications and hospitalization over 6-months of follow-up. The informatic structure of the CIED_AERS database adheres to the international safety reporting guidance issued by the International Conference on Harmonisation. Adverse events were coded according to Medical Dictionary for Regulatory Activities (MedDRA) terminology. Multivariable logistic regression was used to identify factors associated with complications or mortality.
Results: The study cohort included 3,550 consecutive patients who underwent CIED procedures from January, 2014 to December, 2015. Population main characteristics were: age= 66.5±17.3 years; male= 52.4%; left ventricular ejection fraction (LVEF)= 50.6±16.4%; New York Heart Association (NYHA) functional class (FC) I and II= 69.9%; ischemic heart disease= 14.3%; Chagas' disease = 14.9%; presence of atrial fibrillation (AF)= 19.3%; initial CIED implant= 55.3%; pulse generator replacement= 44.7%; pacemaker (PM)= 71.7%; implantable cardioverter-defibrillator (ICD)= 14.2; cardiac resynchronization therapy (CRT)= 8.2% and CRT-ICD = 6.0%. A total of 250 (7.2%) patients experienced at least one complication before the discharge and 715 (20.6%) within the first 6 months. Of these events, 36.8% were considered definitely related to the procedure or CIED. According to Kaplan–Meier estimator, mortality rate was 1.2% and 4.1% in the perioperative and during the 6-month follow-up, respectively. The risk of any complication was higher in older patients (P=0.01), NYHA FC IV (P<0.01), presence of AF (P=0.016), multiple comorbidities (P=0.03), ventricular dysfunction (P<0.01), CRT-PM (P<0.01) or underwent reoperation procedures (P<0.01).
Conclusion: CIED_AERS is a flexible and suitable solution to perform the reporting and monitoring of adverse events in multicenter settings. CIED complications are not uncommon and both patient and procedure-related predictors may identify patients with a particular high risk of complications.
Acknowledgement/Funding: CNPq/REBRATS #401317/2013-7

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Extraction of ICD leads: efficacy and safety comparable with pacemaker lead extraction in a high volume center

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Materials and methods: From 1998 till end of December 2015 we extracted 524 ICD leads of a total of 2194 leads. The number of Sprint Fidelis leads were 188, the number of SJM Riata leads were 24. Median ICD lead age was 5 years, Sprint Fidelis median age 6 years and Riata 8 years. The indication was infection in 156 (29,7%) of the cases, the rest 368 (70,2%) cases were elective. Of the elective cases most of the ICD leads were extracted due to direct or indirect signs of fracture, but a significant portion of the Sprint Fidelis and the Riata leads were extracted prophylactic at the time for generator change. Of the infection cases 67,3% were pocket infections and 32,7% septicemia. Traction alone was used in 110 (21%) of the cases, locking stylet in 404 (77%) cases.The single sheath technique was used in 393 (75%) cases (Sprint Fidelis 158 (85%), Riata 20 (87%)), various fishing techniques in 31 (6%) cases and the Cook Evolution or Spectranetics TightRail in 42 (8%) cases. When more than simple traction was needed, single sheath extraction was the first choice in 94,9% of the cases. Femoral/jugular approach was performed in a higher percent of the Riata cases (9%), as was the use of the Evolution or TightRail sheaths (43%).
The single sheath dilatation technique included a locking stylet (Cook/Spectranetics/Vascomed) and a suture or Cook Bulldog securing the lead. The Cook or Spectranetics single sheath was mounted with a Pin Vise and gently pushed down over the lead, with altering clockwise and counterclockwise rotation. The sheath size was increased when resistance was met. For difficult cases we converted to the more aggressive Cook Evolution or Spectranetics TightRail, or the femoral/jugular approach.
Results: Complete success (all of the electrode removed) was achieved in 97,7% of the cases, compared to 95,3% for the pacemaker leads. Clinical success (removal of all the lead or all the lead except the distal 4 cm) was achieved in 99,2% of the ICD leads, the same as for the pacemaker leads. Major complications 1,1%, no mortality, minor complications 2,3% for ICD leads, compared to 1% major and 1,7% minor complications for all leads.
Conclusions: In our high volume center ICD lead extraction was effective and safe, with single sheath dilatation technique as the first choice in most cases. Femoral/jugular approach and Cook Evolution/Spectranetics TightRail were used more often in the SJM Riata ICD lead cases.

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Transvenous removal of pacing and ICD leads: single Italian referral center experience

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Introduction: Device related complications are rising the need of Transvenous Lead Removal (TLR). Transvenous extraction of Pacing (PL) and Defibrillating Leads (DL) is a highly effective technique. Aim of this report is to analyse the longstanding experience performed in a single Italian Referral Center.
Methods: Since January 1997 to December 2015, we managed 2389 consecutive patients (1830 men, mean age 65.3 years) with 4374 leads (mean pacing period 72.2 months, range 1–576). PL were 3514 (1656 ventricular, 1475 atrial, 383 coronary sinus leads), DL were 860 (839 ventricular, 6 atrial, 15 superior

vena cava leads). Indications to TLR were infection in 81% (systemic 27%, local 54%) of leads. We performed mechanical dilatation using a single polypropylene sheath technique and if necessary, other intravascular tools (Catchers and Lassos, Osypka, Grentzig-Whylen, G); an Approach through the Internal Jugular Vein (JA) was performed in case of free-floating leads or failure of the standard approach.
Results: Removal was attempted in 4364 leads because the technique was not applicable in 10 PL. Among these, 4270 leads were completely removed (97.8%), 45 (1.1%) partially removed, 49 (1.1%) not removed. Among 4279 exposed leads, 678 were removed by manual traction (15.8%), 3173 by mechanical dilatation using the venous entry site (74.2%), 36 by femoral approach (FA) (0.8%) and 298 by JA (7.0%). All the free-floating leads were completely removed, 25.8% by FA and 74.2% by JA. Major complications occurred in 15 cases (0.63%): cardiac tamponade (14 cases, 3 deaths), hemotorax (1 death).
Conclusions: Our experience shows that in centers with wide experience, TLR using single sheath mechanical dilatation has a high success rate and a very low incidence of serious complications. TLR through the Internal Jugular Vein increases the effectiveness and safety of the procedure also in case of free-floating or challenging leads.

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Lead extraction in adults with congenital heart disease

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Introduction: Indications for device implantation are increasing in the growing and aging population with congenital heart diseases (CHD). In parallel, the need to extract transvenous leads is rising. However, safety and feasibility data are limited in this challenging population. Herein, we report the results of lead extraction procedures in adults with CHD over a 20-year period.
Methods and results: A prospective registry for lead extraction procedures was initiated at our center in 1995. A total of 102 leads (43% atrial, 57% ventricular) were extracted in 40 adults with CHD, age 40±14, 42% female, during 60 lead extraction procedures. A total of 22 patients presented with transposition of the great arteries, 6 with tetralogy of Fallot and 2 with atrioventricular septal defect. Main indications for extraction were infection in 28 (47%), lead failure in 17 (28%), device upgrade in 7 (12%) and symptomatic thrombosis in 4 (7%) patients. The median time from lead implantation to extraction was 86 [36; 148] months. A laser was required for 49 (48%) leads and a lasso by a femoral approach in 8 (8%) leads. Complete lead extraction was achieved for 92 leads (90%). Extraction was unsuccessful for 8 ventricular leads and 1 atrial lead (2 failures with locking stylet, 6 with laser, and 1 with lasso). No death in the peri-operative period and no pericardial effusion were observed. However, 1 patient had a pneumothorax and 7 had pocket hematomas. The degree of sub-pulmonary AV valve regurgitation increased in 7 patients (5 with ICD lead). One patient with d-TGA and Mustard baffles and 2 with l-TGA had severe AV valve regurgitation of the subpulmonary ventricle requiring later surgical repair. After a median of 58 [23–110] months of follow-up after a first extraction procedure, 16 patients underwent additional lead extraction procedures (1 to 4). Three deaths occurred during follow-up, due to septic shock after CardioWest implantation, to heart failure, and to cerebral hemorrhage.
Conclusion: Despite complex anatomical issues, lead extraction can be achieved successfully in most adults with CHD, using advanced extraction techniques. Subpulmonary AV valve regurgitation is a prevalent (12%) complication, which occasionally requires surgical repair, particularly in patients with TGA.

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Transvenous lead extraction in young patients. Specificity and disparateness

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There is considerable controversy regarding safety of transvenous lead extraction (TLE) in young pts and children due to different anatomy, stronger connecting tissue scar and its earlier calcification.
Objective: The comparison of safety and feasibility of TLE in young and adult pts.
Methods: Using standard mechanical systems we have extracted ingrown PM/ICD leads from 1041 adult, 110 young patients and in 44 children, within the last 10 years. Pts over 70' were excluded from the study. We compared effectiveness, complications and technical problems during TLE procedures in mentioned three groups of pts.
Results: Results are in Table.
Impression: TLE in children and young pts is much more effort consuming (much stronger connective tissue scar, frequent calcification or mineralization) and entails more experienced operator because lead break is relatively frequent and lead have to be extracted in parts. Rare occurrence of pocket infection in children may be explained by implantation procedure in operation room and not in EPS lab.

Patient / system / procedure information	A; < 19- y	B; 19-35-y	C; 36-70y	A vsC	B vs C
Number of patients	44	101	1041		
Patient's age (SD)	**14,8** ± 3,2	**27,9** ± 4,7	**59,9** ± 8,1	p<0,001	p<0,001
Sex (% of male patients) (%)	29 (**65,9%**)	55 (**54,5%**)	268 (**25,7%**)	p<0,001	p<0,001
Systemic infection (LRIE) (%)	9 (**4,9%**)	15 (**14,8%**)	79 (**29,1%**)	p<0,01	p<0,05
Local (pocket) infection (%)	1 (**2,3%**)	11 (**10,9%**)	119 (**11,4%**)	p=0,099	p=0,999
Non-infective indications (%)	39 (**88,6%**)	75 (**74,3%**)	653 (**62,7%**)	p<0,001	p<0,05
Number of extracted leads in one patient (SD)	**1,33** ± 1,11	**1,93** ± 0,95	**1,66** ± 0,80	p<0,01	p<0,01
Number of leads in the system (SD)	**1,36** ± 1,49	**1,64** ± 0,50	**1,81** ± 0,66	p<0,001	p<0,05
Number of abandoned leads (SD)	**0,14**± 0,41	**0,18** ± 0,52	**0,19** ± 0,53	p=0,537	p=0,856
CS (LA, LV) lead extraction (%)	0 (**0,0%**)	1 (**0,99%**)	140 (**13,4%**)	p<0,05	p<0,001
VH therapy (ICD) lead extraction (%)	7 (**15,9%**)	32 (**31,7%**)	341 (**32,8%**)	p<0,05	p=0,914
Number of procedures before lead extraction (SD)	**1,61** ± 0,78	**1,82** ± 0,94	**1,87** ± 1,18	p=0,148	p=0,680
Mean leads body dwelling time (SD)	88,9 ± 46,6	**107,4** ± 62,1	**87,1** ± 68,7	p=0,863	p<0,01
Major complications (%)	1 (**2,27%**)	2 (**1,98%**)	16 (**1,54%**)	p=0,814	p=0,939
Technical problems during TLE (%)	18 (**37,5%**)	43 (**37,1%**)	227 (**20,9%**)	p<0,01	p<0,001
Full radiological success (%)	**35 (79,5%)**	**93 (92,1%)**	987 (**94.9%**)	p<0,001	p=0,358
Partial radiological success	8 (**18,2%**)	6 (**5,9%**)	42 (**4,0%**)	p<0,001	p=0,515
Death procedure related (intra,post-procedural) (%)	0 (**0,0%**)	0 (**0,0%**)	2 (**0,19%**)	p=0,133	p=0,421
Clinical success (%)	42 (**95,5%**)	99 (**98,0%**)	1021 (**98,1%**)	p=0,507	p=0,735
Full procedural success (%)	35 (**79,5%**)	93 (**92,1%**)	987 (**94,8%**)	p<0,001	p=0,534
Operating room stay-in time (minutes) (SD)	**110,4** ± 32,7	**128,3**± 49,1	**110,2** ± 46,3	p=0,97	p<0,001

Conclusions: 1. Infective indications are much less frequent in children but not in young than adult pts. 2. In spite of simpler systems in children and in young pts., effectiveness of TLE remain slightly lower; break of non-extractable distal lead fragment or tip of lead occurs in one-fourth TLE. 3. Young-age do not influence on appearance of major complications and procedure related death bot on difficulties of procedure and appearance of different technical problems.

ANGIOGENESIS

P222 | BENCH
Impact of cardiovascular risk factors on rAAV.Thymosin b4 mediated vascular regeneration in a pig model of chronic myocardial ischemia

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Despite recent advances in the treatment of coronary heart disease, a significant number of patients show poor response and progressively develop heart failure. Induction of neovascularization using vascular growth factors has emerged as a promising novel approach for cardiac repair and regeneration. Thymosin β4 (Tβ4), a small 4.9 kDa peptide, has been characterized as a major G-actin-sequestering factor regulating the cytoskeletal reorganisation, thus, cell motility, migration and differentiation. In this study, we investigated the rpotential of adeno-associated viral vector mediated Tβ4 overexpression (rAAV.Tβ4) in a pig model of chronic myocardial ischemia with cardiovasuclar risk factors.
Methods: Chronic ischemia was induced via reduction stent graft in the circumflex artery, leading to a total occlusion on day 28 (n=6 per group). Selective pressure-regulated retroinfusion of saline (c) or rAAV2.9 Tβ4 (5x10E12 viral particles) was performed on day 28. On day 28 and 56, global myocardial function (LVEDP) was measured; for the assessment of blood flow, fluorescent microsphere immunoassay (FMI) was performed. Subendocardial segment shortening (SES) and post mortem angiography were obtained on day 56. Tissue samples from ischemic and non-ischemic regions were harvested for histological analysis of capillary density (capillaries/field (C/F)). Hypercholesterinemia was provoked by high-cholesterol-containing diet, given during the entire experiment. Blood samples for quantification of serum triglyceride level were collected before and by the end of the experiment.
Results: Tβ4 overexpression via rAAV significantly enhanced both, capillaries (142±4 (Tβ4) vs. 67±3 (C) C/F) and collaterals (9±1 (Tβ4) vs. 3±1 (c)) in the ischemic area. Furthermore, FMI showed a significant increase of blood flow on day 56 (91±2 (Tβ4) vs. 78±3 (C) % non-ischemic LAD area). In addition, global (LVEDP: 12±2 (Tβ4) vs. 19±2 (c) mmHg) and regional myocardial function (SES at 150 beats/min: 73±5 (Tβ4) vs. 10±6 (c) % of non-ischemic LAD area) significantly improved after Tβ4 overexpression. In the pig model of hypercholesterinaemia, serum triglyceride level rose from 22±3 to 72±4 mg/dl following high-cholesterol diet. However, the improvement of the neovascularization and heart function could be achieved using the regional application of rAAV2/9 Tβ4, albeit at a lower level (capillaries: 88±3 (Tβ4) vs. 62±2 (c) C/F; collaterals: 6±1 (Tβ4) vs. 3±1 (c); LVEDP: 14±1 (Tβ4) vs. 18±2 (c) mmHg; SES at 150 beats/min: 37±5 (Tβ4) vs. 15±1 (c) % of non-ischemic LAD area).
Conclusion: These results suggest that post-ischemic rAAV2/9 Tβ4 administration enables capillary growth in vivo. This process provides enhanced collateralization and perfusion, thereby resulting in improving myocardial function. A comparable effect is seen in the dyslipidaemic hearts, suggesting an attractive therapeutic potential of using rAAV.Tβ4 for otherwise no-option patients with ischemic heart disease.

P223 | BENCH
Akap1 modulates endothelial cells function and ischemia-induced angiogenesis in mouse hindlimb

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Introduction: Mitochondria are the major intracellular source of Reactive Oxygen Species (ROS) in several tissues, including heart and skeletal muscle. ROS production is crucially regulated by mitochondrial A-kinase anchoring proteins (mitoAKAPs), encoded by the Akap1 gene. The role of mitoAKAPs in post-ischemic skeletal muscle angiogenesis and endothelial function is currently unknown.
Hypothesis: Here we tested the hypothesis that mitoAKAPs might play a crucial role in endothelial cells function and in neovascularization of ischemic murine limbs.
Methods: To test this, in vivo unilateral femoral artery ligation was performed in Akap1 knockout mice (Akap1–/–) and wild-type (wt) littermates of either gender. Muscle perfusion was analyzed by laser Doppler in ischemic limbs and contralateral nonischemic limbs of animals from all the groups at 24 hours, 7 days and 28 days after surgery. Capillary density and muscle fibrosis were evaluated by lectin or Syrius red staining. Primary aortic endothelial cells (AECs) were isolated from aortas of Akap1–/– or wt mice and capillary network formation, cell proliferation, apoptotic cell death, ROS production and the signaling pathway elicited by VEGF were analyzed. Mitochondrial morphology in AECs was evaluated by electron microscopy.
Results: Compared to wt mice, Akap1–/– mice were characterized by impaired blood flow and functional recovery after hindlimb ischemia. Moreover, Akap1–/– ischemic limb muscles displayed a significant reduction of capillary density and a significant reduction of Akt phosphorylation compared to wt mice.
Akap1–/– AECs exhibited impaired mitochondrial structure, enhanced apoptosis and ROS production compared to wt cells under hypoxic conditions. Furthermore, Akap1–/– AECs showed an inhibited VEGF-induced capillary-like network formation, reduced migration and proliferation, and impaired VEGF-dependent Akt phosphorylation compared to wt. Interestingly, transfection of Akap1–/– AECs with a constitutively active Akt construct ameliorated cell proliferation and capillary-like network formation in vitro.
Conclusions: These results demonstrate the important role of mitoAKAPs in the modulation of multiple endothelial cell functions in vitro, and of post-ischemic limb neovascularization in vivo. These results suggest that mitochondrial-dependent ROS production might represent a novel therapeutic target in neovascularization.

P224 | BENCH
Mechanism of misguided venous thrombus resolution - The role of Angiopoietin-2 (Ang-2)

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Introduction: Incomplete thrombus resolution followed by vascular remodeling is considered the critical mechanism for the development of chronic thromboembolic pulmonary hypertension (CTEPH) after pulmonary embolism (PE). Thrombus resolution is crucial for the restoration of vascular patency after PE. Angiogenesis and an intact inflammatory response are key mediators of thrombus resolution. Ang-2 has been shown to induce endothelial cell apoptosis leading to cell-cell destabilization and vessel regression. Therefore, we hypothesize that Ang-2 misguides thrombus resolution.
Material and methods: We induced thrombi in the infrarenal vena cava (IVC) using an established mouse model of stagnant flow venous thrombosis by subtotal IVC ligation. Wild type (WT) mice (C57BL/6 background) treated with recombinant Ang-2 via osmotic pumps and untreated WT mice were used. On day 1, 3, 7, 14 and 21 after surgery animals were anaesthetized and thrombus size was analyzed by sonography. Blood was collected to investigate plasma concentrations of Ang-2 by enzyme-linked-immunosorbent-assay (ELISA) 3, 7, 14 and 21 days after IVC ligation. Additionally, thrombi were harvested and (immuno-)histological analyses performed.
Results: Ang-2 plasma levels were higher in mice treated with Ang-2 compared to control mice (median, 1.43 [IQR, 1.7–2.1] vs 1.19 [1.1–1.3] ng/ml; p=0.003) and immunohistological analyses revealed a higher amount of Ang-2 positive cells in thrombi of Ang-2 treated mice as opposed to control thrombi (5.3 [5.3–13.2] vs 1.9 [2.8–8.6] %; $p<0.014$). Moreover, in immunohistochemistry the phosphorylated Tie2 receptor was almost undetectable in Ang-2 treated thrombi compared to the control thrombi. Sonographic analyses showed that thrombi harvested on day 3, 7 and 14 were larger in mice treated with Ang-2 compared to controls (4.2 [3.7–4.7] vs 2.4 [2.2–2.7] mm^2; $p<0.001$). Importantly, no difference in thrombus size was observed on day 1 prior to osmotic pump implantation. Furthermore, change over time calculation showed delayed thrombus resolution in mice treated with Ang-2 compared to controls at all time points (–5.2 [–25.4 to +14.8] vs –24.4 [–33.0 to –11.1)] %; $p<0.001$). Newly formed microvessels, detected as PECAM-1 positive cells, were less frequently detected in thrombi of Ang-2 treated mice as opposed to control thrombi (0.3 [0.1–0.6] vs 0.6 [0.2–1.5]%, p=0.179). Additionally NIMP-R14, a marker for murine neutrophils (PMN), showed a decreased number of PMN invading the thrombi of Ang-2 treated mice compared to the controls (3.8 [2.8–6.2] vs 6.1 [3.3–9.3]%, p=0.222).
Conclusion: Ang-2 significantly delays thrombus resolution in an established murine model of stagnant flow venous thrombosis. A decreased number of newly formed microvessels and influx of PMNs were assumed to be responsible for misguided venous thrombus resolution and thus suggest a potential contribution of Ang-2 in the transition from acute PE to CTEPH.
Acknowledgement/Funding: German Federal Ministry of Education and Research (BMBF01EO1003 and BMBF 01EO1503)

P225 | BENCH
The hypoxamiR miR-210 modulates interactions between circulating pro-angiogenic cells and endothelial cells

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Background/Introduction: Circulating pro-angiogenic cells (PACs) cooperate with resident endothelial cells in post-ischemic vascularization. MicroRNAs induced by hypoxia (hypoxamiRs) may play a crucial modulatory role in this interaction.
Purpose: To unravel the role of master hypoxamiR miR-210 in biological functions of human PACs.
Methods: PACs were culture-enriched from peripheral blood mononuclear cells of i) healthy donors ii) patients with Type 2 Diabetes Mellitus (T2DM), and iii) T2DM with Critical Limb Ischemia (CLI) (4 per group). We first measured miR-210 expression in PACs under normoxia and hypoxia (RT-qPCR) and then assessed the effect of titrating miR-210 on PAC functions (3 biological replicates), using pre-miR mimic, miR inhibitor, or scramble control (SCR). Specifically, PACs were tested in assays of migration towards SDF-1alpha (transwell chambers), in vitro angiogenesis in co-culture with endothelial cells (HUVECs) on Matrigel, and adhesion to HUVECs. Additionally, the release of "exosome-like" extracellular vesicles (30–100 nM as measured by Nano Sight technology) and their effect on Matrigel angiogenesis assay was assessed. Confirmation of effective modulation of downstream signalling was achieved by measuring the expression of miR-210 target gene Ephrin A3 (EFNA3) by immunostaining.
Results: In vitro hypoxia up-regulated mature and pri-miR-210 expression in healthy donors PACs (40- and 20-fold respectively). Likewise, miR-210 expression was found to be up-regulated in PACs isolated from T2DM+CLI donors compared with not complicated T2DM patients (12 fold). When miR-210 expression was increased via pre-miR mimic transfection, healthy-PACs showed enhanced SDF-1alpha-mediated migratory capacity compared with controls. This effect was blocked by anti-miR-210 and was independent on SDF-1alpha receptor CXCR4 expression levels. In addition, pre-miR-210-PACs adhered more efficiently to HUVECs and supported networking on Matrigel. These responses were not associated to increase in exosome release or to exosome-mediated improvement of HUVEC networking. Of note, PACs derived from T2DM+CLI- patients, bearing higher miR-210 levels were more effective in inducing HUVEC networking on matrigel compared to PACs isolated from T2DM donors, suggesting that diabetic vasculopathy leaves miR-210 pro-angiogenic capacity intact. miR-210 target EFNA3 levels was decreased in pre-miR transfected PACs and increased in anti-miR transfected PACs.
Conclusion(s): miR-210 expression increases in PACs upon in vitro hypoxia and in ischemic patients pointing at a miR-210 role in PACs response to low oxygen. Engineering healthy PACs with miR-210 is associated with enhanced in vitro biological functions similar to highly miR-210 expressing CLI-PACs. In conclusion, miR-210 is key in PAC-endothelial cell interaction and may represent a future target to improve angiogenic response in ischemia via concomitant activation of both endothelial cells and PACs.
Acknowledgement/Funding: Cariplo Foundation Project n. 2013-0887

P226 | BENCH
Rspo2 promotes stem cells differentiation towards smooth muscle cell through LGR5/beta-catenin pathway

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Objectives: R-spondin 2 (Rspo2), one member of R-spondin family which contains four secreted proteins plays an important role in skeletal muscle development. However, the impact of Rspo2 on vascular smooth muscle cells (SMC) differentiation is little known. This study aims at revealing the role and mechanism of Rspo2 on SMC differentiation from embryonic stem cells (ESC).
Methods: A well-established model for studying SMC differentiation from ESC were used in which mouse embryonic stem cells (ES-D3) were seeded on collagen IV-coated flasks and cultured in differentiation medium (DM) for 2, 4, 6, 8

days. Smooth muscle markers, including smooth muscle α-actin (SMαA), SM22, smooth muscle myosin heavy chain (SM-MHC) were detected to insure the successful model by qPCR and western blot. After 3-day pre-differentiattion, ESC were treated with recombinant Rspo2 protein, overexpression or shRNA plasmid for 96 hours, and the mRNA and protein expression of smooth muscle markers were detected. To explore the role of Rspo2 in vivo, 3-day ESC incubated with Rspo2-overexpression plasmid were mixed with 50μl of Matrigel and then subcutaneously injected into C57BL/6J mice. After 12 days, mice were sacrificed and the implants were harvested for immunofluorescence staining, qPCR and western blot. Furthermore, electrophoretic mobility shift assay (EMSA), chromatin immunoprecipitation assay (CHIP) and luciferase reporter assay were performed to investigate the transcriptional activity of SMC related transcription factors, including serum response factor (SRF), myocardin (MYO), myocyte-specific enhancer factor 2C (MEF-2C). Involvement of Rspo2 receptor,LGR/5/6, and β-catenin pathway during Rspo2-induced differentiation were also uncovered by overexpression or inhibition of the respective protein.

Results: Our results showed that Rspo2 were significantly and consistently increased during ESC differentiation towards SMC. Recombinant Rspo2 protein and enforced Rspo2 expression in ESC resulted in up-regulation of smooth muscle markers and transcription factors, while knockdown decreased the expression of these genes. Expectedly, Rspo2 overexpression also promotes SMC differentiation in vivo. Mechanistically, our data showed that Rspo2 could promote SRF biding to SM22 promoter region. Evidence also revealed that one of three Rspo2 receptors, LGR5, was up-regulated while the other two, LGR4 and LGR6, was down-regulated. Silencing of LGR5 inhibited Rspo2-induced SMC differentiation, whereas knockdown of LGR4 had no impact. Finally, activation and inhibition of β-catenin could promote or inhibit SMC differentiation, respectively.

Conclusions: Our findings demonstrate for the first time that Rspo2 plays a positive role during SMC differentiation from ESCs. We confirmed that Rspo2 can upregulate smooth muscle markers at transcription level. We also revealed Rspo2 promote smooth muscle cell differentiation through activation of LGR5 receptor and wnt/β-catenin pathway.

Acknowledgement/Funding: National Natural Scientific Foundation of China Grant (81400224, 91339102,81570249)

P227 | BENCH
MiR-146a inhibition augments angiogenesis and myocardial regeneration

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Background: Myocardial infarction (MI) leads to cardiac remodeling and the development of heart failure. Myocardial remodeling and regeneration rely on myocardial capillary density and thus on effective neovascularization after MI. However, the mechanisms underlying myocardial angiogenesis and specifically the regulation of neovascularization by microRNAs are not well understood.

Methods and results: Here, we showed that the small noncoding RNA microRNA-146a (miR-146a) was upregulated in the ischemic myocardium in C57BL/6 mice following ligation of the left anterior descending (LAD) artery, as well as in the ischemic hind limb following ligation of the femoral artery in a time-dependent manner. In vitro, the overexpression of miR-146a significantly attenuated endothelial cell proliferation and migration, abolished endothelial capillary network formation, and inhibited cell sprouting from endothelial spheroids. In contrast, knockdown of miR-146a significantly augmented endothelial cell proliferation, migration, network formation, and sprouting. Mechanistically, NOX4, NOTCH1, and nRAS were identified and validated as direct targets of miR-146a in endothelial cells according to mRNA and protein expression profiles, as well as luciferase gene reporter assays. In vivo, blocking the upregulation of endothelial miR-146a using specific inhibitors (antagomirs) significantly enhanced angiogenesis and re-vascularization in the infarcted myocardium and the ischemic hind limb. This was accompanied by a significantly reduced myocardial infarct size and preserved cardiac function.

Conclusions: Our findings identify miR-146a as a critical regulator of angiogenesis during myocardial regeneration. Moreover, miR-146a may represent an attractive target for future therapeutic interventions for the treatment of ischemic heart disease.

P228 | BENCH
Early atherosclerosis in a chronic proteasome inhibition model lacks association with vasa vasorum neovascularisation

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Background: Neovascularisation of the vasa vasorum (VV) is noted in the early stage of atherosclerosis; however, its pathophysiological role remains unclear. Proteasome inhibition has been shown to yield anti-angiogenic effects and to induce and aggravate atherosclerosis in normal (N) and hypercholesterolemic (HC) pigs.

Purpose: To test the hypothesis that early atherogenesis develops without concomitant VV neovascularization in the setting of proteasome inhibitor treatment.

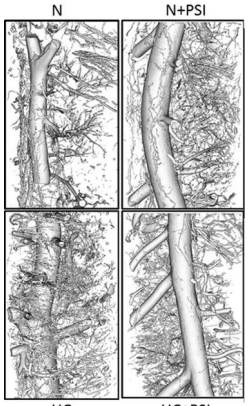
Methods: Female pigs (n=4 per group) were randomized to either N or HC group without or with additional treatment of the proteasome inhibitor MLN-273 (0.08 mg/kg SQ twice weekly, N+PSI or HC+PSI). The coronary arteries were harvested after twelve weeks and processed for micro-CT imaging and tissue analyses.

Results: As presented in the table, compared with N, VV density was increased in HC but not N+PSI or HC+PSI (2.8±0.2 vs. 5.0±0.9, 2.5±0.8, and 2.1±0.1 n/mm^2, $p<0.05$; figure) as was vascular-area-fraction (0.64±0.13 vs. 1.80±0.34, 0.68±0.21, and 0.60±0.07%, $p<0.01$). Compared with N, the percentage of Ki-67-positive VV tended to be higher in HC but not in N+PSI or HC+PSI (5.0±1.4 vs. 16.4±4.2, 13.9±9.2, and 1.0±0.4%, $p<0.01$). HIF-1α expression in the outer media, compared with N, was higher in HC, N+PSI, and HC+PSI (45.0±3.1 vs. 65.9±3.3, 74.8±4.7, and 77.8±3.0%, $p<0.01$ for HC vs. HC+PSI). VEGF staining per field in the adventitia, compared to N, was increased in HC, but not in N+PSI and HC+PSI (7.08±2.14 vs. 24.76±4.34, 2.52±1.70, and 1.03±0.54%, $p<0.01$).

Micro-CT and immunohistochemistry data

	N	N+PSI	HC	HC+PSI
VV-density [n/mm^2]	2.83±0.20	2.51±0.82	5.03±0.87*	2.12±0.13
VV-vascular-area-fraction [%]	0.64±0.13	0.68±0.21	1.80±0.34#	0.60±0.07
n(Ki-67+)/n(vWF+) [%]	4.96±1.36	13.86±9.24	16.40±4.22$	1.03±0.36
Outer media-SMC-nuclei HIF-1α+/all nuclei [%]	45.02±3.10&	74.81±4.70	65.89±3.29h	77.79±2.95
Adventitial VEGF [% staining per field of view]	7.08±2.14	2.52±1.70	24.76±4.34#	1.03±0.54

*$p<0.05$ vs. N, N+PSI, HC+PSI; #$p<0.01$ vs. N, N+PSI, HC+PSI; $sp<0.01$ vs. N; &$p<0.05$ vs. HC+PSI; h$p<0.01$ vs. HC+PSI.



Micro-CT reconstructions

Conclusions: The current study shows that chronic proteasome inhibition prevents the increase in VV density in HC pigs but does not cause a significant decrease in VV density in N pigs. The underlying pharmaceutical mechanism seems to include the HIF-1α-VEGF-pathway.

As chronic proteasome inhibition was shown before to induce and aggravate atherosclerosis in N and HC pigs, the current findings would suggest that the early stage of atherosclerosis did not necessarily require VV neovascularization for its development.

Acknowledgement/Funding: National Institutes of Health grants; Mayo Foundation; Mayo Stiftung

PROGNOSTICATION IN HEART FAILURE

P229 | BEDSIDE
Predicting sudden death and pump failure death in patients with heart failure and reduced ejection fraction: competing risk regression analyses of the PARADIGM-HF trial

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Background: Sudden death (SD) and pump failure death (PFD) are the two leading causes of death in patients with HF-REF. Identifying those at higher risk of each type of death may allow better targeting of individuals for relevant device therapy (e.g. an ICD or a VAD).

Methods: We analysed 7156 patients with HF-REF enrolled in the PARADIGM-HF trial, excluding 1243 patients having an ICD or CRT-D. 58 baseline variables were examined using backward stepwise Fine-Gray regression to separately identify predictors for SD and PFD, counting other deaths as competing risks. Quintiles of risk scores derived from the final models were created to assess model calibration. Model discrimination was assessed using Harrell's C statistic.

Results: There were 525 SD and 261 PFD over a median follow-up of 27 months.

The model for SD and for PFD included 10 and 13 predictors with Harrell's C of 0.68 (95% CI: 0.66–0.71) and 0.80 (95% CI: 0.77–0.83), respectively. The observed and predicted incidences were similar in each quintile at 3 years, with a gradient of predicted incidences across the risk quintiles in each model. The SD model predicted the lowest- and highest-risk quintiles with a median incidence of 3.4% and 18.0% at 3 years respectively. For PFD these were: lowest (0.9%) and highest (13.1%) at 3 years.

Variable	sHR (95% CI)	p value	χ^2
Sudden death			
NT pro BNP 0–6000 pg/ml, per 100 pg/ml	1.018 (1.014–1.022)	<0.001	73.4
Myocardial infarction history	1.80 (1.48–2.19)	<0.001	34.2
Asian race	1.78 (1.46–2.16)	<0.001	32.5
CABG or PCI	0.60 (0.48–0.77)	<0.001	17.0
QRS duration 90–120 msec, per 1 msec	1.014 (1.007–1.020)	<0.001	14.8
Black race	1.99 (1.37–2.88)	<0.001	13.0
NYHA class III	1.38 (1.13–1.67)	0.001	10.5
Male	1.42 (1.13–1.79)	0.003	8.9
Cancer history	0.37 (0.18–0.74)	0.005	7.8
Left ventricular hypertrophy on ECG	1.27 (1.04–1.55)	0.02	5.4
Pump failure death			
NT pro BNP 900–6000 pg/ml, per 100 pg/ml	1.03 (1.02–1.03)	<0.001	56.0
Chloride 90–106 mmol/l, per 1 mmol/l	0.91 (0.88–0.94)	<0.001	25.9
HF duration >5 years vs. ≤1 year	2.60 (1.79–3.76)	<0.001	25.4
Albumin 30–50 g/l, per 1 g/l	0.92 (0.89–0.96)	<0.001	18.1
Ischaemic aetiology	0.65 (0.50–0.83)	0.001	11.5
Creatinine 1.0–2.5 mg/dl, per 0.1 mg/dl	1.08 (1.03–1.12)	0.001	10.8
Systolic BP up to 130 mmHg, per 1 mmHg	0.98 (0.97–0.99)	0.002	10.0
HF duration >1–5 years vs. ≤1year	1.73 (1.21–2.48)	0.003	8.9
Right bundle branch block on ECG	1.72 (1.17–2.54)	0.006	7.7
Haemoglobin 90–140 g/L, per 1 g/L	0.98 (0.97–1.00)	0.008	7.1
Pacemaker implanted	1.57 (1.08–2.29)	0.019	5.5
Ejection fraction up to 40%, per 1%	0.98 (0.96–1.00)	0.022	5.2
NYHA class III	1.37 (1.04–1.80)	0.027	4.9

Conclusions: Our models separately identified patients at risk of SD and PFD which may help decisions about device implantation.
Acknowledgement/Funding: Novartis Pharmaceuticals

P230 | BEDSIDE
Low serum potassium is associated with worse outcomes: Insights from the PARADIGM-HF trial

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Background: Although hyperkalaemia limiting the use of evidence-based therapies has been a recent focus in heart failure with reduced ejection fraction (HFREF), hypokalaemia may also be a concern in these patients.
Purpose: The aim of this study was to examine the relationship between serum potassium concentration (K^+) and outcomes in the 8399 HFREF patients randomized in PARADIGM-HF (patients with hyperkalaemia during the trial run-in were excluded).
Methods: The association between K^+ and the primary composite outcome of cardiovascular (CV) death or heart failure (HF) hospitalization, its components and all-cause mortality was examined using the following K^+ categories: low <3.5, low-normal 3.5–3.9, normal 4.0–4.7, high-above normal 4.8–5.4, and high >5.5 mmol/L, adjusted as described below. The association between K^+ and these outcomes was also examined using K^+ as a continuous time-updated covariate, modelled as a restricted cubic spline adjusted for baseline prognostic variables and time-updated eGFR (see Figure legend).
Results: Low K^+ was associated with a higher risk of the primary composite outcome (adjusted HR compared with normal K^+=2.04 [95% CI 1.53–2.71]), CV death (2.34 [1.67–3.26], P<0.001), HF hospitalization (2.33 [1.64–3.32], P<0.001) and all-cause mortality (2.32 [1.70–3.16], P<0.001). Low-normal K^+ was also associated with a higher risk of CV death or HF hospitalization (HR=1.24 [1.07–1.58], P=0.006) and all-cause mortality (HR=1.22 [1.02–1.46], P=0.031). Analysis of K^+ as a continuous variable gave similar results (Figure). In the carefully selected patients in PARADIGM-HF, higher K^+ was associated with worse outcomes in crude models but not after adjusting for other prognostic variables, including eGFR.
Conclusion: Low K^+, even in the normal range, was associated with worse outcomes after multivariable adjustment in patients with HFREF.

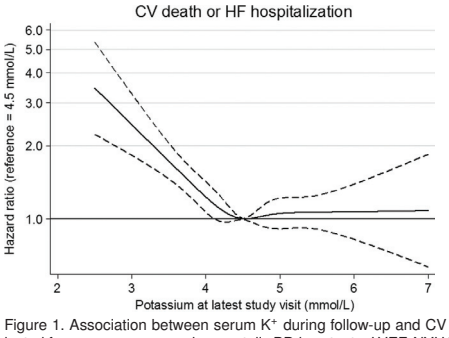

Figure 1. Association between serum K^+ during follow-up and CV death/HF hospitalization. Adjusted for age, sex, race, region, systolic BP, heart rate, LVEF, NYHA class, history of HF hospitalization, duration of HF, history of diabetes, prior MI, prior stroke, atrial fibrillation, bundle branch block on ECG, haemoglobin, sodium, albumin, BMI, log NT-proBNP, randomized treatment, diuretic and MRA use at baseline, and eGFR at latest study visit.

P231 | BEDSIDE
Impact of combined atrial fibrillation and heart failure on mortality: 14-year naturalistic follow-up study

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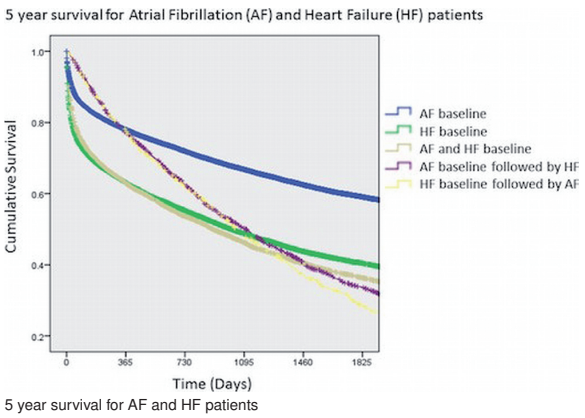
Background: Atrial fibrillation (AF) and heart failure (HF) frequently co-exist conferring considerable morbidity and mortality, yet current treatment options remain limited, creating a paradox whereby those most in need have the fewest therapeutic choices.
Purpose: To investigate the association between HF and AF and their impact on mortality from a large 14-year naturalistic follow-up study.
Methods: Anonymous data of adult patients aged ≥18 with all types of HF and AF admitted to several hospitals in the North of England between 2000 and 2013 was obtained and processed using the ACALM study protocol. ACALM uses the ICD-10 and OPCS-4 coding systems to identify patients. Unadjusted analyses were performed comparing mortality between patients with HF, AF and combined HF and AF at baseline and their development during follow-up.
Results: At baseline, of 929,552 adult patients 29,164 (3.1%) had AF, 19,474 (2.1%) had HF, and 5,728 (0.6%) had both HF and AF. Patients with combined AF and HF at baseline had increased mortality compared to those with baseline AF (RR 1.39, 95% CI 1.28–1.50, p<0.0001) but not baseline HF (RR 1.06, 95% CI 0.99–1.13, p=0.09). Of those with AF at baseline, 1,647 (5.6%) developed HF during follow-up, and of those with HF at baseline, 824 (4.2%) developed AF during follow-up. Patients with combined HF and AF at baseline had reduced mortality compared to those with AF at baseline that developed HF (RR 0.94, 95% CI 0.89–0.99, p=0.04), and patients with HF at baseline that developed AF (RR 0.86, 95% CI 0.82–0.91, p<0.0001).

Demographics of AF and HF groups

	AF baseline	HF baseline	AF and HF baseline	AF baseline followed by HF	HF baseline followed by AF
n	29164	19474	5728	1647	824
Age ± SD	74±13	73±14	77±12	77±11	77±11
Male, %	52.4	51.0	49.8	48.0	49.3
Caucasian, %	87.6	82.9	86.8	92.2	90.2
South Asian, %	1.7	4.0	1.8	1.6	2.4
Afro-Caribbean, %	0.8	1.6	1.2	0.4	0.6
Other, %	1.4	1.8	1.5	1.0	0.6
Crude mortality rate per 1000	485	636	672	715	778
Mean survival (days)	722	631	692	880	922

AF, atrial fibrillation; HF, heart failure; SD, standard deviation.



5 year survival for AF and HF patients

Conclusion: Concomitant AF and HF is associated with increased mortality, ir-

respective of which disease develops first. In light of limited current treatment for these patients, future therapies to specifically target the combined HF and AF group are required.

P232 | BEDSIDE
Predictors of 30-day mortality in patients with acute heart failure at emergency department admission: derivation and validation of the MEESSI-AHF scale

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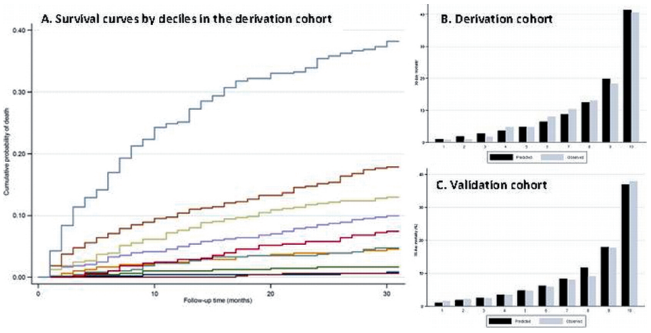
Background: For patients with acute heart failure (AHF), further insight is needed on how best to predict short-term prognosis and identify who is at high (or low) risk of adverse outcome.
Purpose: To develop a reliable risk scoring for 30-day mortality from data readily available on at emergency department (ED) admission.
Methods: MEESSI-AHF (Multiple Estimation of risk based on the Emergency department Spanish Score In AHF) is a risk score based on a registry of ED admissions for AHF in 34 Spanish hospitals. Two cohorts of 4867 patients in 2009 and 2011–12 were used to develop a risk model based on 89 candidate variables recorded on each patient. A risk score for 30-day mortality was developed using multiple logistic regression (forward stepwise variable selection). The risk score was then validated on a further cohort of 3229 patients in 2014.
Results: 500 patients (10.3%) died within 30 days. We identified 13 highly significant independent predictors of 30-day mortality, all recorded at ED, which were (ordered by weight in the model): Barthel index, systolic blood pressure, age, NYHA class IV, NT-proBNP, positive levels of troponin, respiratory rate, low output symptoms, oxygen saturation, creatinine, episode associated with acute coronary syndrome, potassium and hypertrophy at ECG. When combined into a new risk score, excellent discrimination was achieved (c-statistics = 0.809; 95% CI 0.789–0.828). There was a steep gradient in 30-day mortality across risk groups: over 35% mortality for the top decile and around 1% in the bottom quintile (see Figure). Application of the risk score to 2014 validation cohort produced very similar findings (c-statistics = 0.794; 95% CI 0.766–0.822) (see Figure).



30-day mortality

Conclusion: We describe a new user-friendly risk score system to reliably identify AHF patients at high (and low) risk of dying within 30 days. This may guide appropriate patient management strategies, especially identifying which low-risk patients are suitable for direct ED discharge and which high-risk patients have a foreseeable adverse short-term outcome.
Acknowledgement/Funding: Spanish Ministry of Health (Instituto de Salud Carlos III; grants PI15/01019, PI15/00773, PI11/01021) and Fundacio La Marató de TV3 (20152510)

P233 | BEDSIDE
The impact of T-lymphocytes on atrial fibrillation and mortality in patients with chronic heart failure

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Background: Atrial fibrillation (AF) represents the most common cardiac arrhythmia within the Western societies. Especially in patients with chronic heart failure (CHF) the development of AF represents a severe complication resulting in hemodynamic instability. However the exact pathophysiology in the development of AF in this highly vulnerable patient collective is still incompletely understood. While a genetic predisposition is postulated as a trigger of AF, data on the immunological aspect in the development on AF and its impact on the patient outcome remain scarce.
Methods: Therefore we prospectively enrolled 112 patients with CHF defined by New York Heart Association (NYHA) functional class > II and left ventricular ejection fraction (LVEF) <40%. Patients were stratified in two subgroups according to patients developing AF (n=50) and patients developing no AF (n=62). Cells from fresh heparinized blood were stained and analyzed using BD FACS Canto II flow cytometry. Cox regression hazard analysis was used to assess the influence of T Cells on survival. The multivariate model was adjusted for age, gender, type of CHF, LVEF and nt-proBNP.
Results: Comparing AF to non-AF patients we found a significantly higher total lymphocyte count (p=0.005), a significantly higher proportion of CD3+ T cells (p=0.003), and a higher fraction of CD4+ cells (p=0.007) in the AF subgroup. More specifically, there was a significantly higher number of cytotoxic T cells characterized by the loss of CD28 within CD4 T cells (p=0.035) detectable in individuals with AF. Interestingly we were able to demonstrate that the number of regulatory T cells was significantly lower (p<0.001) in patients with AF. After a mean follow-up time of 4.5 years 32 (28.6%) patients died due to cardiovascular causes. The loss of CD28 within CD4+ T cells was significantly associated with cardiovascular mortality in patients with AF, with an adjusted HR per one standard deviation (1-SD) of 1.59 (95% CI 1.13–2.24; p=0.008), but not in patients free of AF with an adjusted HR per 1-SD of 1.27 (95% CI 0.86–1.87; p=0.216). Interaction analysis of the predictive value of CD4+CD28- T cells with AF showed borderline significance (p=0.062).

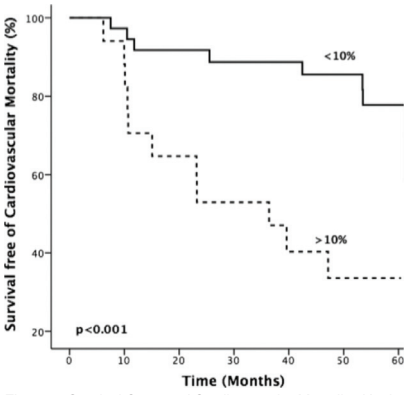

Figure 1. Survival Curves of Cardiovascular Mortality. Kaplan-Meier plots showing cardiovascular mortality in patients with atrial fibrillation according to CD4+CD28- frequencies in CD4+ cells, compared using log-rank test.

Conclusion: Our results might indicate a potential influence of T cells in the pathogenesis of atrial fibrillation. Specifically, cytotoxic CD4 T cells characterized by the loss of CD28 were associated with cardiovascular mortality in CHF-patients with AF.

P234 | BENCH
Galectin 3 is markedly elevated in severe heart failure and predicts improvement in LV volumes post cardiac resynchronisation therapy

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Background/Introduction: Cardiac Resynchronisation Therapy (CRT) is commonly used in the management of patients with chronic systolic heart failure (CHF). Although CRT will improve symptoms and survival in most patients, about one-third of CRT recipients do not obtain clinical benefit from the therapy and are considered clinical non-responders. The exact mechanisms underlying this phenomenon are poorly understood and there are no well-established biomarkers to predict the response to CRT. It has been suggested that fibrosis, as occurs in most forms of CHF, may play a role in determining the response to CRT.
Galectin 3 is a soluble β-galactoside-binding lectin that has regulatory roles in fibrosis, inflammation and tissue repair. Several recent clinical studies have reported an association between circulating galectin 3 levels and cardiac remodeling as well as adverse clinical outcomes in patients with CHF. However, the association between baseline galectin 3 levels and response to CRT in severe CHF has not been established.
Purpose: To investigate the relationship between: i) galectin-3 levels and presence of CHF vs age-matched healthy population; and ii) baseline plasma galectin-3 levels and reverse remodeling in patients undergoing CRT implantation.
Methods and results: Plasma Gal-3 levels were compared in 67 patients, age (68±6 yrs), without existing cardiovascular disease or previous antihypertensive therapy and 28 patients (aged 71.2±9.4) with predominantly severe CHF (70% NYHA class III or IV) and planned CRT irrespective of the aetiology of heart failure. Transthoracic echocardiogram (TTE) and blood collection for routine biochemistry, NT pro-BNP and galectin-3 levels were performed in the healthy cohort and in the severe CHF cohort prior to and 6 months post-CRT implantation. There was a significant increase in Gal-3 levels in patients with CHF vs healthy ageing (Figure 1A). However, there was no relationship between baseline Gal-3 levels and LV volumes (left ventricular end systolic volumes (LVESV) or end di-

astolic volumes (LVEDV) in either the healthy ageing cohort or those with CHF. Baseline Gal-3 levels correlated with significant improvement in LVESV (p=0.01) and LVEDV (p=0.02) in CHF patients post CRT (Figure 1B and 1C). On multivariate analyses, galectin 3 remained the only independent predictor of the improvements in LVESV (p=0.015) and LVEDV (p=0.02) post-CRT after adjustment for age, gender, NT pro-BNP and NYHA class.

Figure 1A:

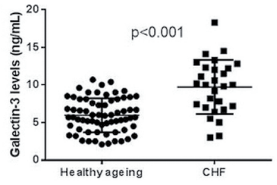


Figure 1B:

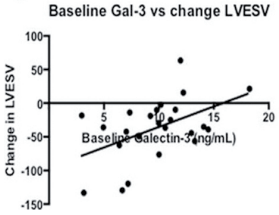
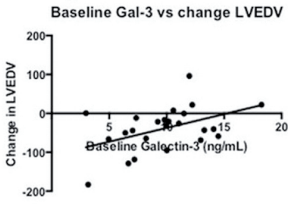


Figure 1C:



Conclusion: Plasma galectin 3 is a promising biomarker of improvement of LV volumes in response to CRT. It has discriminatory potential between patients with severe symptomatic CHF and patients with normal physiological change in LV volumes.

Acknowledgement/Funding: Supported by THRF fellowship

P235 | BEDSIDE

Low appendicular skeletal muscle mass is associated with adverse outcomes in patients with acute decompensated heart failure

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Introduction: Heart failure (HF) is a clinical syndrome associated with diverse metabolic disturbances. Recent studies suggest that failing heart through secretion of soluble myostatin may induce skeletal muscle wasting in HF patients and skeletal muscle plays an important role in pathogenesis of exercise intolerance in patients with chronic HF. The prevalence of sarcopenia is reported as 5–13% in general 60–70year-olds and as about 20% in patients with chronic HF. However, the clinical significance of skeletal muscle mass in patients with acute decompensated HF (ADHF) remains unclear.

Purpose: The purpose of this study was to investigate that low appendicular skeletal muscle mass could predict the occurrence of future cardiovascular (CV) events in patients with ADHF.

Methods: We assessed lean body mass by dual energy X-ray absorptiometry in 108 patients with ADHF (age 72±11, left ventricular ejection fraction (LVEF) 37±15%, B-type natriuretic peptide (BNP) levels on admission 732 [394–1315] pg/ml). Low appendicular skeletal muscle mass index (ASMI, appendicular skeletal muscle mass/height2) was defined according to the Asia Working Group for Sarcopenia criteria (<7.0kg/m^2 in male, <5.4kg/m^2 in female). ADHF patients were followed until occurring CV events (CV death, nonfatal myocardial infarction, ischemic stroke, unstable angina, HF re-hospitalization, or coronary revascularization).

Results: ASMI significantly correlated with age (r=-0.43, P<0.001), male sex (r=0.50, P<0.001), body mass index (r=0.59, P<0.001), systolic blood pressure on admission (r=0.18, P=0.05), and BNP levels on admission (r=-0.37, P=0.04). ADHF patients with low ASMI (n=61, 56%) had higher BNP levels (841 [530–1661] versus 504 [275–892], p=0.001) and higher rate of clinical scenario 2–3 (46% versus 15%, p=0.002) than those with normal ASMI. 48 patients developed CV events (median follow-up, 17 months). Kaplan-Meier analysis demonstrated a significantly higher probability of CV events in the low ASMI group than those in the normal ASMI group (57% versus 28%, log-rank test, P=0.003). Multivariate Cox hazard analysis including systolic blood pressure, LVEF, and BNP levels on admission demonstrated that diabetes mellitus (hazard ratio 2.04, 95%-confidence interval 1.15–3.62, P=0.02), hemoglobin levels (hazard ratio 0.89, 95%-confidence interval 0.79–0.99, P=0.04), and low ASMI (hazard ratio 2.50, 95%-confidence interval 1.31–4.77, P=0.006) were independently correlated with the future CV events in patients with ADHF.

Conclusions: Low ASMI could predict the future CV events in patients with ADHF, irrespective of LV systolic function and other clinical profile. Skeletal muscle plays a crucial role in the pathogenesis of ADHF.

INTERPLAY BETWEEN EXERCISE AND CARDIAC PATHOLOGY

P236 | BENCH

Characteristic distinction of energy-dependent hemodynamics in physiological and pathological left ventricular hypertrophy is related to different myocardial expression of mithocondrial regulators

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Background and purpose: Left ventricular (LV) hypertrophy is a physiological (athlete's heart) or pathological response of LV myocardium to increased cardiac load. To date, a direct comparison of functional consequences of PhyH and PaH and possible underpinning mechanisms is missing. We aimed at comparing hemodynamic alterations in well established rat models of physiological (PhyH) and pathological hypertrophy (PaH) by using LV pressure-volume analysis and investigating underlying molecular mechanisms (oxidative stress, inflammatory markers, mitochondrial regulators).

Methods: PhyH and PaH were induced in rats by swim training and by abdominal aortic banding, respectively. Morphology of the heart was investigated by echocardiography. Detailed characterization of cardiac function was completed by LV pressure-volume analysis. In addition histological and molecular biological (gene expression analysis) measurements were performed. All data were normalized to the corresponding control group.

Results: Echocardiography revealed myocardial hypertrophy of similar degree in both models (LV mass index: +21.7±2.1% PhyH vs. +27.3±3.3% PaH, n.s.), which was confirmed by post-mortem heart weight data. In aortic-banded rats we detected subendocardial fibrosis. Reactivation of fetal gene program could be observed only in PaH model. PhyH was associated with increased stroke volume, whereas unaltered stroke volume were detected in PaH along with markedly elevated end-systolic pressure values. Sensitive indices of LV contractility were increased in both models, in parallel with the degree of hypertrophy. Active relaxation was ameliorated in athlete's heart, while it showed marked impairment in PaH (time constant of LV pressure decay (τ): -7.7±2.6% PhyH vs. +37.0±11.1% PaH, p<0.01). Mechanical efficiency and ventriculo-arterial coupling were improved in PhyH, whereas remained unchanged in PaH (mechanical efficiency: +20.8±4.7% PhyH vs. +4.7±4.9% PaH, p<0.05). Myocardial gene expression of regulators related to mitochondrial biogenesis showed marked differences between PaH and PhyH (peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α): +19.1±10.3% PhyH vs. -37.8±7.2% PaH, p<0.01; nuclear respiratory factor 1 (NRF1): -4.5±2.8% PhyH vs. -27.4±7.6% PaH, p<0.05). Alterations in myocardial expression of oxidative stress and inflammatory markers did not differ between the two models.

Conclusions: We provided the first comparative hemodynamic characterization of PhyH and compensated PaH in relevant rodent models. Increased LV contractility could be observed in both types of LV hypertrophy, characteristic distinction was detected in energy-dependent diastolic function (active relaxation) and mechanoenergetics (mechanical efficiency), which might be explained by differences in expression of key regulators related to mitochondrial biogenesis.

Acknowledgement/Funding: Hungarian Scientific Research Fund (OTKA 105555) to Bela Merkely

P237 | BEDSIDE

The effect of exercise on the aortic root diameter in young elite athletes with bicuspid aortic valve disease

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Introduction: Bicuspid aortic valve (BAV) disease is one of the most common congenital cardiac malformations (0.9- 2%). BAV can lead to valve dysfunction and progressive aortic dilation. There is a paucity of data pertaining to the natural course of aortic root size in young athletes with BAV disease, in whom the haemodynamic stress of regular and intense exercise may lead to early acceleration of aortic root dilation.

Purpose: To explore the progression of aortic root dilation in young professional soccer players with BAV disease.

Methods: 20 consecutive professional soccer players with BAV (BA) diagnosed on routine transthoracic 2D echocardiogram through pre-participation screening, were compared with 24 age-matched non-athletes with BAV. A third group comprising 22 consecutive healthy athletes with a normal tricuspid aortic valve was used as a comparison. The aortic root diameter at the level of the sinuses of Valsalva (absolute and indexed for body surface area, BSA) was documented for all subjects at baseline and on ≥1 subsequent follow up echocardiogram.

Results: All subjects were males with the mean ages at baseline for BAV athletes and BAV non-athletes were 24.3±12.1 years and 30.3±8.2 years respectively. Healthy athletes with a tricuspid aortic valve were aged 26±7.2 years. After indexing for body surface area, BAV non-athletes had the largest baseline aortic root diameter of the 3 groups (19.6±1.8 mm vs. BAV athletes 16.8±2.3 mm, p=0.013; vs athletes with a tricuspid aortic valve 15.6. ± 1.8 mm, p<0.001). There were no differences in absolute aortic root diameters between the 3 groups at

baseline (BAV athletes 33.6±6.0 mm, BAV non-athletes 33.2±6.9 mm, athletes with a tricuspid aortic valve 29.5±3.5 mm, p = NS).
After a mean follow-up of 7.8±1.9 years, the healthy athletes with tricuspid aortic valves continued to have the smallest aortic root diameter (indexed for BSA) compared to those with BAV (15.9±1.5 mm vs. athletes with BAV 18±1.2 mm, p=0.01) and non-athletes with BAV (18.4±2.4 mm, p=0.003).
Athletes with BAV demonstrated an indexed aortic root increment of 0.8±0.3 mm/year. However, no significant difference was observed when comparing the trends of change within non-athletes with BAV disease and athletes with a tricuspid aortic valve.
Conclusion: Our findings do not support that exercise alone contributed to aortic root dilation in young athletes with BAV disease during our period of observation. Exercise did not significantly increase aortic root diameter in any of our three groups. Other factors such as genetic predisposition, maladaptive cell-matrix remodelling processes and haemodynamic and biomechanical pertubations are thought to account for the natural history of aortopathy associated with bicuspid aortic valve disease. Such factors have age-related penetrance and these time-dependent experssions support regular surveillance with cardiac imaging.

P238 | BEDSIDE
Non-ischemic left ventricular scar as a substrate of life-threatening ventricular arrhythmias and sudden cardiac death in competitive athletes

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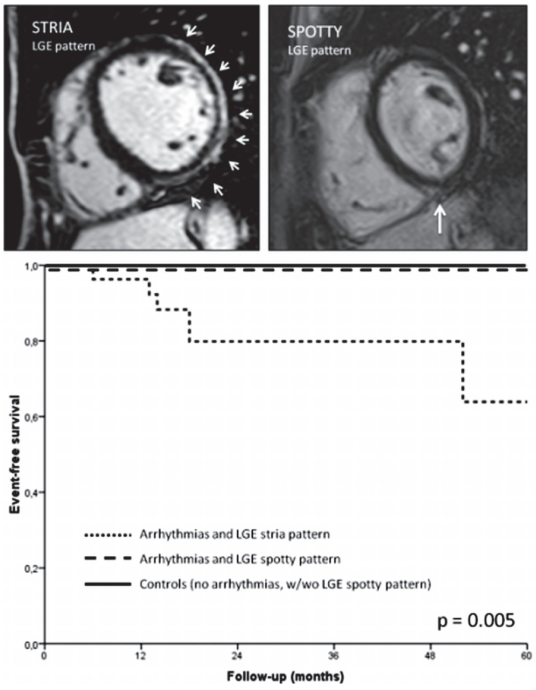
Background: The clinical profile and arrhythmic outcome of competitive athletes with isolated non-ischemic left ventricular (LV) scar as evidenced by contrast-enhanced cardiac magnetic resonance (CE-CMR) remains to be elucidated.
Aims: To characterize the clinical and imaging profile and the arrhythmic outcome of a cohort of competitive athletes showing isolated non-ischemic LGE on CE-CMR, which was performed for clinical evaluation of apparently idiopathic ventricular arrhythmias.
Methods: We enrolled 35 competitive athletes (80% males, age range 14–48 years) with frequent or complex ventricular arrhythmias and isolated LV subepicardial/midmyocardial late-gadolinium-enhancement (LGE) on CE-CMR; a control group included 40 healthy athletes matched for age and gender.The pattern of LGE distribution and morphology was characterized as either epicardial/midmyocardial "stria" or patchy/junctional "spotty". If more than one pattern was present, the distribution was characterized on the basis of the predominant pattern.
Results: A LGE "stria" pattern with subepicardial/midmyocardial distribution, mostly involving the lateral LV wall, was observed in 27/35 (77%) athletes with arrhythmias versus 0 controls (p<0.001), while a "spotty" LGE localized at the junction of the right ventricle to the interventricular septum in 11 (31%) and 10 (25%), respectively (p=0.52). All 27 athletes with a LGE "stria" pattern showed ventricular arrhythmias with a predominant right-bundle branch block morphology, 48% (13/27) ECG abnormalities mostly consisting of low QRS voltages in limb leads and T-wave inversion in infero-lateral leads, and 19% (5/27) echocardiographic hypokinesis of the lateral LV wall. During a mean follow-up of 35±22 months, 6/27 (22%) athletes with a LGE "stria" pattern experienced malignant arrhythmic events such as appropriate ICD shock (N=4), sustained ventricular tachycardia (N=1), or sudden death (N=1), compared with none of those with junctional LGE "spotty" pattern (p=0.005).
Conclusions: The LGE "stria" with a subepicardial/midmyocardial wall distribution could act as a substrate for life-threatening arrhythmias and sudden death in the athlete. Because of its peculiar non-transmural location, the LV scar is often echocardiographically invisible and may be only detectable by CE-CMR. The junctional LGE "spotty" pattern showed a similar prevalence in athletes with and without arrhythmias and was associated with an uneventful outcome.
Acknowledgement/Funding: This study was funded by the TRANSAC Strategic Research Grant CPDA133979/13, University of Padua, Italy; Target Projects 331/12, Regional Health Syste



Arrhythmic follow-up and LGE pattern

P239 | BEDSIDE
The impact of ECG interpretation variation in pre-participation screening of young athletes

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Introduction: Electrocardiogram (ECG) screening of young athletes is recommended by several international sporting bodies. However, the accuracy of the ECG is highly dependent on individual interpretation, and an important concern of the ECG as a screening tool is the variation of ECG interpretation especially in inexperienced hands. Contemporary ECG interpretation criteria have reduced false positive rates and cost, but their impact on variability of ECG interpretation is not known. This study evaluated the variation in interpretation of athletes' ECG's between cardiologists with and without experience in ECG screening, the impact of the 3 main ECG interpretation guidelines on variation, and the financial impact of variation in ECG interpretation.
Methods: 8 cardiologists (4 with ≥3 years' experience and 4 with no experience of ECG screening of athletes) each reported anonymised ECG's of 400 asymptomatic athletes consecutively evaluated through a screening program in 2012, and were blinded to clinical details other than age, gender and ethnicity. They were instructed to assign the ECG's as normal or abnormal based on the 2010 European Society of Cardiology (ESC), Seattle (SC) and refined (RC) criteria. All cardiologists were also required to list any additional investigations they would arrange for athletes with abnormal ECG's,the cost of which were calculated based on the UK National Health Service tariffs.
Results: Athletes were aged 20±5 years (14–35 years) and were predominantly male (71%) and Caucasian (79%). 11% were Afro-Caribbean.18 sports were represented. The percentage of agreement overall for each criteria is reported in Figure 1. The degree of agreement for abnormal ECG's between experienced cardiologists was moderate for all criteria: κ=0.42 (ESC), 0.59 (SC) and 0.51 (RC). For inexperienced cardiologists, the agreement was poor to borderline moderate: κ=0.15 (ESC), 0.25 (SC) and 0.41 (RC). Further investigations were requested for 8% (4–11%) and 15% (8–19%) of ECG's by experienced and inexperienced cardiologists respectively. The agreement on ECG's requiring further investigation for experienced and inexperienced cardiologists was κ=0.47 and κ=0.22 respectively. The cost of further investigations was €30 (€15–52) per athlete for experienced cardiologists and €88 (€43–119) for inexperienced cardiologists. One (0.3%) athlete with cardiac disease (long QT syndrome) was identified by all cardiologists irrespective of experience and/or ECG criteria.

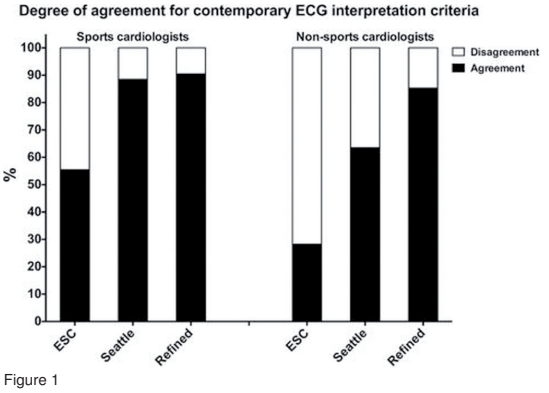

Figure 1

Conclusion: A higher degree of agreement in ECG interpretation is observed with more experienced reporters. Contemporary ECG screening criteria reduces the interpretation gap between experienced and inexperienced cardiologists, although there remains a high degree of variability in ECG interpretation of abnormality irrespective of experience. ECG screening programs should be aware of the significant impact of inter-observer variability on resource management and costs of screening.

P240 | BENCH
Impact of physical activity on the risk of cardiovascular disease in middle-aged and older adults

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Background: There is broad consensus that regular physical activity (PA) yields major health benefits. However, current guidelines on PA are mainly aimed at middle-aged adults. Little is known whether PA also translates into cardiovascular health benefits in elderly.
Purpose: To investigate the impact of different levels of PA on the risk of cardiovascular disease (CVD) in elderly.
Methods: The relationship between age categories, PA and risk of CVD events was assessed in the EPIC-Norfolk prospective population study. Cox proportional hazards models were used to analyze the association between PA levels and time to CVD events in age categories <55, 55–65, and >65 years. Interaction between age categories and PA levels was assessed.
Results: The study compromised 24,502 study participants aged 39 -79. A total of 3230 CVD events occurred during 275,556 person-years follow-up. Among individuals aged >65 years, HR for CVD were 0.81 (95% CI 0.72–0.92), 0.78 (95% CI 0.67–0.90) and 0.80 (95% CI 0.67–0.94) in moderately inactive, moderately active and active people, respectively, compared to inactive people. In age category 55–65 years, similar associations were observed. Among people <55 years, the associations were directionally similar, but not statistically significant (table). The interaction term between PA levels and age categories was not significant (p=0.85).

The risk of cardiovascular events

PA		Inactive	Moderately inactive	Moderately active	Active
Age <55	HR	1.00 (ref)	0.88	0.89	0.91
	95% CI		0.67–1.16	0.67–1.18	0.68–1.21
	p-value		0.37	0.43	0.50
Age 55–65	HR	1.00 (ref)	0.78	0.90	0.78
	95% CI		0.65–0.94	0.75–1.08	0.63–0.96
	p-value		0.01	0.26	0.02
Age >65	HR	1.00 (ref)	0.81	0.78	0.80
	95% CI		0.72–0.92	0.67–0.90	0.67–0.94
	p-value		0.001	0.001	0.008

HR = hazard ratio; PA = physical activity.

Conclusion: As expected, there was an inverse association between PA and the risk of CVD in elderly >65 years and middle-aged individuals. Even moderately inactive people are at lower CVD risk than inactive people, suggesting that even minimal PA is better than none at all.
Acknowledgement/Funding: The EPIC-Norfolk Study is funded by Cancer Research UK grant number 14136 and the Medical Research Council grant number G1000143.

P241 | BEDSIDE
Exercise intolerance can explain the obesity paradox in patients with systolic heart failure data from the mecki score research group

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Background: Obesity has been found to be protective in heart failure (HF), a finding leading to the concept of an obesity paradox. We hypothesised that a preserved cardiorespiratory fitness in obese HF patients may affect the relationship between survival and body mass index (BMI) and explain the obesity paradox in HF.
Methods and results: 4623 systolic HF patients (Left ventricular ejection fraction, [LVEF], 31.5±9.5%, body mass index [BMI] 26.2±3.6 kg/m^2) were recruited and prospectively followed in 24 Italian HF centres belonging to MECKI Score Research Group. Besides full clinical examination, patients underwent maximal cardiopulmonary exercise test at study enrolment. Median follow-up was 1113 (553–1803) days. Study population was divided according to BMI (<25, 25–30, 25–30 kg/m^2) and predicted peak oxygen consumption (peak VO2, <50%, 50–80%, >80%) [14]. Study endpoints were all-cause death and cardiovascular deaths including urgent cardiac transplant.
All-cause and cardiovascular deaths occurred in 951 (28.6%, 57.4 per 1000 person/year) and 802 cases (17.4%, 48.4 per 1000 person/year), respectively. In the high BMI groups, several prognostic parameters presented better values [LVEF, peak VO2, ventilation/carbon-dioxide slope, renal function, haemoglobin (P<0.01)] with respect to the lower BMI groups. Both BMI and peak VO2 were significant positive predictors of longer survival: both higher BMI and peak VO2 groups presented lower mortality (p<0.001). At multivariable analysis and using a matching procedure (age, gender, LVEF and peak VO2), the protective role of BMI disappeared.
Conclusion: Exercise tolerance affects the relationship between BMI and survival. The cardiorespiratory fitness mitigates the obesity paradox, observed in HF subjects.

P242 | BEDSIDE
Cardiac dysfunction is the main mechanism of aggravation of exercise intolerance in homozygous sickle cell disease patients

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Background: Sickle cell disease (SCD) is the most frequent genetic hemoglobinopathy worldwide associated with a marked exercise intolerance. Mechanisms underlying this exercise limitation are multifactorial, complex and difficult to discriminate in clinical practice.
Purpose: To examine the role of cardiac dysfunction in the exercise limitation in homozygous SCD patients.
Methods: 60 SCD patients (32.9±10.6 years, 36 women) with dyspnea and 20 controls matched for age and gender underwent a stress echocardiography combined with gas exchange measurements during a symptom-limited exercise ramp protocol. Peak exercise oxygen uptake indexed to weight (VO2) and peak cardiac index (Ci) were measured. The difference between arterial and venous oxygen content (Ca-vO2) was calculated using Fick principle.
Results: Compared to controls, SCA patients exhibited a low peak VO2 (19.6±4.1 vs. 36.4±9.5 ml/min/kg; p<0.001), a dramatic decrease in Ca-vO2 (7.5±1.5 vs. 15.8±3.1 ml/dl; p<0.0001) whereas Ci was markedly increased (9.6±1.6 vs. 8.4±1.6 l/min/m^2; p=0.005) suggesting a compensatory mechanism of the reduced peripheral oxygen transfer.
The SCD patients were next classified in tertiles according to peak VO2. While hemoglobin level and Ca-vO2 were similar, SCD patients in the lower tertile of VO2 exhibited a reduced peak Ci (Table 1). In multivariable analysis, older age and left atrial function as assessed by peak longitudinal strain were independently related to exertional intolerance.

Table 1

	Lower VO2 tertile† (n=20)	Other VO2 tertiles‡ (n=40)	p value
Age (years)	40.3±10.1	29.2±8.8	0.0001
Peak Cardiac index (l/min/m^2)	8.6±1.0	10.1±1.7	0.0001
Peak Ca-vO2 (ml/dl)	7.0±1.4	7.8±1.5	0.07
Hemoglobin (g/dl)	8.3±1.3	8.8±1.2	0.13
LV diastolic volume index (ml/m^2)	91.9±23.0	92.2±21.5	0.95
LV ejection fraction at rest (%)	60.7±7.9	62.2±5.1	0.46
Cardiac index at rest (l/min/m^2)	4.5±0.9	4.3±0.8	0.38
Tricuspid velocity at rest (m/s)	2.5±0.3	2.4±0.2	0.28
Left atrial volume index at rest (ml/m^2)	54.7±16.9	44.0±11.3	0.02
Left atrial longitudinal strain at rest (%)	30.7±5.4	38.9±7.2	<0.0001

†VO2 <16.1 ml/min/kg in women (n=12), VO2 <19.2 ml/min/kg in men (n=8). ‡VO2 ≥16.1 ml/min/kg in women (n=24), VO2 ≥19.2 ml/min/kg in men (n=16).

Conclusion: The exercise intolerance of SCD patients is mainly related to the impairment of Ca-vO2 which is compensated by a high cardiac output.
However, the aggravation of exertional intolerance in SCD is due to the alteration of cardiac function related to ageing and to left atrial function deterioration.

CHALLENGES IN CONGENITAL HEART DISEASE

P243 | BEDSIDE
Mortality rates according to deterioration of various follow-up parameters in PAH-CHD

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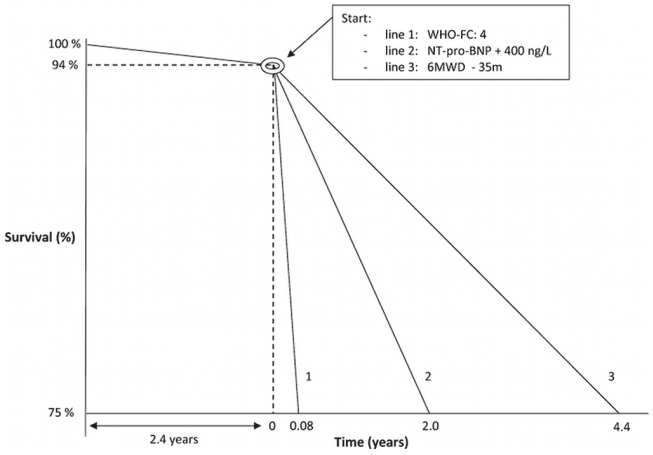
Purpose: Adult patients with pulmonary arterial hypertension due to congenital heart disease (PAH-CHD) suffer from a high mortality. This underlines the importance of adequate risk stratification to guide treatment decisions. Several cross-sectional clinical variables have been associated with mortality, but nowadays longer follow-up is available. Therefore we investigated the prognostic relevance of serial measurements in patients with PAH-CHD.
Methods: In this prospective observational cohort study, we included consecutive adult patients with PAH-CHD between 2005 and 2015. Control visits on the outpatient clinic of two tertiary centres were standardised, including WHO functional class (WHO-FC), six-minute walk distance (6-MWD) and NT-pro-BNP. All patients were treated with bosentan following the first visit. We evaluated prognosis of PAH-CHD patients from onset of deterioration; first time worsening to WHO-FC 4, 6-MWD decrease of 35 meters and NT-pro-BNP increase of 400 ng/L during follow-up.
Results: Eighty-seven patients with PAH-CHD were included (mean age 43 years, 35% male, 36% Down, 74% Eisenmenger). During a median follow-up of 5.5 years (IQR 3.1–9.0), 29 patients died (33%). In our risk stratification model during follow-up (Figure 1), worsening to WHO-FC 4 occurred in 10 patients, 6-MWD decrease of 35 meters in 56 patients and NT-pro-BNP increase of 400 ng/L in 37 patients. The median time to deterioration was 2.4 years (IQR 0.7–

4.2 years). Time from onset of deterioration to 25% mortality was 0.08 years for deterioration of WHO-FC, 2.0 years for NT-pro-BNP and 4.4 years for 6-MWD.



Conclusion: Deterioration of WHO-FC, NT-pro-BNP and 6-MWD each has a specific impact on mortality rate. Mortality rate is highest in patients who deteriorate to WHO-FC 4, followed by those with NT-pro-BNP increase of 400 ng/L and 6-MWD decrease of 35 meters.

Acknowledgement/Funding: Our research group was sponsored by an unrestricted grant from Actelion Pharmaceuticals

P244 | BEDSIDE
The burden of atrial arrhythmias in adult congenital heart disease: observations over a 20 year period

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Introduction: Adults with congenital heart disease (ACHD) are a growing population. Due to advances in medical therapy and surgical techniques more than 90% are now expected to survive into adulthood. Specialist centres now face the challenges involved in managing this ageing population and its multiple morbidities. In particular, arrhythmias become increasingly common and are likely to impact on quality of life in terms of recurrent hospitalisation, exercise tolerance, development of strokes and increased risk of sudden cardiac death.
Methods: The electronic ACHD database at a large quaternary specialist centre was retrospectively reviewed for patients with confirmed atrial arrhythmias. The database contained approximately 4000 patients seen between 1996 and 2015. Data was collected on baseline demographics, comorbidities, previous operations, thromboembolic events and causes of mortality. Patients were then grouped depending on their structural defect with the defect of greatest complexity taking priority.
Results: We identified 347 patients with ACHD and co-existing atrial arrhythmias. 41% had atrial septal defects, 10% had Tetralogy of Fallot, 6% had a Fontan circulation, 13% had complex congenital heart disease and 30% have other congenital heart diseases. 12% of patients had at least one thromboembolic event (TE). 7% of patients with repaired Tetralogy of Fallot developed an atrial arrhythmia with 14% of these developing strokes at a mean age of 46 years. The mean CHADSVASC prior to the thromboembolic event was 1.4. 9% of patients with uncomplicated atrial septal defects (ASDs) and atrial arrhythmias developed thromboembolic events. AF was asymptomatic in 40% of cases and 56 years was the average age of AF onset with average age of stroke being 58 years. AF prevalence in the Fontan cohort was 10% and AF was symptomatic in 90%. All patients were anticoagulated with warfarin and despite this 25% developed thromboembolic events. 84% of Fontan patients had at least one hospitalisation due to their arrhythmia. The incidence of TEs was 20% in VSD, 18% in valvular disease, 10% in transposition of the great arteries and 60% in patients with Eisenmengers syndrome. There were no TEs in those with Ebsteins anomaly, patent ductus arteriosus and coarctation of the aorta.
Discussion: Atrial arrhythmias are common in ACHD, occur at a younger age and are associated with high rates of thromboembolic events. It is therefore unclear if CHADSVASC is applicable to these patients. The risk of stroke in certain groups appears high and anticoagulation should be considered even in the absence of other risk factors. AF is frequently asymptomatic in those with ASDs and lifelong active screening for atrial arrhythmia should be considered.

P245 | BEDSIDE
Body mass index in adult congenital heart disease patients: distribution, association with exercise capacity and prognostic implication

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Background: Abnormal body mass index (BMI) is associated with increased mortality in various cardiovascular cohorts. Increasing rates of obesity raised concerns on the prognostic implications of a high BMI in adults with congenital heart disease (ACHD). We aimed to assess the distribution of BMI and its association with symptoms, exercise capacity and survival in this population.
Methods and results: We included 3,069 ACHD patients (median age 32.6 years) under follow-up at our institution between 2001 and 2015. Patients were classified based on BMI as underweight (<18.5), normal weight (18.5–25), overweight (25–30) or obese (>30) and symptoms and objective exercise capacity were assessed. Overall, 6.2% of patients were underweight, 28.2% overweight and 14.6% obese. A lower BMI was associated with more symptoms and lower absolute and percentage predicted peak oxygen uptake ($p<0.05$ for both). Moreover, higher BMI values were associated with lower all-cause and cardiac mortality on univariable Cox analysis and this effect persisted after adjustment for age, defect complexity, cyanosis and objective exercise capacity. As illustrated in Figure 1, underweight patients had the worst survival prospects, while overweight patients had significantly better survival compared to normal weight patients. In patients with a complex cardiac defect who had repeated weight measurements, weight loss was also associated with a worse survival (HR 1.82, 95% CI 1.02–3.24, p=0.04).

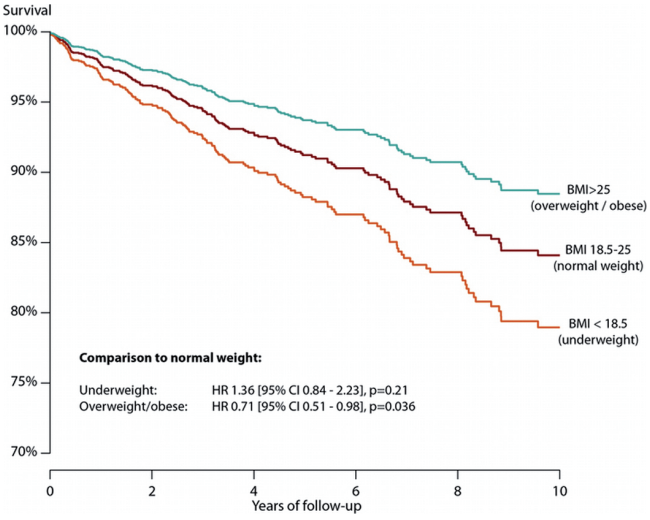

Figure 1

Conclusions: ACHD patients with a higher BMI were less symptomatic and had a higher objective exercise capacity and lower mortality. The association between BMI and mortality was especially pronounced in symptomatic patients with complex underlying cardiac defects, suggesting that cardiac cachexia may play a role. Indeed, weight loss was linked to an even higher mortality in complex ACHD.

P246 | BEDSIDE
Disease burden and mortality in tetralogy of Fallot patients over 50 years old

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Background: Progress in surgical and medical management of patients with tetralogy of Fallot (TOF) has led to survival beyond the age of 50 years. However, little is known regarding morbidity and mortality of these elderly TOF patients.
Purpose: To determine major cardiovascular morbidity and all-cause mortality in elderly TOF patients.
Methods: This multicenter study included patients aged at least 50 years old from a prospective registry. The presence of five major atherosclerotic risk factors (smoking, diabetes, hypertension, hypercholesterolemia, family history) was obtained. Outcome variables included: TOF-related cardiovascular events, acquired

cardiovascular events occurred and all-cause mortality. All-cause mortality was compared to age and gender matched reference population. Univariable Cox hazards regression analysis was used to determine predictors for the outcome variables.
Results: A total of 167 patients (mean age 53±6 years, 54% male, 63% at least one atherosclerotic risk factor) were included. During a mean follow-up of 6.4 (±3.8) years, in 26 (16%) patients TOF-related cardiovascular events occurred (ventricular arrhythmias (n=4) and progressive heart failure (n=22)) and in 18 (11%) patients acquired cardiovascular events occurred (myocardial infarction/coronary artery disease (n=10) and CVA/TIA (n=8)). Overall, a total of 22 TOF patients died (heart failure related in 54%) during follow-up (HR 3.11 (compared to reference), 95%C.I.: 2.04–4.73, p<0.001) (figure 1). The number of atherosclerotic risk factors predicted acquired cardiovascular events (HR:1.61/risk factor, 95%C.I.:1.04–2.50, p=0.034) but not TOF-related events or all-cause mortality (p=NS for both).

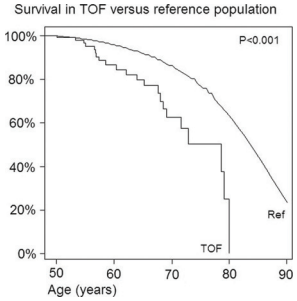

Figure 1

Conclusions: TOF patients aged 50 years or older had over threefold higher mortality risk compared to reference population. Importantly, almost two-thirds of TOF patients had at least one major atherosclerotic risk factor. The number of risk factors predicted acquired but not TOF-related major cardiovascular events.
Acknowledgement/Funding: Interuniversity Cardiology Institute of the Netherlands (ICIN), Nuts Ohra foundation and Parelsnoer institute

P247 | BEDSIDE
Aortopathy in various types of adult congenital heart disease

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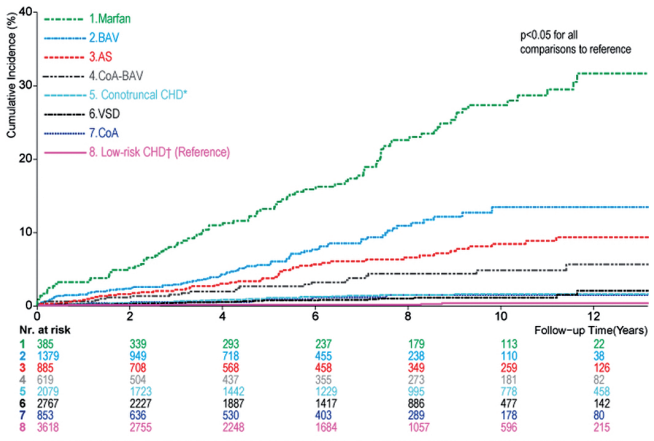
Background: Proximal aortic dilatation is frequently found in adults with certain types of congenital heart disease (CHD), giving rise to concerns about increased risk of aortic complications. Guidelines on prophylactic proximal aortic replacement in these patients are mostly based on Marfan syndrome (MFS) and bicuspid aortic valve (BAV).
Purpose: To prospectively determine contemporary risk of aortic dissection and proximal aortic replacement in adults with CHD-types at risk for proximal aortopathy, relating it to risk in patients with low-risk CHD and patients with MFS.
Methods: From an adult CHD registry, patients with a native proximal (neo-)aorta and the following main CHD diagnoses were selected: "CHD risk" (BAV [n=1379], aortic coarctation with/without BAV [CoA-BAV; n=619/CoA; n=853], aortic stenosis [AS; n=885], ventricular septal defect [VSD; n=2767], Tetralogy of Fallot/pulmonary atresia with VSD [ToF/PA+VSD; n=1353], double-outlet right ventricle [DORV; n=131], transposition of the great arteries [TGA; n=595]); 2. "CHD reference" (atrial septal defect [ASD; n=2457], pulmonary stenosis [PS; n=1161]); 3. MFS (n=385). Incidence rates were calculated using Poisson regression. Survival was calculated using the complement Kaplan-Meier estimator, comparing groups using the log-rank test.
Results: 8 dissections occurred in 54,090 person-years [py] in the CHD risk- (55% male; median age 32 years), 2 in 20,554 py in the reference- (36% male; 40 y) and 24 in 3,182 py in the MFS group (45% male, 34 y). Dissection incidence rate in the CHD risk-group (1.48/10,000 py; 95% CI: 0.68–2.75) was lower than in the MFS group (75.43; 49.13–109.76, p<0.001) but did not differ significantly from the CHD reference-group (0.97; 0.16–3.00, p=0.902). The FIGURE shows cumulative incidence of dissection or proximal aortic replacement in the constituent defects of the CHD risk-group, the CHD reference and MFS-groups. With considerable variation, all constituent defects showed greater risk of this outcome, compared to the reference-group, but none approached the high risk of the MFS-group.
Conclusions: Our results show that the cumulative incidence of aortic dissection or proximal aortic replacement in patients with CHD-types at risk for proximal aortopathy is low in contemporary practice. Of all CHD types, risk is highest in patients with BAV, but still considerably lower than in MFS.

Figure. Cumulative incidence of aortic dissection or proximal aortic replacement in patients with specific types of CHD and a native proximal aorta at inclusion



Abbreviations: AS, aortic stenosis; BAV, bicuspid aortic valve; CHD, congenital heart disease;CoA, aortic coarctation; VSD, ventricular septal defect
*ToF/PA+VSD, TGA, DORV
†ASD, PS

P248 | BEDSIDE
Efficiency of implantable loop recorder in identifying causes of syncope in children with and without cardiac pathology

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Prior studies have demonstrated a high value of the implantable loop recorders (ILR) in identifying causes of syncope and palpitations in adults. At the same time, evidence on indications and benefits of ILR in pediatric population is still thin. In 15 to 20% of children with recurrent unexplained syncope (UnS), patients' and family history as well as physical examination are not sufficient to determine the underlying cause of UnS. This study compares the efficiency of the ILR-based long-term ECG monitoring in children with UnS with low risk in children with UnS and high risk for developing malignant cardiac arrhythmias.
Methods: ILRs were implanted in 265 children (49% boys) aged 2.5 to 17 (12.2±4.4) with recurrent UnS. 230 of them (87%) had structurally normal hearts whose clinical course is not consistent with neurocardiogenic syncope (group 1) and 35 (group 2) had structural heart diseases (congenital heart diseases (CHD) - 18 pts) or primary electrical cardiac abnormalities - LQTS. Personal and family history, physical examination including ECG, stress test, holter monitoring, tilt-table and other tests were unable to identify the cause of syncope.
Results: For 228 pts ILR monitoring was completed due to the symptom-rhythm correlation or detecting of arrhythmia (52% - clinically positive cases) or due to the end of 36-mnth follow up. Among children with structurally normal hearts, the diagnostic yield was 54.2% (109 positive from 201 complete cases). Arrhythmogenic syncope (ArrS) were diagnosed in 35 (34 – severe asystole and 1- ventricular fibrillation (VF)) and non-ArrS – in 53 pts (60.2%). Among children of group 2, the efficiency of ILR monitoring was 37% (10 positive from 27 complete cases): 53.8% - in children with CHD and 21.4% - in children with LQTS. ArrS were diagnosed in 7 pts (5 caused by severe asystole and 2 caused by VF), non-ArrS - in 3 pts. In group 2, VF was diagnosed only in pts with LQTS.
Conclusion: In children with structurally normal hearts and CHD, ILR technology is an efficient and secure method for diagnosis the cause of UnS. The efficiency of ILR monitoring in children with structurally normal hearts and those with CHD is the same (about 54%). It is lower in children with LQTS – 21.4%. For children with LQTS ILR can be useful for differential diagnosis of life-threatening syncope or for detecting asymptomatic VF.

P249 | BEDSIDE
Value of 18F-FDG PET/CT-angiography in the diagnosis of infective endocarditis in patients with congenital heart disease

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Purpose: To evaluate the added value of 18F-FDG-PET/CT-Angiography (PET/CTA) in the diagnosis of infective endocarditis (IE) in patients with congenital heart disease (CHD), where Duke criteria (DC) and echocardiography (ECHO) have limitations due to a complex anatomy and frequent prosthetic material.
Methods: A prospective study was conducted in a tertiary centre with a multidisciplinary IE and CHD Units. PET/CTA was performed and compared with ECHO in all consecutive patients with CHD and suspected IE. Initial diagnosis with DC, PET/CTA and DC+PET/CTA information were compared with a final expert team

diagnostic consensus performed with all clinical, microbiological and imaging information.
Results: Nineteen patients (10 men; median age 37 year; median time from last surgery 42.8 months) from Nov-12 to Jan-16 entered the study. Based on their major underlying heart defect patients had:8 Tetralogy of Fallot type, 6 Transposition type, 4 Aortic/Subaortic stenosis and 1 ventricular septal defect (VSD). As for prosthetic material, there were:16 prosthetic valves and conduits, 11 patches for VSD closure, 6 cardiac devices, 5 shunt grafts and 11 miscellanea.
IE was early in 47% and healthcare-associated in 67%. The most frequent microorganisms was S. epidermidis (37%). Surgery was performed in 42% and 2 patients died during the intervention.
ECHO was positive in 7, negative in 7 and doubtful in 5. PET/CTA was positive in 15 and negative in 4. PET/CTA and ECHO were concordant in 47%. Among discordant cases, PET/CTA confirmed IE in 9 false negative/doubtful ECHO and ruled out IE in 1 false positive ECHO. Table shows the IE classification. DC+PET/CTA allowed reclassification of 91% of the (P) IE cases confirming (9) or ruling out (1) the diagnosis, and the expert team could give a more conclusive diagnosis (D/R) in 95% of cases.

IE classification

IE clasification	DC	PET/CTA	DC+PET/CTA	Expert team consensus
Definitive (D)	6 (32%)	15 (79%)	15 (79%)	15 (79%)
Posible (P)	11 (58%)	0	1 (5%)	1 (5%)
Rejected (R)	2 (10%)	4 (21%)	3 (16%)	3 (16%)

Sensitivity, specificity, PPV, NPV and accuracy were 38.9%/80%/88.6%/24.7%/59.4% for DC at admission, increasing significantly with the addition of PET/CTA information:88.9%/80%/94.7%/64.3/83.4%, respectively. PET/CTA also provided an alternative diagnosis in 2 (R) cases and detected peripheral pulmonary embolisms in 2 patients.
Conclusions: PET/CTA was a very useful diagnostic tool in patients with CHD and suspected IE with an added diagnostic value to the modified DC (increased sensitivity) and improving cases classification.

DUAL ANTIPLATELET THERAPY: THE LONG AND THE SHORT OF IT!

P250 | BEDSIDE
Clinical outcomes in patients with diabetes mellitus receiving dual antiplatelet therapy more than 12 months after second-generation drug eluting stent implantation

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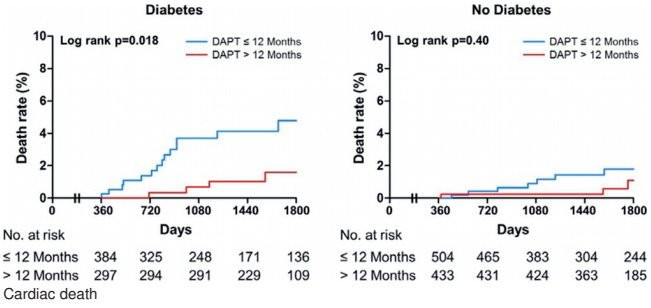
Background: Extended dual antiplatelet therapy (DAPT) was reported to decrease death or myocardial infarction (MI) in patients with diabetes mellitus (DM) receiving first-generation drug eluting stent (DES). However, it is not known whether extended DAPT improves clinical outcomes in diabetic patients receiving second-generation DES.
Methods: We studied 1622 patients receiving second-generation DES who were event-free at 12 months after the index procedure. Patients were divided according to diabetes mellitus and DAPT duration (>12 month versus ≤12 month). Landmark analysis at 12 months was performed for risk evaluation. The primary outcome was cardiac death and the secondary outcomes included all-cause death, non-fatal MI, repeat revascularization, and cerebral vascular accident (CVA).
Results: During the follow-up period (median 55 months), extended DAPT >12 month was associated with a decreased risk of cardiac death in patients with DM (hazard ratio [HR]: 0.32; 95% confidence interval [CI]: 0.10 to 0.98; p=0.046), but not in patients without DM (HR: 0.54; 95% CI 0.21–1.40; p=0.20) after multivariate adjustment. However, there were no significant differences in the risk of all-cause death, non-fatal MI, repeat revascularization, and CVA between the >12 months DAPT group and the ≤12 month DAPT group regardless of diabetic status.



Conclusion: Extending the duration of DAPT more than 12 months may decrease cardiac death in patients with DM after second-generation DES implantation.

P251 | BEDSIDE
Three-year clinical outcomes after six-month versus twelve-month dual antiplatelet therapy in patients with everolimus-eluting and sirolimus-eluting stents

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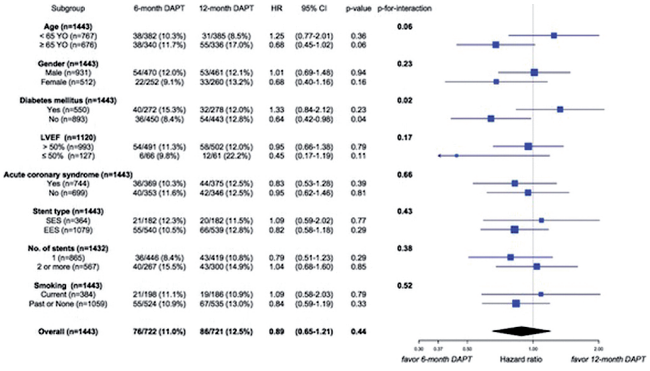
Background: The EXCELLENT trial, a prospective, randomized, open label, multi-center trial (NCT00698607), has reported the non-inferiority of 6-month dual antiplatelet therapy (DAPT) to 12-month DAPT regarding target vessel failure at 12 months, as well as the non-inferiority of everolimus-eluting stent in comparison to sirolimus-eluting stent. We are reporting 3-year long-term clinical outcomes of the trial.
Methods: Total 1,443 patients were randomized to receive 6- or 12-month DAPT (1:1). The primary endpoint was major adverse cardiovascular and cerebrovascular events (MACCE) difined as a composite of death, myocardial infarction, any revascularization, stent thrombosis and stroke. In addition, major bleeding according to the Thrombolysis in Myocardial Infarction criteria was investigated. The patient were followed further until 3 years (median 3.0; interquartile range 2.9–3.1)
Results: MACCE occured similarly in both 6- and 12-month DAPT groups (11.0% vs. 12.5%, respectively; hazard ratio [HR] 0.89, 95% confidence interval [CI] 0.65–1.21, p=0.44). In the subgroup analysis, DAPT duration affected differently according to the presence of diabetic mellitus. (Figure) Specifically, 6-month DAPT group had fewer MACCE in non-diabetic patients. (HR 0.64, 95% CI 0.42–0.98, p=0.037) However, myocardial infarction, stent thrombosis and target-vessel revascularization increased with 6-month DAPT in diabetic patients. (Table)



Conclusions: The overall long-term prognosis of 6-month DAPT was comparable with that of 12-month DAPT. However, DAPT duration affected differently according to the presence of diabetic mellitus. DAPT duration should be determined individually considering risk factors of each patients.
Acknowledgement/Funding: Korea Healthcare Technology R&D Project and the Mid-career Mid-career Researcher Program through NRF grant funded by the MEST, Republic of Korea

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longer dual antiplatelet therapy beyond 9 months does not influence neointimal condition after second generation drug eluting stent implantation

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Purpose: Although the guideline recommends prolonged dual antiplatelet therapy (DAPT) more than 6–12 months after drug eluting stent (DES) implantation, it does not indicate how long DAPT should be continued beyond 6–12 months. On the other hand, longer administration of DAPT increases the risk of hemorrhagic complications. So we evaluated the neointimal characteristics of DES in patients with DAPT at 18 months after implantation using optical coherence tomography (OCT).
Methods: Forty patients who received serial OCT study at both 9 and 18 months after second generation DES implantation were enrolled. Patients were divided into 2 groups, as 26 patients who continued DAPT (68.2y/o) and 14 patients who were treated only with aspirin (65.9y/o) at 18 months follow-up. Neointimal characteristics and presence of thrombus within stented segment at both follow-up periods were evaluated by OCT.
Results: Clinical and procedural parameters were similar between 2 groups. At 9 months follow-up, all patients had received DAPT, and there are no significant differences in the OCT characteristics and measurements of neointima between 2 groups. At 18 months follow-up, any degree of in-stent thrombus was not seen in both groups. Neointimal volume was increased in both groups from 9 to 18 months, but increment value of neointimal proliferation was similar (0.18±0.30 vs 0.31±0.32 mm^3/mm, p=0.23).

Conclusions: Interrupting DAPT from 9 months after DES implantation did not affect the development of in-stent thrombus or unstable neointimal characteristics at 18 months follow-up compared with continuing DAPT. Our study supports shortening the duration of DAPT after second generation DES implantation.

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Longer-term oral antiplatelet use in stable post-MI patients: Insights from the TIGRIS study

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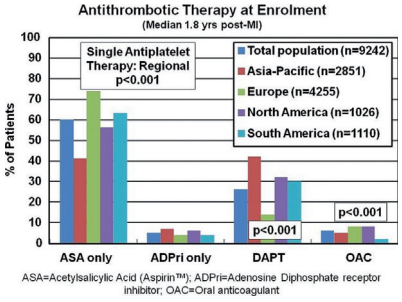
Background: It is unclear how consistently randomized clinical trial (RCT)-based and international guideline-recommended antiplatelet treatment patterns for patients with stable coronary artery disease (CAD) post-myocardial infarction (MI) are applied.
Purpose: To describe contemporary use of dual antiplatelet therapy (DAPT; acetylsalicylic acid [ASA]+ADP receptor inhibitor [ADPri]) ≤1 and >1 year post-MI.
Methods: Patients ≥50 years with prior MI 1–3 years ago and ≥1 risk factor (age ≥65 yrs, treated diabetes, 2nd prior MI>1 yr ago, multivessel CAD, creatinine clearance 15-<60 mL/min) were enrolled by 354 physicians (96% cardiologists) in 25 countries (2013–14) in the prospective TIGRIS study (NCT01866904).
Results: 9,242 patients were enrolled a median 1.8 years post-MI: 52% with prior ST- elevation MI, median age 67 years, 24% women, 65% caucasian, 55% had ≥2 additional qualifying risk factors, 14% current smokers, 67% are overweight/obese, 29% with blood pressure ≥140/90 mm Hg. 81% had undergone percutaneous coronary intervention (PCI; 66% with drug-eluting stents) for the index MI. 74% of patients were discharged on DAPT, mainly ASA+clopidogrel (75%). 58% of these patients discontinued their treatment (mainly clopidogrel, 60%) before enrolment, most commonly by physician recommendation (90%). At enrolment, 95% were taking an antithrombotic drug (Figure), 92% were taking an antiplatelet (most commonly ASA [87%]), with 27% on DAPT (median duration 1.6 years); continued DAPT use >1 year was highest (40%) in Asia-Pacific and lowest (12%) in Europe.



TIGRIS figure

Conclusions: Despite guideline recommendations, 1 in 4 post-MI patients with ≥1 atherothrombotic risk factor did not receive DAPT for ~1 year. Further, in contrast to RCT evidence supporting newer ADPris, clopidogrel was mainly prescribed as part of DAPT. Prior to recent RCT data supporting DAPT >1 year post-MI/PCI, >1 in 4 patients have continued on DAPT, though with substantial international variability
Acknowledgement/Funding: TIGRIS is sponsored by AstraZeneca

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Duration of dual antiplatelet therapy in patients treated with second generation drug-eluting stents: a systematic review and meta-analysis

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Objective: To evaluate the optimal duration of dual antiplatelet therapy (DAPT) after percutaneous coronary intervention (PCI), especially in the era of second generation drug-eluting stents (DES).

Methods and results: The study was conducted between November 2014 and April 2015. All randomized controlled trials (RCTs) comparing short (<12 months) vs. long (≥12 months) DAPT in patients treated with second generation DES were analyzed. Sensitivity analyses were performed for length of DAPT and type of DES. All-cause death was the primary endpoint, while cardiovascular death, myocardial infarction (MI), stent thrombosis, and major bleeding were secondary endpoints. Results were pooled and compared with random effect models and meta-regression analysis.
Eight RCTs with 18,810 randomized patients were included. The studies compared 3 vs. 12 months of DAPT (two trials), 6 vs. 12 months (three trials), 6 vs. 24 months (one trial), 12 vs. 24 months (one trial), and 12 vs. 30 months (one trial). Comparing short vs. long DAPT, there were no significant differences in all-cause death (OR 0.87: 95% CI 0.66–1.44), cardiovascular death (OR 0.95: 95% CI 0.65–1.37), and stent thrombosis (OR 1.20: 95% CI 0.79–1.83), and no differences were present when considering everolimus-eluting and fast-release zotarolimus-eluting stents separately. Shorter DAPT was inferior to longer DAPT in preventing MI (OR 1.35: 95% CI 1.03–1.77). Conversely, major bleeding was reduced by shorter DAPT (OR 0.60: 95% CI 0.42–0.96). Baseline features did not influence these results in meta-regression analysis.
Conclusions: DAPT for ≤6 months is reasonable for patients treated with everolimus-eluting and fast-release zotarolimus-eluting stents, with the benefit of less major bleeding at the cost of increased MI, with similar survival and stent thrombosis rates. An individualized patient approach to DAPT duration should take into account the competing risks of bleeding and ischemic complications after current generation DES.

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Short- versus long-term dual antiplatelet therapy after drug-eluting stent implantation in patients with or without diabetes: a patient-level meta-analysis of randomised trials

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Background: Major adverse cardiac events (MACE) and bleeding have been studied in multiple randomized controlled trials comparing short-term and long-term dual antiplatelet therapy (DAPT) after drug-eluting stent (DES) placement. However, the impact of diabetes on these outcomes remains unexplored.
Objectives: We conducted a patient-level pooled analysis with the aim to compare clinical outcomes between short-term (≤6 months) and long-term (1 year) DAPT after DES implantation in diabetic and non-diabetic patients.
Methods: Randomized controlled trials comparing DAPT durations after DES placement were searched through the MEDLINE, SCOPUS, EMBASE, and Cochrane databases. We pooled individual patient data from 6 trials of DAPT (RESET, OPTIMIZE, PRODIGY, EXCELLENT, SECURITY, ITALIC PLUS). The primary study outcome was 1-year risk of MACE (cardiac death, myocardial infarction, or definite/probable stent thrombosis). The main secondary outcome was 1-year risk of any bleeding. Analysis was conducted by intention to treat.
Results: 6 trials including 11,473 randomized patients were pooled. Of these patients, 3,681 (32.1%) had diabetes and 7,708 (67.2%) did not (mean age 63.7±9.9 and 62.8±10.1 years respectively), with 84 patients (0.7%) missing this information. Diabetes was an independent predictor of MACE (hazard ratio [HR]:2.302; 95% confidence interval [CI]:1.006–5.266; p=0.046). At 1-year follow-up, long-term DAPT did not decrease the risk of MACE versus short DAPT in diabetics (HR:1.061; 95% confidence interval [CI]:0.742–1.518; p=0.75) and non-diabetics (HR:0.842; 95% CI:0.628–1.130; p=0.25; pint=0.33). Myocardial infarction did not differ between the two DAPT regimens (diabetics: HR:0.936; 95% CI:0.597–1.467; p=0.77; non-diabetics: HR:0.883; CI:0.615–1.270; p=0.50; pint=0.85). There was however a trend towards stent thrombosis reduction with 12-month DAPT in diabetics (HR:0.437; 95% CI:0.180–1.062; p=0.068) as opposed to a null effect observed in non-diabetics (HR:1.419; 95% CI:0.678–2.971; p=0.35), with positive interaction testing (pint=0.045), although the landmark analysis excluding events within 3–6 months showed a trend towards benefit in both groups.
One year DAPT duration was associated with higher rates of bleeding, irrespective of diabetic status (diabetics: HR:1.803; 95% CI:1.058–3.072; p=0.03; non-diabetics: HR:1.358; CI:0.927–1.988; p=0.12; pint=0.42).
Conclusions: 12-month as compared to 6-month DAPT tended to reduce the 1-year rate of ST, however, increased bleeding in both diabetic and non-diabetic patients without reducing 1-year MACE in either group.
Acknowledgement/Funding: GG is supported by a research grant from EAPCI

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Long term dual antiplatelet therapy after drug eluting stents: a meta-analysis of randomised studies

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Background: Conflicting evidence regarding the effects of prolonging dual antiplatelet therapy (DAPT) beyond 12 months, as compared to 12-month DAPT, in patients undergoing drug-eluting stent implantation exists. Recently the OPTImal DUAL antiplatelet therapy (OPTIDUAL) trial reported lack of significant differences in ischaemic complications and major bleeding between these two regimens.
Purpose: The aim of this study was to assess the benefits and risks of an extended DAPT duration for more than a year as compared with 12-month DAPT.
Methods: We performed a meta-analysis of randomised studies comparing prolonged DAPT beyond a year with 12-month DAPT after drug-eluting stent implantation. Trial-specific odds ratios (ORs) with 95% confidence interval (CI) were combined with fixed-effects or random-effects model, as appropriate.
Results: Four randomised trials enrolling 17,650 participants were included. Extended DAPT was associated with a significantly lower risk of myocardial infarction as compared with 12-month DAPT (1.55% vs 2.85%, OR 0.54, 95% CI 0.43 to 0.66, p<0.001); but it did not significantly reduce the risk of stent thrombosis (0.28% vs 0.82%, OR 0.46, 95% CI 0.16 to 1.27, p=0.13), or stroke (0.78% vs 0.85%, OR 0.91, 95% CI 0.65 to 1.26, p=0.56), nor did it affect cardiovascular death (1.0% vs 0.98%, OR 1.03, 95% CI 0.72 to 1.46, p=0.88). Compared with 12-month DAPT, extended DAPT significantly increased the risk of major bleeding (0.96% vs 0.65%, OR 1.49, 95% CI 1.06 to 2.11, p=0.02), with no increase in all-cause mortality (1.88% vs 1.58%, OR 1.11, 95% CI 0.79 to 1.57, p=0.53).
Conclusions: Compared with 12-month DAPT, extended DAPT duration for more than a year reduces the risk of myocardial infarction but increases major bleeding, with no effect on all-cause or cardiovascular mortality.

BREAKING DOWN BARRIERS IN SECONDARY PREVENTION

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Improvement of medication adherence by administration timing simplification protocol (ATSP) in cardiovascular disease patients

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In chronic diseases, keeping adherence to medication is very difficult. The objective of this study was to evaluate the impact of administration timing simplification protocol (ATSP) on the medication adherence and the clinical parameters of cardiovascular diseases.
210 patients with cardiovascular disease taken drugs ≥2 pills/day were enrolled. Intervention group was simplified administration schedule by ATSP having two main strategies as followed; to move medication from “pc” (30 minute after meal) to “stat. pc” (immediately after meal); to move from “at evening” to “at morning”. Both groups were equally educated by one research pharmacist about medication name and effect.
The mean age of the patients was 66.0±9.9 years old, 58% was male, 95.6% had hypertension, 95% had hyperlipidemia and 37.8% had diabetes mellitus. The mean duration of cardiovascular diseases was 3.7±2.8 years. The patients had on average 4.9±2.1 pills. In the intervention group, the administration timing was simplified from 2.9±1.0 times/day to 1.5±0.6 times/day following ATSP application (P<0.001).
In both groups, medication knowledge was significantly improved by education. However, medication adherence was only improved in the intervention group. Blood pressures were not significantly changed in either group. However, total cholesterol and triglyceride levels were significantly decreased in the intervention group only. The decrease in the serum cholesterol concentration was significantly correlated with the improvement of the adherence evaluated MMAS-8 items (r = 0.507, P<0.001).
In conclusion, ATSP could be effective strategy in improving adherence in chronic cardiovascular disease patients.

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Depression and anxiety prevalence and characteristics in patiens with established coronary heart disease and ischemic stroke srvivors: a comparison

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Background: A high prevalence of anxiety (A) and depression (D) has been found in coronary heart disease (CHD) patients and in stroke survivors, adversely influencing their further prognosis.
Purpose: To assess and compare the prevalence and covariates of A and D in patients with established CHD and in those after ischemic stroke.
Methods: The Czech EUROASPIRE IV study (EA IV, 2012–2013), EUROASPIRE III–Stroke Specific Module (EA III Stroke, 2007), and ESH Stroke Survey (ESH Stroke, 2012) were cross-sectional surveys carried out in the Czech Republic in identical centers. Patients <80 years of age, hospitalized either for elective or emergency coronary revascularization and/or acute myocardial infarction or ischemia (EA IV), or for ischemic stroke (EA III Stroke and ESC Stroke) were identified retrospectively. Data were collected through an interview with examinations at least six months after hospitalization. A and D were assessed according to the Hospital Anxiety and Depression Scale (HADS), subjective health according to the Short Form Health Survey (SF-36).
Results: In EA IV, 493 and, in stroke studies, 765 patients were investigated. The index event–interview interval was 1.33 and 1.51 years, respectively. A (HADS score >8) was found in 17.5 and 21.8%, and D (HADS score >8) in 23.5 and 32.2% of patients, respectively. A and D in CHD and stroke patients inversely correlated with subjective health (p<0.0001). In CHD patients, A and D correlated with CHD severity (assessed by pro-BNP; p<0.01), and were more pronounced in patients after AMI than after revascularization procedures. In stroke patients, A and D correlated with persistent neurological deficit (p<0.001 for both), vision impairment (p<0.036 and p<0.004), disability (p<0.001 both), and dependency on other people’s help (p<0.02 and p<0.0001, respectively). In CHD as well as in stroke patients, we found a lower prevalence of A and D in men, lower prevalence of A in patients with higher blood pressure, higher prevalence of A and D with lower physical activity and higher prevalence of D in smokers. Prevalence and control of other cardiovascular risk factors and medical treatment did not influence the prevalence and severity of A and D significantly. Anxiolytic or antidepressant medication was being taken by only 3% of CHD and 4% of stroke patients.
Conclusion: Anxiety and depression in patients with established CHD and in ischemic stroke survivors are frequent, related to impaired quality of life, CHD severity and persistent neurological deficits and have similar covariates. In such patients, anxiolytic and antidepressant medication should be used more frequently.
Acknowledgement/Funding: Internal Grant Agency, Ministry of Health, Czech Republic, grant No 9 333, 12102 and 13186

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Bisphosphonates for cardiovascular risk reduction. A systematic review and meta-analysis

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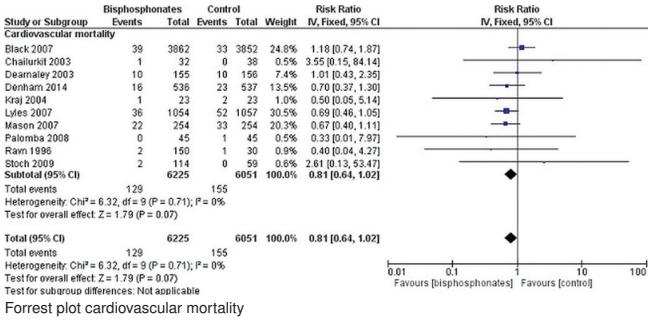
Background: Bisphosphonates might be effective in reducing cardiovascular events due to their ability to reduce calcification in arterial walls.
Methods: Pubmed, Embase and the Cochrane Library were systematically reviewed by two independent investigators for randomized controlled studies published up to January 2016 in which the effect of bisphosphonates on arterial wall disease, cardiovascular events, cardiovascular mortality or all-cause mortality were investigated. There was no restriction for the type of population used in the trials. Random-effects model were used to calculate the pooled estimates.
Results: 61 trials reporting the effects of bisphosphonates on the outcomes of interest were included. Bisphosphonates had beneficial effects on arterial wall disease regarding arterial calcification (pooled mean percentage difference -11.52 (95% CI -16.51- -6.52, p<0.01, I2 13%), but not on arterial stiffness (pooled mean percentage difference -2.82; 95% CI -10.71–5.07; p=0.48, I2 59%). No effect of bisphosphonate treatment on cardiovascular events was found (pooled RR 1.03; 95% CI 0.91–1.17, I2 16%), while a lower risk for cardiovascular mortality was observed in patients treated with bisphosphonates (pooled RR 0.81; 95% CI 0.64–1.02; I2 0%) although not statistically significant. Patients treated with bisphosphonates had a reduced risk of all-cause mortality (pooled RR 0.90; 95% CI 0.84–0.98; I2 53%).



Forrest plot cardiovascular mortality

Conclusions: In this systematic review and meta-analysis it is shown that bisphosphonates reduce arterial wall calcification but have no effect on arterial stiffness or on cardiovascular events. Bisphosphonates tend to reduce the risk of

cardiovascular mortality and reduce all-cause mortality in various patient groups, including osteoporosis patients and cancer patients.

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Medical compliance after acute myocardial infarction in STEMI and NSTEMI patients in the Netherlands

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Purpose: Optimal medical treatment is associated with increased survival and lower rate of new cardiovascular incidents. In the current study we aimed to assess medical compliance one year after acute myocardial infarction in 91 Dutch hospitals.
Methods: In the Netherlands, all inhabitants are by law obliged to have health insurance and all claim data are centrally registered. In 2012 and 2013, national diagnose-codings of 91 Dutch hospitals of STEMI and NSTEMI patients from the Dutch Information System Hospital Care (IZiZ) were acquired. Furthermore, data on medication in surviving patients was extracted from the Dutch Pharmacy Information System (FIS). Optimal medical treatment was defined if patients used at least aspirin, thienopyridine, statin, beta-blocker and ACE-inhibitor in the year following acute myocardial infarction.
Results: In total, 59.524 patients (67±13 years, 66% male) had a diagnose coding for a STEMI or NSTEMI. After one year, 52.662 patients were alive, with a total of 54.723 diagnose codings for STEMI (n=23.654) and NSTEMI (n=31.069). Of these patients, 81% used aspirin, 76% thienopyridines, 85% statins, 69% beta-blockers and 68% ACE-inhibitors. Overall, 37% of patients was on optimal medical treatment one year after acute myocardial infarction. STEMI-patients more often received optimal medical treatment compared to NSTEMI-patients (respectively 46% vs 31%).

Table 1. Differences in medical compliance

	All patients*	STEMI	NSTEMI
At the time of myocardial infarction	n=59,524	n=26.737	n=35,029
Age (yrs, mean ± SD)	67±13.2	64±13.0	69±12.9
Male gender, n (%)	39.540 (66%)	18.676 (70%)	22.460 (64%)
One year after myocardial infarction	n=52,662	n=23,654	n=31,069
Aspirin, n (%)	42.708 (81%)	20.354 (86%)	24.111 (78%)
Thienopyridines, n (%)	39.982 (76%)	20.297 (86%)	21.493 (69%)
Statins, n (%)	44.540 (85%)	21.192 (90%)	25.196 (81%)
Beta-blockers, n (%)	36.578 (69%)	16.799 (71%)	21.261 (68%)
ACE-inhibitors or AT2-antagonists, n (%)	36.061 (68%)	17.119 (72%)	20.443 (66%)
All five, n (%)	18.136 (34%)	10.156 (43%)	8.827 (28%)
All five (coumarin substitutes aspirin), n (%)	1.432 (3%)	743 (3%)	766 (3%)

*Unique patients when combining STEMI and NSTEMI patients. ACE-inhibitor = angiotensin-converting enzym; AT2-antagonist = angiotensine-II-antagonist.

Conclusion: In total, 37% of patients received optimal medical treatment one year after myocardial infarction in the Netherlands. STEMI-patients more often received optimal medical treatment compared to NSTEMI-patients.

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Are clinicians following statin intensity recommendations? Insights in 135 U.S community practices in the PALM registry

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Background: Current ACC/AHA Guidelines recommend using high intensity statins for patients with severely elevated LDL cholesterol, prior atherosclerotic cardiovascular disease (ASCVD) or diabetes with high 10-year risk. Moderate intensity statins are recommended for other statin benefit groups.
Methods: We examined statin use and dosage intensity among 6,198 patients meeting indications for statins for primary or secondary prevention in 2015 at 135 primary care and specialty clinics in the PALM registry.
Results: Overall, 4519 (72.9%) of patients in a statin benefit group were on a statin. Of those recommended for a high intensity statin (n=3240, 52% overall), only 28.9% were on one; 71.1% were undertreated (either not on treatment or on a lower intensity statin than recommended - TABLE). In patients recommended for moderate intensity statins (n=2958, 48% overall), 58.9% were on a moderate or higher intensity statin; 41.2% were undertreated. Undertreated patients were younger (median age 66 vs 68 years), more likely to be female (48.2% vs 41.7%), African American (15.4% vs 10.6%), have diabetes 45.9% vs 33.9%), and less likely to be seen by a cardiologist (38.2% vs. 48.2%, $p<0.01$ for all comparisons) than those who were treated per guidelines.
Conclusion: One year after guidelines changed, gaps exist in both statin use as well as dosage intensity.
Acknowledgement/Funding: Regeneron and Sanofi Pharmaceuticals

Statin use by recommended intensity

	Moderate intensity recommended	High intensity recommended
Overall	N=2958	N=3240
On high intensity statin	411 (14%)	936 (29%)
On moderate intensity statin	1329 (45%)	1396 (43%)
On lower intensity statin	220 (7%)	227 (7%)
Not on statin	998 (34%)	681 (21%)
Primary prevention	N=2033	N=1105
On high intensity statin	194 (10%)	175 (16%)
On moderate intensity statin	870 (43%)	486 (44%)
On lower intensity statin	144 (7%)	97 (9%)
Not on statin	825 (41%)	347 (31%)
Secondary prevention	N=925	N=2133
On high intensity statin	217 (23%)	761 (36%)
On moderate intensity statin	459 (50%)	910 (43%)
On low intensity Statin	76 (8%)	130 (6%)
Not on statin	173 (19%)	332 (16%)

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Management of overweight and obesity in patients at high cardiovascular risk across Europe: results from EUROASPIRE IV survey

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Background: EUROASPIRE IV in primary care was a cross-sectional survey carried out by the European Society of Cardiology, EURObservational Research Programme in 2014–2015 in 14 European countries. The main objective was to determine whether the 2012 Joint European Societies' guidelines on cardiovascular disease (CVD) prevention in people at high cardiovascular risk have been followed in everyday clinical practice.
Purpose: To determine the prevalence and management of obesity and central obesity in people at high risk of developing cardiovascular disease
Methods: Patients without a history of coronary or other atherosclerotic disease either prescribed blood pressure and/or lipid and/or glucose lowering treatments were identified retrospectively from general practices medical records and interviewed and examined at least six months after the start of medication.
Results: 6,700 medical notes were reviewed and 4,579 patients (59% women; mean age 58.8 (SD 11.3) years) interviewed using standardised methods and instruments (interview rate 68%). Overall, 83% were overweight (BMI $\geq$25kg/m^2), 43% obese (BMI $\geq$30kg/m^2) and 64% centrally obese (waist circumference of $\geq$88 cm for women and $\geq$102 cm for men). Obesity and central obesity were more prevalent in women (46% women, 40% men) and (72% women, 52% men), respectively. Obesity was a major health problem across all 14 countries (18% in Bosnia & Herzegovina up to 56% in Russian Federation). Similar variations were observed for central obesity (50% in Bosnia & Herzegovina up to 86% in Bulgaria). Nearly 20% of the obese patients claimed to have never been told being overweight, only 44% of them tried actively to lose weight during the past month and 52% intended to do so next month. Since their hospital discharge, just half of the obese patients (50%) had followed dietary recommendations to lose weight, 37% tried to engage in more physical activity and 3% used weight reduction drugs. 12% of obese patients were not aware of their weight. The comparison with the previous survey demonstrated no change in terms of obesity; the central obesity rates increased by 6% (p=0.053).
Conclusions: The management of obesity and central obesity in patients at high CVD risk across Europe is a cause of concern. More intensive preventive cardiology programmes, appropriately adapted to medical and cultural settings in each country, focusing on diet and especially physical activity are required in order to reduce the future risk of cardiovascular disease.
Acknowledgement/Funding: European Society of Cardiology through unrestricted educational grants from Amgen, BMS/AstraZeneca, F. Hoffmann La Roche, GlaxoSmithKline, Merck & Co

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Barriers to uptake of cardio-protective treatment in a community elderly population of stage B heart failure

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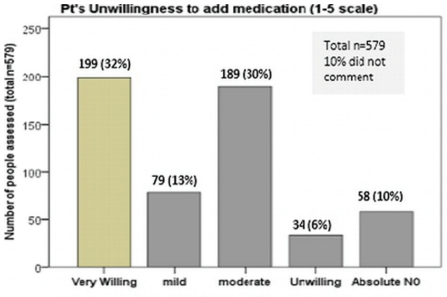
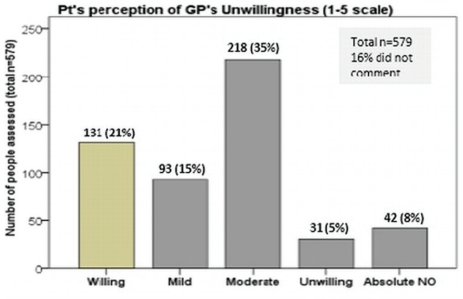
Background: The detection of stage B heart failure (SBHF), has been facilitated by modern imaging, but improved outcomes have not been proven. We performed a community screening and intervention trial of cardio-protection for SBHF.
Method: Between 9/2013 and 11/2015, 610 asymptomatic community-based patients with HF risks were randomized to advanced echocardiography (AE; myocardial deformation and detailed diastolic function examination) for diagnosis of SBHF and subsequent cardio-protective intervention or control (C; ejection fraction alone). At an interval of 3 months, a process evaluation was conducted using a telephone interview and questionnaire. Adherence was defined by initiation and

optimization of treatment. Patients were followed for 1 year for the primary composite end point of death from cardiovascular causes and new HF.

Results: Of 308 randomized individuals, 219 were identified by AE as having SBHF and treatment was advised. At 3 months, 206 responded to evaluation, of whom 87 (42%) were adherent and 119 (58%) were not. Of the entire cohort, 59% reported some degree of unwillingness and 10% were very unwilling. From the perspective of participants, 62% of their physicians were somewhat unwilling to adopt therapy, and 8% were very unwilling. Non-adherence was associated with unwillingness of either the internist or patient ($p<0.027$) and difficulties to obtain medication, but was not associated age, gender, clinical characteristics, socio-economic disadvantage and difficulties in accessing medication ($p\geq0.054$). At 1 year follow-up, 61 developed new HF and 2 died of cardiovascular causes, an annualized incident rate of 9.5%. No outcome difference was observed between the two imaging arms.





	OR (95%CI)	p value
Age (year)	0.987 (0.93, 1.04)	0.641
Gender male	1.218 (0.70, 2.12)	0.485
Duke activity score index (MET)	0.894 (0.75, 1.06)	0.207
General Health utility (EQ5D)	0.305 (0.05, 1.72)	0.179
Minnesota Living with H^F (score)	1.011 (0.99, 1.03)	0.256
Depression status (PHQ9)	1.032 (0.95, 1.12)	0.453
Anxiety status (GAD7)	1.129 (0.99, 1.28)	0.054
Social economical ranking(SEIFA)	0.988 (0.88, 1.10)	0.826
Education level ≥ University	1.394 (0.68, 2.87)	0.366
Living alone	1.034 (0.58, 1.86)	0.910
Private Health insured	1.095 (0.59, 2.01)	0.771
Financial difficulty to pay for pills	1.135 (0.81, 1.60)	0.471
Difficult to obtain pills	1.667 (0.87, 3.19)	0.124
Pt's Unwillingness	1.287 (1.03, 1.61)	0.025
Pt's perception of GP's unwillingness	1.329 (1.03, 1.71)	0.027

Conclusion: Participant non-adherence to treatment is a potential obstacle in HF prevention among SBHF. Attitude to additional therapy seemed the main barrier of success, more so than conventional clinical and social economical determinants.

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Low socioeconomic status is associated with recurrent atherosclerotic cardiovascular disease event in a population with stable coronary heart disease

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Background: Short and long term survival after myocardial infarction (MI) has increased with improved treatment. It is unclear if current risk assessment for atherosclerotic cardiovascular disease (ASCVD) in healthy individuals is applicable to the growing population with prevalent cardiovascular disease. New predictive risk factors are warranted to better stratify patients in secondary prevention for incident ASCVD. The association of socioeconomic status (SES) with ASCVD has not been studied previously in the stable phase post MI.

Purpose: We sought to investigate whether SES is associated with a second incident ASCVD in a population with stable coronary heart disease after MI.

Methods: A total of 29952 men (73%) and women (27%), mean age 63 (40–76) years, were identified from the Swedish nationwide registry: Secondary Prevention after Heart Intensive Care Admission (SEPHIA) 2005–2014 at revisits 11–15 months after their first MI. Statistics Sweden and the National Board of Health and Welfare provided data on disposable income the year before MI, marital status, level of education (SES variables) and subsequent ASCVD as defined by 2013 ACC/AHA Guideline on the Assessment of Cardiovascular Risk.

The association between SES variables and incident ASCVD was estimated using multivariable Cox regression analysis adjusted for age, gender and smoking-status.

Results: During a mean follow-up of 4.1 years, 2405 (8%) patients suffered a second ASCVD event. There was an independent association between disposable income level (Table 1), as well as divorced marital status (HR 1.14 95% CI 1.02–1.26) compared with married, and incident ASCVD. A lower level of education was associated to incident ASCVD in crude analysis.

Table 1

Disposable income per household unit† (quintiles)	ASCVD event per person-year	Incidence rate per 1,000 person-years (95% CI)	Multivariable adjusted‡ HR (95% CI)
Q1 (lowest)	697/26,870	25.9 (24.1–27.9)	1.00
Q2	568/25,594	22.2 (20.4–24.1)	0.87 (0.77–0.98)
Q3	466/25,351	18.4 (16.8–20.1)	0.76 (0.67–0.87)
Q4	368/23,920	15.4 (13.9–17.0)	0.68 (0.59–0.78)
Q5 (highest)	302/21,091	14.3 (12.8–16.0)	0.64 (0.55–0.75)

†The year before first MI. ‡Variables: age, gender, smoking status, level of education and marital status.

Conclusion: Low income and being divorced were independent predictors of subsequent ASCVD in a large representative population with stable coronary heart disease post MI. Our data indicate that SES should be included in risk assessment for secondary prevention post MI.

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Improvement in achievement of lipid targets in France: comparison of data from the DYSIS I and DYSIS II studies

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Background: Hyperlipidaemia is a major contributor to the development of coronary heart disease (CHD), with a direct correlation between all-cause mortality and low-density lipoprotein cholesterol (LDL-C). In DYSIS I, almost half of statin-treated patients missed their therapeutic LDL-C goal, highlighting a gap between guidelines and clinical practice.

Purpose: To determine whether attainment of lipid therapeutic targets has improved in France, by comparing data from the observational DYSIS I and II studies.

Methods: DYSIS I was a multinational cross-sectional study involving patients ≥45 years seen in primary/secondary care on statin treatment for ≥3 months (September 2008-February 2009). DYSIS II was a multicentre prospective cohort study involving patients ≥18 years with stable CHD or hospitalized with an acute coronary syndrome (July 2013 to October 2014). We present comparative data from patients enrolled in France in DYSIS I and DYSIS II.

Results: Compared with DYSIS I CHD patients, fewer patients in DYSIS II had hypertension, heart failure or diabetes (Table). Mean statin dose (atorvastatin equivalent) had increased in DYSIS II whereas the proportion on combination lipid-lowering therapy had decreased. The mean LDL-C value had decreased, with more than twice as many patients achieving the LDL-C target of <1.8 mmol/L.

Variable (% or mean ± SD)	DYSIS I (n=1470)	DYSIS II (n=591)	P value
Age, years	67.7±9.9	67.7±11.9	0.63
Men	78.8%	81.0%	0.25
Hypertension	71.5%	56.9%	<0.0001
Diabetes	35.1%	26.7%	<0.001
Heart failure	14.8%	4.7%	<0.0001
Statin treatment	100%	92.9%	<0.0001
Statin dose (atorvastatin equivalent), mg/day	19.6±17.2	30.2±25.1	<0.0001
Statin+other LLT	18.1%	12.6%	<0.01
Statin+ezetimibe	16.1%	12.1%	<0.05
LDL-C, mmol/L [mg/dL]	2.62±0.88 [101.5±33.9]	2.17±0.80 [84.1±30.9]	<0.0001
LDL-C <1.8 mmol/L (70 mg/dL)	15.3%	34.5%	<0.0001
Distance to target (<1.8 mmol/L), mmol/L [mg/dl]	1.0±0.79 [39.3±30.6]	0.79±0.63 [30.5±24.3]	<0.0001
LDL-C <2.5 mmol/L (100 mg/dL)	52.8%	72.1%	<0.0001

Conclusions: These data show substantial improvements in attainment of therapeutic LDL-C goals, but nearly two-thirds of patients still have elevated LDL-C and remain at greater risk of a cardiovascular event.

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Forty year trends in premature CHD mortality among men and women in Eastern and Southwestern Finland

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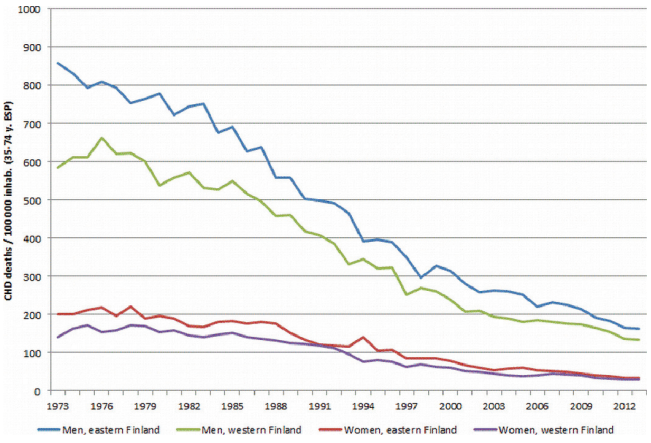
Purpose: In the 1960s and early 1970s, coronary heart disease (CHD) mortality in Finland was the highest in the world, and within Finland, mortality was particularly high in the eastern part of the country. North Karelia Project, the first large community-based CVD prevention program was established in 1972 in order to reduce the extremely high CHD mortality through behavioral change and reduction of the main CVD risk factors among the whole population of North Karelia, the easternmost province of Finland. In the present study we describe forty year trends in premature CHD mortality among men and women in Eastern and Southwestern Finland.
Methods: Study population consists of permanent residents of the province of Southwestern Finland and North Karelia and North Savo provinces in Eastern Finland. Data on CHD mortality were obtained from the National Causes of Death Register. The following ICD codes were classified as CHD deaths: ICD 8 and 9 410–414, and ICD 10 I20-I25. CHD deaths at age between 35 and 74 years were considered as premature. Mortality rates were standardized for European Standard population. The study covers the period from 1973 to 2013.
Results: In the early 1970s, premature CHD mortality in Eastern Finland was about 37% higher in men and 23% higher in women, compared with the southwestern part of the country. During the four decades premature CHD mortality declined markedly in both areas, but the decline was faster in Eastern Finland. In Eastern Finland, age-adjusted mortality reduced from 858 to 163 per 100,000 among men, and from 202 to 34 per 100,000 among women. In Southwestern Finland the decline was from 585 to 135 and from 140 to 29 per 100,000, respectively. The average annual decline was 4.4% ($p<0.001$) in men and 4.9% ($p<0.001$) in women in Eastern Finland, and 4.2% ($p<0.001$) in men and 4.8% ($p<0.001$) in women in Southwestern Finland.



Conclusions: Premature CHD mortality declined markedly both in Southwestern and Eastern Finland, but the decline was faster in Eastern Finland. At the end of the survey period differences in premature CHD mortality between the two areas had nearly disappeared. Even though the genetic background in Southwestern and Eastern Finland may be different, CVD mortality decline is explained by environmental factors, mainly changes in major cardiovascular risk factors.

METABOLISM, ADIPOSE TISSUE AND CARDIOVASCULAR DISEASE

288 | BENCH
The novel heart-specific ring finger protein 207 regulates energy metabolism in cardiomyocytes

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Background: RING-finger proteins constitute a large protein family in the human genome and play essential roles in various biological processes. However, few reports have revealed that RING-finger proteins are associated with developing cardiac dysfunction. Moreover, little is known about heart-specific RING-finger proteins and those relations with cardiac functions. We performed the comprehensive analysis of the expression profiles of various kinds of RING-finger proteins and found that RING-finger protein 207 (RNF207) was largely expressed in the heart. The purpose of our study was to elucidate a role of RNF207 in the heart.
Methods and results: Reverse transcription qPCR (RT-qPCR) and immunoblot analysis revealed that RNF207 was predominantly expressed in the heart at the mRNA and protein level, respectively. Next, we examined whether the expression of RNF207 changed in mouse models of cardiac disease, including transverse aortic constriction (TAC) model, ischemia/reperfusion (I/R) model and coronary ischemic heart failure (HF) model. 4 weeks after TAC or 24 h after reperfusion, mRNA level of RNF207 was significantly decreased to approximately 40% of that in sham mice. Moreover, we found that the protein level of RNF207 in the hearts with HF was significantly reduced to 70% of that in sham mice. Considering the well-known facts that rates of ATP turnover in the hearts are much larger than those of any other organs and that cardiac energy metabolism changes and the levels of ATP in cardiomyocytes are reduced in those three model mice, we hypothesized that RNF207 was associated with cardiac energy metabolism. To investigate the hypothesis, using small interfering RNA (siRNA) we depleted RNF207 in rat neonatal cardiomyocytes (RNC) and performed metabolomic analysis to determine the amounts of various intracellular metabolites. Metabolomic analysis revealed that ATP concentration and NADH/NAD+ ratio were significantly lower in RNF207 depleted RNC, compared to control NRC. In addition, mitochondrial function in RNF207 depleted NRC was significantly reduced, compared to control NRC. Intriguingly, the amount of almost all amino acids was also significantly decreased in RNF207 depleted RNC. Next, to adress the molecular mechanism by which RNF207 had effect on cardiac energy metabolism, we explored RNF207-associated proteins by mass spectrometric analysis. We identified voltage-dependent anion channel 1 (VDAC1) as a RNF207-associated protein. It has been shown that VDAC1 exists in the outer mitochondrial membrane and plays a crucial role in mitochondrial functions, such as energy metabolism. We confirmed that RNF207 directly interacted with VDAC1 by in vitro binding assay. These results strongly indicate that RNF207 functions as a regulator of cardiac energy metabolism.
Conclusion: RNF207 is a novel heart-specific protein and regulates energy metabolism in cardiomyocytes.

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Diet-induced obesity requires signalling through Tumor Necrosis Factor Receptor-Associated Factor 1 (TRAF-1) in adipocytes

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Background: Accumulation of inflammatory leukocytes is a prerequisite of adipose tissue inflammation during cardio-metabolic disease. We recently reported that a genetic deficiency of the intracellular signalling adaptor TRAF-1 attenuates inflammatory cell recruitment and vascular inflammation in atherosclerosis. Here, we tested the contribution of TRAF-1 to diet-induced obesity (DIO) in mice.
Methods and results: To test the association of TRAFs and obesity we screened for expression of different TRAFs in adipose tissue. We found an up-regulation of TRAF-1 mRNA in obese mouse and human adipose tissue, resulting from higher gene expression in adipocytes, but not in adipose tissue macrophages. To test a functional relevance of TRAF-1 signalling in obesity, WT or TRAF-1–/– mice consumed a high fat diet HFD for 20 weeks. Surprisingly, genetic deficiency of TRAF-1 abolished diet-induced weight gain by suppressing peripheral fat depositions. Consequently, TRAF-1–/– mice demonstrated ameliorated glucose levels after glucose and insulin tolerance tests and dampened insulin signalling. Consistently, we also found reduced accumulation of adipose tissue macrophages. Mechanistically, TRAF-1–/– mice demonstrated no differences in basic energy metabolism, such as in energy expenditure. However, TRAF-1–/– adipocytes had higher expression of Adipose Triglyceride Lipase (ATGL) and Hormone-sensitive Lipase (HSL), suggesting increased lipid breakdown in adipocytes. In accord, plasma levels of free fatty acids were higher, while leptin levels were reduced in TRAF-1–/– mice. Finally, in a collective of patients with a high prevalence of the metabolic syndrome, TRAF-1 expression correlated with the metabolic syndrome, suggesting clinical relevance of our findings.
Conclusion: We present the novel finding that the signalling adapter TRAF-1 correlates with obesity in mice and humans. Genetic deficiency of TRAF-1 attenuates diet-induced obesity by increasing lipolysis in adipocytes. These findings identify TRAF-1 as a novel therapeutic target in obesity and adipose-tissue inflammation.

290 | BENCH
Maternal fructose exposure during pregnancy and lactation in rats modulates the cardiac stress response in the offspring

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Background: Recent studies demonstrated that the adult metabolic syndrome and high risk in cardiovascular diseases could be elicited by the developmental programing which is regulated by the prenatal environment.
Methods: We examined the effects of maternal uptake of fructose during pregnancy and lactation on cardiac development and the prognosis after pressure overload-induced cardiac hypertrophy in 12-weeks old adult rat offspring.
Results: Echocardiographic examination found that the heart weigh, interventricular septal thickness in diastole (IVD; d), and left ventricular posterior wall thickness in diastole (LVPW; d) were higher in offspring with maternal fructose

exposure (MFE), however, the left ventricular ejection function was not affected. Histopathological examination showed the indices of fibrosis and oxidative stress were higher in offspring with MFE. Molecular examination showed the phosphorylation of p38 was significantly increased with MFE. Next generation sequence (NGS) analysis indicated the expression levels of several cardiac hypertrophy-associated genes, including GPR22, Myh7, Nppa, P2rx4, and Npy were regulated by MFE. The insulin-mTOR nutrition sensing signaling were also regulated by MFE. Furthermore, results of RT-PCR also indicated the expression levels of genes related to cardiac hypertrophy and oxidative stress were also regulated by MFE. In the stress response to pressure overload, MFE significantly increased the fibrotic areas and morality rate after induction of pressure overload by transverse aortic constriction.

Conclusion: MFE during pregnancy and lactation modulated the myocardial gene expression profiles and the stress response to pressure overload in the rat offspring.

Acknowledgement/Funding: Chang Gung Memorial Hospital, CMRPG 8C0061 8C0062 8C0063

DRUG-ELUTING STENT

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Ten year clinical outcome of a large registry with unrestricted use of DES

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Background: The long-term prognostic differences between bare metal stents (BMS) and drug eluting stents (DES) after percutaneous coronary intervention (PCI) remain unclear. The goal of this study was to investigate BMS vs first generation DES for target lesion revascularization (TLR) as primary endpoint and all-cause mortality, myocardial infarctions (MI), target vessel revascularization (TVR), non-TLR as secondary with major adverse cardiac events (MACE) as a composite endpoint during 10 years of follow-up.

Methods and results: 7669 different patients received a PCI in the Erasmus MC between January 2000 until March 2007 with a BMS or a first generation DES. Patient and procedural characteristics were prospectively entered into a dedicated database. An increase in PCI indication between the BMS and DES group towards STEMI (22.5% vs 33.9%) was observed. The drug eluting stents showed lower event rates and hazard ratios for mortality, TLR, and TVR respectively: 28.9% vs 26.7%, HR: 0.88 (0.78–0.99), 13.8% vs 11.6%, HR: 0.53 (0.45–0.63), 22.4% vs 17.7%, HR: 0.54 (0.47–0.62) MACE only showed a lower hazard ratio, HR: 0.85 (0.78–0.92) for MACE. There were no differences in MI rate and non-TLR. Use of DES had the highest impact on TLR and TVR with the clear separation between early vs late follow-up. For the first year the HR of DES for TLR was 0.35 (0.28–0.44), but after the second year the HR of DES for TLR was increased: 1.45 (1.03–2.04) resulting in a rate of 0.9% TLR per year for DES vs 0.4 for BMS. Predictors of early (0–1 year) and late (2–10 year) DES were similar: Diabetes, prior PCI, and total stent length, while smallest stent diameter had only an impact on early TLR and as mentioned use of DES for late TLR.

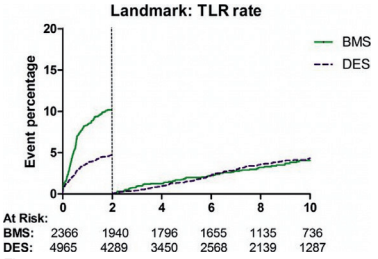

Figure 1

Conclusions: During a 10 year follow-up after PCI with DES or BMS, drug eluting stents were associated with lower all-cause mortality. However, there does appear to be a catch up effect in TLR, MI, TVR, and non-TLR rates at the expense of DES.

Acknowledgement/Funding: Abbott Vascular

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Long-term risk of stent thrombosis and restenosis after treatment with drug-eluting stents: A report from SCAAR

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Background: Studies have shown that drug-eluting stents (DES) differ in safety and efficacy. Long-term effects of DES are not well-studied. The aim of this study was to compare commonly used DES in regard to long-term risk of restenosis and stent thrombosis.

Methods: We used data from the SCAAR registry (Swedish Coronary Angiography and Angioplasty Registry) for the PCI procedures performed in Sweden. The database contains information about all procedures performed at five PCI centers (~20% of all SCAAR data). All consecutive procedures performed between 2004 and 2015 for stable angina, UA/NSTEMI and STEMI were included in the analysis. We compared three different DES: Cordis Cypher Select [C-CS, (n=2210)], Abbott Xience Xpedition [A-XX, (n=2006) and Medtronic Resolute Integrity [M-RI, (n=9790)]. The three DES used during the study period are the result of biannual stent procurement procedures in our region. We used multilevel Cox proportional-hazards regression with stents as the primary observational unit with patients and hospitals as random effect variables. To adjust for differences in patient's characteristics the following variables were used: age, gender, hypertension, hyperlipidemia, smoking status, diabetes, severity of coronary artery disease, indication for PCI (stable angina, UA/NSTEMI and STEMI), stent length and stent diameter. The primary combined endpoint was time to first occurrence of either stent thrombosis or restenosis. The secondary endpoints were time to stent thrombosis and time to restenosis.

Results: During the study period, 14,006 stents were implanted in 6969 patients. The mean follow-up time was 705 days for A-XX, 429 days for M-RI and 2288 days for C-CS. There were 527 events of which 139 (25.8%) were stent thromboses. Treatment with M-RI was associated with lower risk for restenosis or stent thrombosis compared to A-XX (HR 1.38; 95% CI: 1.03–1.86; P=0.03) and C-CS (HR 2.47; 95% CI: 1.94–3.16; P<0.001). Compared to M-RI, the risk for stent thrombosis was higher in C-CS (HR 1.78; 95% CI: 0.11–2.84; P=0.02) while no difference was observed between M-RI and A-XX (HR 1.52; 95% CI: 0.92–2.49; P=0.10). Similarly, the risk for restenosis was lower in M-RI compared to C-CS (HR 2.84; 95% CI: 2.10–3.83; P<0.001) while no difference was observed between in M-RI and A-XX (HR 1.35; 95% CI: 0.93–1.95; P=0.11).

Conclusion: In this observational study, treatment with M-RI stents was associated with the lower risk of restenosis and stent thrombosis compared to A-XX and C-CS stents.

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Long-term clinical outcomes of biolimus-eluting stents with biodegradable versus bare-metal stents in patients with acute STEMI: 5 Year results of the randomized COMFORTABLE AMI trial

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Background: Biolimus-eluting stents with biodegradable polymer (BES) were designed with the aim to improve long-term safety and efficacy by elimination of the permanent surface polymer used for drug release in order to overcome delayed arterial healing, a particular concern in patients with ST-segment elevation myocardial infarction (STEMI) patients. The performance of BES as compared with bare-metal stents (BMS) in STEMI patients after cessation of dual antiplatelet therapy beyond one year remains unknown. We report here the final outcomes of the randomized COMFORTBALE AMI trial at 5 years.

Methods: This was a multicentre superiority trial. Between September 19, 2009, and January 25, 2011, 1157 patients with STEMI were randomly assigned to treatment with BES (n=575) or BMS (n=582) at 11 international centers. Clinical follow-up was performed throughout 5 years. The primary endpoint was a composite of cardiac death, target-vessel related reinfarction (TV-MI) and ischemia-driven target-lesion revascularization (ID-TLR).

Results: Follow-up was available in 95.6% of BES and 94.5% of BMS group. MACE occurred in 8.6% of BES and in 14.9% of BMS treated patients (HR 0.56, CI 0.39–0.79, p=0.031). The difference was driven by a lower risk of TV-MI (2.2% versus 5.0%, HR 0.44, 95% CI 0.22–0.87, p=0.018) and ID-TLR (4.4% versus 10.4%, HR 0.41, 95% CI 0.25–0.66, <0.001) in BES treated patients. There were no differences between BES and BMS treated patients in terms of cardiac death (4.9% versus 5.5%, HR 0.87, 95% CI 0.52–1.47, p=0.61). The patient-oriented composite of death, reinfarction and revascularization was less frequent in BES treated patients (22.6% versus 28.1%, HR 0.77, 95% CI 0.61–0.98, p=0.03). The overall rate of definite stent thrombosis was numerically lower in BES compared with BMS treated patients (2.2% versus 3.9%, HR 0.57, 95% CI 0.28–1.16, p=0.12) and very late stent thrombosis occurred at a similar frequency (1.3% versus 1.6%, p=0.77). No difference in cardiovascular medication including antiplatelet regimen was observed throughout 5 years.

Conclusion: BES is associated with a significant reduction in MACE throughout 5 years, driven by a significant reduction in target-vessel related reinfarction and ischemia-driven target-lesion revascularization.

Acknowledgement/Funding: Swiss National Science Foundation

ONE TO TEN IN EXERCISE, PHYSICAL ACTIVITY AND CARDIOLOGY

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Contemporary reference values for peak oxygen uptake in healthy European children and adolescents

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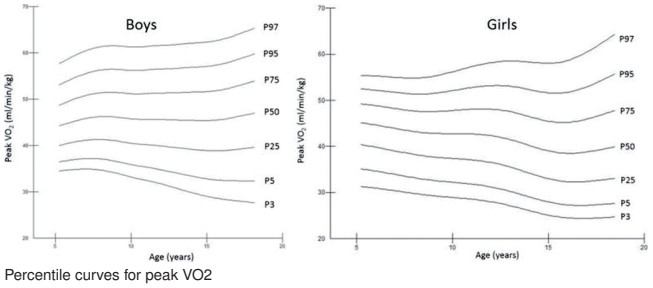
Background: The aim of the present study was to establish prediction equations and to describe contemporary reference values for healthy boys and girls from West-Europe.
Design: Cross sectional multicenter study.
Methods: Between January 2000 and April 2015, 1580 healthy children (1010 boys; mean age 12.4 years; range 5–18) completed a maximal graded exercise test until volitional exhaustion either on a bicycle or on a treadmill. Minute ventilation, oxygen uptake (VO2), and carbon dioxide (CO2) production were measured on a breath-by-breath basis and continuous electrocardiography was performed. Peak VO2 was expressed per kg bodyweight. Prediction equations based on sex, age and weight were calculated by means of regression analysis and cross-validated through concordance correlation coefficient determination and Bland-Altman analyses. LMS chart maker was used to provide age-related percentile curves.
Results: Multivariate regression analysis revealed age, sex and weight as statistically significant determinants of peak VO2. Hence, following prediction equation was established and cross-validated: peak VO2 = 44.5 – 218*sex + 27.1*age + 37.4*weight ($p \leq 0.001$; sex=0 for boys and sex=1 for girls). Finally, the distribution of peak VO2 per kg body weight with age was descripted by percentile curves (Figure) and reference values were established for boys and girls separately.



Percentile curves for peak VO2

Conclusions: Our study is the largest and most recent population-based study to provide sex-specific reference data and a prediction equation for peak VO2 for a West-European population of healthy children between the ages of 6–18 years.

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Referance values for cardiopulmonary function in older men and women: the generation 100 study

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Background: Reference values on cardiopulmonary function at rest and during exercise in elderly are limited, and derived from relatively small studies. In addition, previous studies exclusively exclude people with cardiovascular diseases. The aim of this study was to establish reference values for cardiopulmonary function and objectively measured fitness in a general older population.
Methods: All men and women born in the years 1936 to 1942 (n=6966) who were residents in our city, were invited to participate. In total 1567 (790 women) fulfilled the inclusion criteria for the study. Clinical examinations and cardiopulmonary exercise tests (CPET) were performed.
Results: Data from the CPET test show that there were a significantly gender difference in peak oxygen uptake (26.2±5.0 and 31.3±6.7 mL/min/kg for women and men, respectively), peak CO2 production (2.9±0.2 and 1.9±0.1 L/min for women and men, respectively), peak ventilation 61.1±21.6 and 96.2±21.7 L/min for women and men, respectively), and peak breathing frequency 39.7±7.1 and 41.8±8.0 breath/min for women and men, respectively). Anaerobic threshold was achieved at 87.7±7.8 and 86.9±7.9% of VO2peak for women and men, respectively. Peak oxygen uptake was 19.5% lower for women with cardiovascular disease compared to those who report to use no medication ($p<0.01$). Men with cardiovascular disease had a 19.5% lower peak oxygen uptake compared to men reporting to use no medication ($p<0.01$). Peak heart rate was significantly lower for both women and men with cardiovascular disease compared to those who report no use of medication (–5 and –9 beats per minutes for women and men, respectively).
Conclusion: Our study represents the largest reference material on objectively measured fitness and cardiopulmonary function in elderly men and women. This study is the first to included older adults with cardiovascular diseases in the material.

Acknowledgement/Funding: The K.G. Jebsen foundation, Central Norway Regional Health Authority, Research Council of Norway

386 | BEDSIDE
Exaggerated blood pressure increase with exercise and risk of all-cause mortality and major cardiac events in patients with known or suspected coronary artery disease

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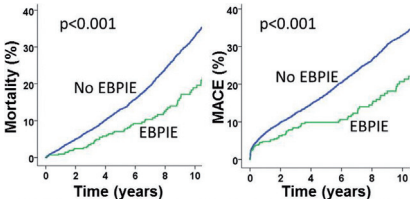
Purpose: The association of exercise blood pressure response with outcome remains controversial. We sought to assess the association between an exaggerated blood pressure increase with exercise (EBPIE) with the risk of all-cause mortality and major cardiac events in patients with known or suspected coronary artery disease (CAD).
Methods: Exercise echocardiography was performed in a community-based sample of 10,047 patients with known or suspected CAD between March 1995 and December 2013. Patients who had received betablockers within 48 hours before testing and those in whom systolic blood pressure failed to increase with exercise over baseline values were excluded. An EBPIE was defined as an increase in systolic blood pressure with exercise higher than the 95th percentile value (i.e., >80 mmHg). The endpoints were all-cause mortality and major cardiac events (MACE), including cardiac death or nonfatal myocardial infarction.
Results: Mean age was 62±12 years, and 6,105 patients (60.8%) were male. A total of 573 patients exhibited an EBPIE during the tests. Over a mean follow-up of 4.8 years, there were 1,950 deaths (including 725 cardiac deaths), 1,477 myocardial infarctions, and 1,900 MACE. The cumulative 10-year rates of all-cause mortality, cardiac death, nonfatal myocardial infarction and MACE were 32.9%, 13.1%, 26,9% and 33% in patients who did not develop an EBPIE vs. 18.9%, 4.7%, 17.5% and 20.7% in those experiencing an EBPIE, respectively ($p<0.001$ for all comparisons) (Figure). In Cox regression analyses, an EBPIE remained predictive of all-cause mortality (hazard ratio [HR] 0.72, 95% confidence interval [CI] 0.58–0.89, p=0.003), cardiac death (HR 0.67, 95% CI 0.46–0.99, p=0.04), myocardial infarction (HR 0.67, 95% CI 0.53–0.87, p=0.002), and MACE (HR 0.69, 95% CI 0.56–0.87, p=0.001).



Mortality and MACE curves

Conclusions: An EBPIE was associated with a significantly lower risk of mortality and MACE in a series of patients with known or suspected CAD referred for exercise echocardiography.

387 | BENCH
Vagal tone and exercise capacity

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Background: Higher baroreflex sensitivity, an enhanced high frequency component of heart rate variability and a faster heart rate recovery after cessation of exercise in elite athletes suggests plasticity in the central nervous mechanisms which control the heart. This experimental study was designed to directly test the hypothesis that the strength of parasympathetic tone determines exercise capacity. We hypothesised that vagal withdrawal should decrease and vagal recruitment should enhance exercise capacity. We targeted vagal preganglionic neurones of the dorsal motor nucleus of the vagus nerve (DVMN) which provide functional innervation of the left cardiac ventricle.
Methods: In male Sprague-Dawley rats (380–420g) DVMN neurones were transduced to express an inhibitory Gi-protein-coupled Drosophila allatostatin receptor (AlstR) (n=8) or green fluorescent protein (GFP) as a control (n=8). Application of the insect peptide ligand allatostatin (5 μl) produces selective and rapid inhibition of targeted neurones. A pharmacological study investigated the role of muscarinic and neuronal nitric oxide-mediated mechanisms using systemic treatment with atropine methyl nitrate (2 mg/kg, i.p., n=5) or selective neuronal NO synthase inhibitor 7-nitroindazole (7-NI) (30mg/kg, i.p., n=8). For optogenetic activation, DVMN neurones were targeted to express an optogenetic construct ChiEF (n=9) or control transgene GFP (n=10) and stimulated with blue laser light (445 nm, 10 ms pulses, 15 Hz, 15 min). Exercise capacity was determined using a single lane treadmill with a shock grid set at the minimum threshold of 0.1 mA. Rats were preselected for their compliance after a three-day recruitment protocol and

randomized. The experimental protocol involved starting speeds of 20–30 cm/s over 5 min after 15 min acclimatisation. Speeds were then raised in increments of 5 cm/s every 5 min until the hind limbs made grid contact 4 times within a 2 min period. The calculated work (Joules, J) was used as an index of exercise capacity.
Results: Acute inhibition of the DVMN neurones by allatostatin resulted in a dramatic reduction in exercise capacity (8±2 vs 202±27J; P<0.0001; ANOVA). In rats given atropine and vehicle no significant differences in exercise capacity were observed (113±20 vs 112±22J, p=0.9; t-test). Systemic administration of 7-NI was associated with a significant reduction in exercise capacity (33±19 vs 129±19J, p=0.0002; t-test), as did 4h of atropine treatment (63±12J vs 116±20J, p=0.0019; t-test). Rats expressing ChIEF by the DVMN neurones displayed significantly higher exercise capacity following 4 days of optogenetic stimulation (94±11 vs 47±6J; p=0.002; ANOVA). Improvements were similar to that observed in the naïve rats trained to exhaustion over the same time period (105±16 vs 47±6 J in rats expressing eGFP; p<0.0001; ANOVA).
Conclusion: These results suggest that the strength of parasympathetic tone determines exercise capacity.

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The introduction of focused echo in the pre-participation screening for non-elite athletes: is it sustainable?

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Introduction: The modalities of pre-participation screening to prevent sudden cardiac death in athletes are controversial. In Italy Ecg is mandatory but ECHO is uncommon. A focused echocardiogram is a useful modality to identify structural abnormalities in asymptomatic athletes, but its cost-effectiveness is uncertain.
Purpose: The primary aim of this study was to determine the incremental value of focused echocardiography added to a screening program consisting of history, physical examination and ECG in a large cohort of non-elite athletes with a wide range of age (6 to 72 years). We also sought to measure the cost of carrying out such a screening program.
Methods: We examined 1837 non-elite athletes (78.4%men; 25.1±14.9 years; 25% over 35years). All athletes underwent a standardized medical history, physical examination, resting and stress ECG and Focused Echo (12min/8images). Ecg was interpreted based on Refined-criteria. For the purpose of the study we included also a "Standard-Echo" as reference, to calculate the specificity and sensitivity of each screening program. Athletes with abnormalities underwent further examinations according to the European Guidelines. Costs involved with this study included the costs of both overall screening program until diagnosis. The estimated cost to carry out screening modalities was € 45.00 and € 80.00 for screening without and with focused echo respectively.
Results: Eight athletes had cardiac findings associated with an elevated risk for sudden death: prolonged QTc>500 ms (n=1), WPW pattern (n=2) and hypertrophic cardiomyopathy (n=1) identified with ECG; dilated cardiomyopathy (n=1), significant aortic root dilation (n=2) and hypertrophic cardiomyopathy (n=1) detected by Echo. Ninety-two athletes (5%) underwent additional investigations after the ECG, while Thirty-eight athletes (2%) were recommended for further examinations after ECG and Focused Echo. Thirty-one (1.68%) had a minor abnormality: bicuspid aortic valve (n=7), mitral valve prolapse (n=2), atrial septal defect (n=1), ventricular septal defect (n=1), mild and moderate aortic regurgitation (n=8) and mild hypertrophy (n=6) identified only by Focused Echo. Focused echo avoided for 81 (4,41%) athletes cardiology referrals or later additional imaging for findings on physical examination and electrocardiogram.
The cost per athlete was € 60.00 for screening considering only the Ecg and € 92.00 with focused echo while the average cost per athlete with cardiac disorder was € 9,985.00 (cost per athletes at risk of SCD € 27,461.00) and € 4,336.00 (€ 21,141.00) with focused-echo.
Conclusions: The addition of a focused echo to the screening protocol reduced the number of false positive and allows to identified more athletes at risk for sudden death. Furthermore, with the introduction of focused echo there was a significant decrease of average costs per athlete with cardiac disorder.

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Cardiorespiratory fitness predictes outcomes among patients with depression: the henry ford exercise testing (FIT) project

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Background: Cardiorespiratory fitness (CRF) is a strong protective factor for all - cause mortality. Hypothesis: We hypothesized that CRF is associated with lower risk of all-cause mortality and non - fatal myocardial infarction (MI) among patients with depression treated with an anti-depressant medication (ADM).
Methods: We included 5,208 patients on ADM who completed a clinical exercise stress test between 1991 and 2009. Patients were followed for a mean duration of 11.5 years for all-cause mortality ascertained by a search of social security death index in April 2013 and non-fatal MI was ascertained by hospital and clinical documentation. CRF was estimated in metabolic equivalents (METs). Cox proportional hazards regression models were used to examine the relationship of CRF with all - cause mortality and MI after adjustments for age, sex, risk factors for coronary artery disease, medications (aspirin, β blockers and statins), reason referred for a stress test, and history of coronary artery disease.
Results: Patients with ADM that achieved ≥10 METs (versus those that achieved ≤6 METs) were younger (46±10 vs. 61±12 years), more often males (70% vs. 30%), black (15% vs. 4%), hypertensive (68% vs. 32%), diabetics (84% vs. 16%), smokers (56% vs. 44%) and dyslipidemia (29% vs. 20%). In fully adjusted Cox regression model, CRF was associated with lower all - cause mortality [Hazard ratio (HR) per 1 MET increase in CRF, 95% Confidence Interval (95% CI) 0.82 (0.79–0.85); p<.0001)] and non-fatal MI [0.92 (0.87–0.97); p=0.004)]. A graded decreased risk of mortality was observed with increase in CRF (Table 1).

Table 1: Cardiorespiratory fitness and anti – depressant medication use

METs achieved	Risk of All – Cause Mortality		
	Model 1*	Model 2[δ]	Model 3[±]
<6	Reference	Reference	Reference
6- 9	0.40 (0.33, 0.50)	0.44 (0.36, 0.54)	0.44 (0.38, 0.59)
10 – 11	0.22 (0.17, 0.28)	0.24 (0.36, 0.32)	0.27 (0.20, 0.35)
≥12	0.14 (0.09, 0.21)	0.15 (0.19, 0.32)	0.17 (0.11, 0.27)
p-trend	<0.001	<0.001	<0.001
	Risk of Non-Fatal Myocardial Infarction		
<6	Reference	Reference	Reference
6- 9	0.52 (0.37, 0.75)	0.52 (0.37, 0.75)	0.78 (0.54, 1.13)
10 – 11	0.44 (0.29, 0.65)	0.44 (0.29, 0.65)	0.71 (0.47, 1.07)
≥12	0.22 (0.11, 0.45)	0.22 (0.11, 0.45)	0.38 (0.19, 0.77)
p-trend	<0.001	<0.001	0.047

*Model 1: Adjusted for age, sex, race
δ Model 2: Adjusted for history of risk factors (hypertension, smoking, obesity, diabetes, family history of CV disease and dyslipidemia), medications (aspirin, β blockers and statins), and reason referred for a stress test
±Model 3: Adjusted for known coronary artery disease

Conclusions: CRF had a strong graded protective association with both all - cause mortality and non-fatal MI in patients with depression on ADM. These results highlight the potential importance of assessing fitness to identify risk, as well as promoting an active lifestyle.

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Leisure time physical activity reduces the risk of cardiovascular death and an acute CVD event also among older adults

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Purpose: The role of physical activity on cardiovascular disease prevention is well established among working age population. Relatively little is known on the effect of regular physical activity on CVD risk among the elderly. We investigated whether leisure time physical activity (LTPA) is independently associated with CVD mortality and CVD incidence in older adults.
Methods: Prospective cohort of 2409 men and women aged 65–74 years who participated in a baseline risk factor survey between 1997 and 2007 in Finland. The study protocol included a self-administered questionnaire, health examination at the study site and blood sample for laboratory analysis. Mortality data were obtained from the National Causes of Death Register and data on incident CVD (coronary heart disease and stroke) events from the National Hospital Discharge Register. The median follow-up time was 11.8 years. Self-reported LTPA was classified into three levels: low, moderate and high.
Results: Age, area, study year and sex adjusted hazard ratios of moderate and high physical activity level, compared to the low level, were 0.42 (0.31–0.58) and 0.29 (0.17–0.49) (p for trend <0.001) for CVD mortality and 0.65 (0.51–0.82) and 0.50 (0.35–0.71) (<0.001) for an incident CVD event, respectively. Multifactorial adjusted (previous model + smoking, body mass index, systolic blood pressure, serum total cholesterol, education and marital status) hazard ratios were 0.46 (0.33–0.64) and 0.34 (0.20–0.59) (p for trend <0.001) for CVD mortality and 0.69 (0.54–0.88) and 0.55 (0.38–0.79) (0.002) for an incident CVD event, respectively. Further adjustment for self-reported inability to practice physical activity reduced the protective effect slightly.
Conclusions: Physical activity associates with a reduced risk of CVD mortality and incident CVD events in older adults independently of the major known CVD risk factors. The protective effect of physical activity is dose dependent with a higher level of physical activity showing a stronger association.
Acknowledgement/Funding: The Finnish Foundation for Cardiovascular Research

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Differential effects of aerobic endurance, interval and resistance training on cellular senescence and inducible NO synthase

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Background: The molecular effects of exercising are incompletely characterized.

The aim of this prospective, randomized and controlled training study was to assess the molecular effects of physical training in circulating mononuclear cells and to test whether different training modalities exert differential effects on molecular regulators of cellular ageing.
Methods: n=124 healthy non-smokers without regular physical activity aged 30–60 years were randomized to a control group (control; no change of inactive lifestyle) or aerobic endurance training (AET, continuous running), high-intensity interval training (IT, 4x4 method) or resistance training (RT; circle training on 8 devices). The intervention consisted of 3 training sessions per week (45 min each) for a total duration of 6 months. Physical performance capacity was determined by treadmill testing at baseline (pre) and after the training period (post). Telomerase activity (TRAP assay) and mRNA expression (real-time PCR) of telomere-associated factors TRF2, POT1, Ku70 as well as senescence marker p16 and inducible NO synthase (iNOS) were measured in freshly isolated mononuclear cells (MNC).
Results: No changes were observed the in control group. Fitness parameters related to running speed were elevated more by endurance than by resistance exercise (control: -0.1±0.1; AET: 1.1±0.1; IT: 1.4±0.1; RT: 0.4±0.1 km/h max. running speed). Maximum oxygen uptake was increased in all training groups (VO2max: control: -1.01±0.5; AET: 2.69±0.7; IT: 2.76±1.0; RT: 2.97±1.0 ml/kg*min). Telomerase activity was increased strongly in both endurance exercise groups, but not in resistance training (% post vs. pre: control 106±17%; AET 245±19; IT 196±16%; RT 146±15%). Real-time PCRs showed increased expression of senescence inhibitors TRF2 (% post vs. pre: control 114±17; AET 243±17; IT 253±29; RT 342±17%), POT1 and Ku70 and decreased p16 expression (% post vs. pre: control 103±35; AET 40±24; IT 54±26; RT 53±39) in all three trainings groups. Comparably to telomerase, expression of iNOS was up-regulated in the endurance exercise groups only with no effect of resistance training (% post vs. pre: control 87±28; AET 279±43; IT 380±35; RT 123±30).
Conclusion: This randomized, prospective, controlled training study shows that specific modalities of physical exercise mediate differential molecular effects on cellular senescence. The activity of telomerase and inducible NO synthase expression were increased by aerobic endurance- and in high-intensive interval training, but not after strength training.

392 | BENCH
Effects of long-term exercise on cardiac remodeling in a marfan mouse model

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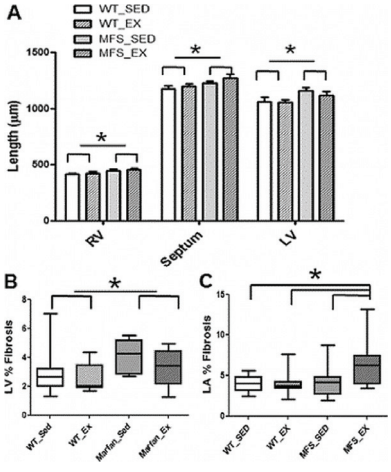
Background: Marfan syndrome (MFS) is a genetic disorder characterized by the formation of ascending aortic aneurysms caused by mutations in the FBN1 gene that codifies for fibrilin-1. Exercise guidelines for patients who have MFS remain controversial and the effects of training in MFS animal models are not documented.
Purpose: To assess cardiac remodeling after long-term training in a mouse model of MFS.
Methods: Fbn1((C1039G/+)) mice (n=10, MFS_EX) and wild type mice (n=10, WT_EX) underwent moderate intensity exercise (1h, 20cm/s, with a 20% inclination) in a treadmill, 5 days a week during 20 weeks. Sedentary Fbn1((C1039G/+)) mice (n=7, MFS_SED) and wild type mice (n=11, WT_SED) served as controls. Heart hypertrophy (wall thickness), fibrosis (Red Picrosirius) and small intramyocardial vessels remodelling were assessed in histological slides.
Results: The long-term exercise regime did not induce any cardiac hypertrophy changes in control mice. Right and left ventricle free wall and septum thickness (Fig. A) was higher in MFS mice compared to WT mice with no changes induced by the exercise. Fibrosis analysis showed no changes in right atria and right ventricle fibrosis between groups, meanwhile there was an increase in left ventricle fibrosis in MFS mice (Fig. B). Left atria fibrosis was increased in MFS_EX mice when compared to the remaining three groups (Fig. C). Also, the percentage of lumen area relative to vessel area of intramyocardial vessels was significantly reduced in all groups compared to WT_SED mice.



Conclusions: The exercise regime did not lead to hypertrophy changes in WT mice but had a deleterious effect in the intramyocardial vessels remodelling. MFS mice presented right ventricle, left ventricle and septum hypertrophy and left ventricle fibrosis with no training-induced changes, indicating phenotype changes linked to the fibrilin-1 mutation. Nevertheless, enhanced left atria fibrosis was detected only in trained MFS mice, and such fibrosis could be the basis of a higher arrhythmogenic substrate. Our findings provide important insights into increased adverse cardiac remodeling in MFS mice and adverse atrial remodeling in MSF mice subjected to exercise. Such results provide evidence that caution should be used when prescribing exercise to MFS patients.

393 | BENCH
Effects of high-intensity resistance training isolated and associated with aerobic exercise on hemodynamics, collagen deposition and inflammatory profile in heart failure rats

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Background/Introduction: The resistance training (RT) has been associated with positive responses in clinical status of patients with cardiovascular disease, and when it is combined with aerobic training (AT), the adaptations appear to be more pronounced. However, the effects of high-intensity loads in RT isolated or associated to AT in cardiac rehabilitation remain unclear.
Purpose: The aim was to test if the RT with high-intensity associated to AT can present better responses in the hemodynamic function, collagen deposition and the inflammatory status of rats with heart failure (HF).
Methods: Twenty-four male Wistar rats (90 days old), randomly allocated in 4 groups: resistance training with HF (RT-HF, n=6), aerobic training with HF (AT-HF, n=6), resistance training and aerobic training with HF (RT+AT-HF, n=6) and sedentary with HF (SED-HF, n=6). Trained animals were submitted to RT protocol in adapted squat apparatus for rats (4 bouts, 6–8 rep, 90 s of interval, 3x/week, 75% to 85% of one maximum repetition (1MR), for 8 weeks). The animals submitted to AT were conducted 3x/week and lasted 50 min/session at 16 m/min, for 8 weeks, representing an aerobic protocol and corresponding to an intensity of 55% VO2max. The animals of combined exercise performed two exercise protocols. This study followed the Principles of Laboratory Animal Care (NIH Publication no. 85–23 revised 1985). It was employed the one-way ANOVA, with Tukey' post-hoc. The level of significance was set at 5%.
Results: The size of the infarct areas were not different among the groups: RT-HF, AT-HF, RT+AT-HF and SED-HF with averages of 41.9±3%, 44.9±3%, 45.8±3% and 42.9±2% respectively. Regarding the hemodynamic responses, left ventricular end-diastolic pressure (LVEDP) was lower in RT-HF, AT-HF and RT+AT-HF groups compared to SED-HF (10.07±3.8; 14.8±1.6, 7.3±3.4 vs 24.9±6.3 mmHg, $P<0.05$). The RT-HF and RT+AT-HF groups showed greater strength gains in the last 1RM test (fourth test) when compared to AE-HF and SED-HF groups (1891±316.7; 1982±101 vs 1059±21.92; 1084±53.48g ($P<0.05$). The collagen volume fraction was lower in RT-HF, AT-HF and RT+AT-HF groups when compared to SED-HF group (0.9±0.2; 0.9±0.1; 0.7±0.1 vs 1.7±0.5%, $P<0.05$). No changes in IL-10 and TNF-α plasma levels were found among groups.
Conclusion: The high intensity RT isolated or combined with AT was able to improve a cardiovascular cellular component (collagen deposition) and attenuated the LVEDP, which is a marker of cardiac dysfunction. However, the inflammatory markers did not change. We conclude that the increase in strength gained through high intensity helped to improve some parameters, but is still necessary a better balance between intensity and volume of physical training in the field of cardiovascular diseases.
Acknowledgement/Funding: Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES)

BEST POSTERS SESSION 1

BEST POSTERS IN e-CARDIOLOGY

P474 | BEDSIDE
Image-based ffrangio during coronary catheterization

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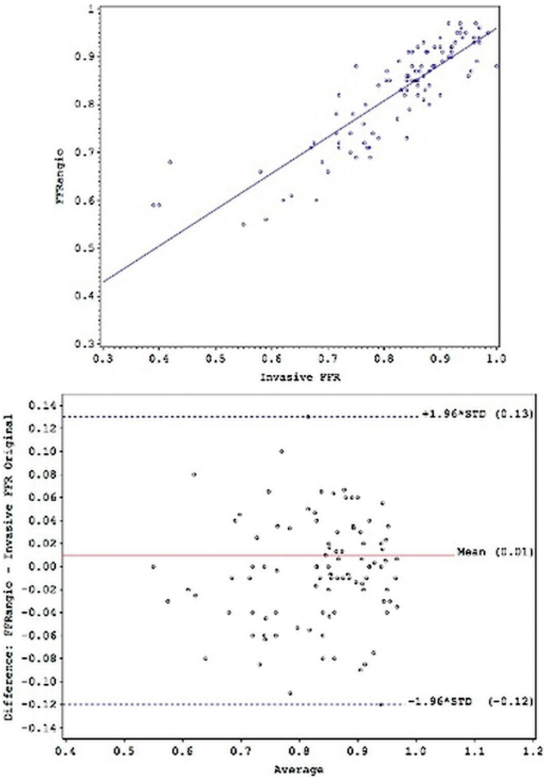
Background: FFR is considered the standard for evaluating the ischemic potential of coronary stenoses and the expected benefit from revascularization. Moreover, as a highly reproducible diagnostic measure, FFR is increasingly being used in clinical trials as an inclusion criteria or as an end-point, or to validate new diagnostic modalities.
Purpose: To evaluate in a blind manner the diagnostic performance of angiography-based FFR (FFRangio) in comparison with invasive-FFR.

Methods: An FFRangio technology relying solely on available angiographic images was developed by CathWorks (Raanana, Israel). The algorithms of this technology estimate the functional significance of a coronary lesion, similar to invasive FFR, by defining the dynamic characteristics of the vessel as well as the patient's hemodynamic data, and provides a non-invasive adenosine-free measurement of the FFR index for each lesion. Any lesion indicated for invasive FFR measurement, was analyzed by FFRangio from multiple views of a regular angiogram. The three dimensional shape of the vessels was used to initiate the flow analysis, and the FFR index at the exact location of the wire tip was compared to the pressure-based measurement.
Results: 88 patients were enrolled in 2 centers. 101 (DS 30–95%) lesions (58 LAD; 20 LCX; 20 RCA; 2 Intermediate; 1 Diagonal) were analyzed. FFRangio correlated well (r=0.87; p<0.0001) with invasive FFR over a large range of stenoses severity. The Bland-Altman analysis indicates that the limits of agreement between the two methods were narrow and there was no trend. The accuracy of FFRangio was 80% when compared to invasive FFR (sensitivity 91%; specificity 94%).



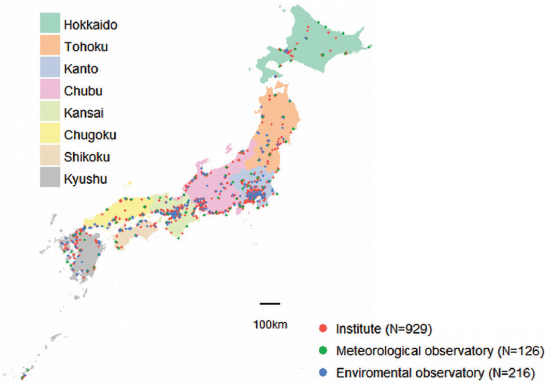
Scatter plot of FFRangio vs. Invasive FFR

Conclusions: FFRangio correlates well with invasive FFR in this cohort of patients in whom the measurements were performed in a blinded manner. FFRangio is therefore a promising tool to obtain simultaneously and at low cost, anatomic and functional information of the epicardial arteries.
Acknowledgement/Funding: Grant provided by the Cardiopath PhD program

P475 | BEDSIDE
Association between occurrence of ST-segment elevation myocardial infarction and daily ambient temperature along with air pollutant levels in a Japanese nationwide PCI registry (J-PCI)

K. Yamaji[1], S. Kohsaka[2], T. Morimoto[3], K. Fujii[4], T. Amano[5], S. Uemura[6], T. Akasaka[7], K. Kadota[8], M. Nakamura[9], T. Kimura[10] on behalf of J-PCI Registry Investigators. *[1]Kokura Memorial Hospital, Kitakyushu, Japan; [2]Keio University, Tokyo, Japan; [3]Hyogo College of Medicine, Nishinomiya, Japan; [4]Sakurabashi-Watanabe Hospital, Osaka, Japan; [5]Aichi Medical University School of Medicine, Nagakute, Japan; [6]Kawasaki Medical School, Kurashiki, Japan; [7]Wakayama Medical University, Wakayama, Japan; [8]Kurashiki Central Hospital, Kurashiki, Japan; [9]Toho University Ohashi Medical Center, Tokyo, Japan; [10]Kyoto University Graduate School of Medicine, Kyoto, Japan*

Background: It is well known that cardiovascular events more often occur in winter than in warmer seasons. Prospective cohort studies showed that long-term exposure to air pollutants contributed to the excess mortality. In the meanwhile, effects of daily fluctuation of ambient temperature and concentrations of air pollutants on the occurrence of cardiovascular events have not been well studied.
Purpose: To elucidate the short-term effect of weather and air pollution on the occurrence of ST-segment elevation myocardial infarction (STEMI) in Japanese nationwide cardiovascular database.
Methods: Between January 2011 and December 2012, a total of 56,863 consecutive STEMI patients who underwent primary percutaneous coronary intervention (PCI) were registered in a nationwide academic PCI registry (J-PCI registry) from 929 institutes. The median inter-institutional distance was 2.6 km. We constructed generalized linear mixed models in which presence or absence of STEMI patients per day per institute (present: N=51,495 [7.6%] and absent: N=627,604 [92.4%]) was included as a binomial response variable, with daily meteorological and environmental data obtained from their respective observatories nearest to the institutes (median distance of 9.7 km and 5.6 km), day of week, national holidays and 8 administrative districts as the explanatory variables.
Results: Both lower mean temperature, and increase in maximum temperature from the previous day were independently associated with the STEMI occurrence throughout the year (OR 0.925 [95% CI 0.915–0.935], per 10℃, P<0.001, and OR 1.012 [95% CI 1.009–1.015], per ℃, P<0.001, respectively). Decrement in minimum temperature from -4 day to -3 day before the event date was marginally associated with the STEMI occurrence, only during the wintertime (OR 0.991 [95% CI 0.982–0.999], per ℃, P=0.03). As for the air pollutants, sulfur dioxide, nitrogen oxides and particle matter were not correlated with the occurrence of STEMI after adjusting for the meteorological and livelihood variables, both for the entire study period, and that for weekdays excluding national holidays.



Distribution of institues

Conclusions: Both the absolute value and relative change in the ambient temperature were associated with the occurrence of STEMI, whereas the associations with the air pollutant levels were less clear after adjustment for these meteorological variables in Japan.

P476 | BEDSIDE
3D printing for precision medicine: a prototype with dofetilide

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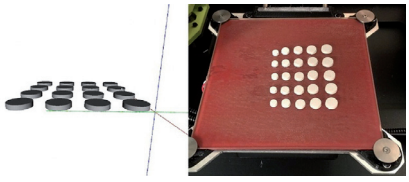
Background: Precision medicine requires personalizing medication dosages based on a person's clinical and biological profile. Current pharmaceutical industrials may not fully meet this need due to pre-determined formulations with limited dose ranges. We hypothesize that precision drug therapy can be achieved through 3D printing based on patients' clinical and biological information.
Methods: The study used dofetilide, which has a narrow therapeutic window, as a test model. Pharmacokinetics and pharmacodynamics of dofetilide were obtained from the US Food and Drug Administration documents submitted by Pfizer. A personalized dosing computer program specific to dofetilide was developed. By inputting each patient's clinical profile data into the program, personalized doses were calculated in 12 "virtual" patients with variable clinical profiles (age, gender, creatinine clearance and QTc interval). Computerized pills were transformed into 3D models, converted into 3D printable STL files (Figure), and printed using a 3D printer. Printed "pills" were weighed electronically and compared to calculated doses to verify accuracy.
Results: A total of 48 "pills" with variable doses were 3D printed based on decrements of 5 mg/min/m^2 creatinine clearance (>60 mg/min/cm^2 to ≥20 mg/min/cm^2) and increments of 10 msec QTc (450–550 msec). Printed doses ranged from 122–503 mcg. Precision of 3D printed pills was confirmed by calculating the standard deviation (1.27–6.13 mcg) within any specific dose. Accuracy was validated using the percentage difference (2.79±1.28%) between calculated


Computed and Printed Precision Pills

dose and 3D printed doses. These standards meet and exceed current pharmaceutical industrial standards (≤10% variation).
Conclusion: Personalized drug therapy based on a patient's clinical and biological profile can be accurately printed using 3D printing. Further study is warranted to test if this personalized dosing approach can be applied in the clinical setting.

P477 | BEDSIDE
Remote monitoring improves long-term prognosis in heart failure patients with implantable cardioverter-defibrillators in real-life

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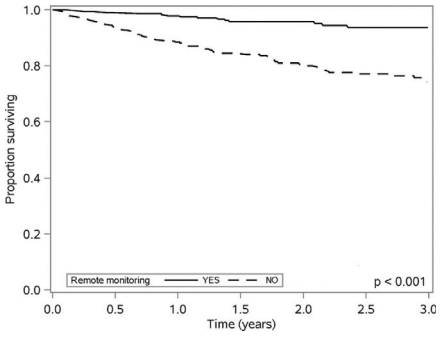
Introduction: Implantable cardioverter-defibrillators (ICDs) and cardioverter - defibrillators for resynchronization therapy (CRT-D) have an essential role in patients with HF, significantly improving prognosis. Remote monitoring (RM) of ICDs/CRT-Ds may improve quality of care and prognosis in HF patients.
Purpose: To analyze the impact of RM on long-term prognosis in HF patients with ICDs/CRT-Ds.
Methods: COMMIT-HF is a single-center, ongoing prospective observational registry. The study population is formed by consecutive non-selected patients hospitalized in cardiology wards and intensive cardiac care units with a diagnosis of systolic HF. For the purpose of this study HF is defined as a set of symptoms resulting from left ventricle (LV) systolic dysfunction, with LV ejection fraction ≤35%. Patients with ACS during the index hospitalization are excluded from the registry. Complete patient demographics, medical history, complete hospitalization data, in-hospital results, implantation procedure characteristics are collected. The study was designed as population-based matched cohort study. Patients are divided in two groups based on RM presence and matched according to clinical characteristics. The primary end-point of this study is long-term (12 months and 3 years) all-cause mortality.
Results: 822 patients with the first implantation of ICD/CRT-D in our center out of 1429 patients with HF from COMMIT-HF Registry, were included to analysis. The study population after matching contained 274 patients in RM-group and 286 patients in control group. Mean age at enrolment was 62.8 y (56.04–69.51) in RM group and 61.94 y (53.25–70.75) in non- RM group. 84% of patients were men. Analysed echocardiographic and electrocardiogaphic parameters altogether with pharmacological treatment were similar between both groups, except from the more frequent incidence of atrial fibrillation diagnosed during hospitalization in RM group (61% vs 50.5%; p=0,012). Patients in RM group have a lower number of cardiology out-patient visits in one-year observation according to control group (3,52 vs 3,95 visit/per patient; p=0,06). During one – year observation 39 patients died (6 in RM group and 33 in non-RM group). There was a statistically significant lower one-year mortality in RM group (2,2% 11,5%, p<0,0001). This significant difference was also maintained during three-year follow-up (6,4 vs 25,7%; p=0,01)



Long-term survival rate

Conclusion: Remote monitoring of ICDs/CRT-Ds in HF patients significantly reduces one-year and three -year mortality.

BEST POSTERS IN ANTICOAGULANTS IN DAY TO DAY PRACTICE – ISSUES TO BEAR IN MIND

P479 | BEDSIDE
Long term follow up after successful percutaneous balloon mitral valvuloplasty

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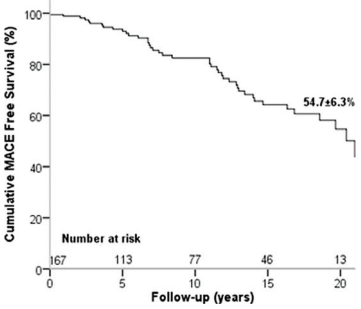
Background: Percutaneous balloon mitral valvuloplasty (PMV) is the cornerstone of the treatment of rheumatic mitral stenosis in suitable patients. Previous studies reported low technical failure and major complications, and good long-term results after successful PMV.
Purpose: We sought to assess very long-term outcome after PMV in a single tertiary center.
Methods: Between 1991 and 2014, 213 consecutive patients (pts) underwent PMV in a single center. The criterion used to define successful procedure was post-procedural valve area ≥1.5cm^2 and regurgitation less than grade III, without in-hospital major cardiac or cerebrovascular events. The primary endpoint evaluated during follow-up period was the occurrence of cardiovascular death and need for mitral re-intervention (percutaneous or surgical). Kaplan-Meier curves were generated to determine event rates and predictors of major cardiac events were determined by Cox regression analysis.
Results: 190 pts (89%) had a successful PMV, of which 88% keep follow-up in our center. During a mean follow-up of 11.2±7.3 years, occurred at least one MACE in 25.1% of patients (6.6% all cause deaths, 6.6% repeated PVM and 21% needed mitral surgery). Cumulative event-free survival at 20 years was 54.7±6.3% (figure). At univariate analysis, echocardiographic score [hazard ratio (HR)=1.25 (1.00–1.70), p<0.05], left atrial diameter [HR=1.06 (1.01–1.11), p<0.05] and mean mitral valve gradient after procedure [HR=1.25 (1.02–1.55), p<0.05] were predictors of events. At multivariate analysis, echocardiographic score was the only independent predictor of the primary outcome [HR=1.75 (1.16–2.64), p<0.01].



Conclusions: Up to 20 years after successful PMV, a sizeable proportion of patients are event-free, which confirms the late efficacy of PMV. In our cohort, echocardiographic score before PMV was the only independent predictor of event-free survival.

P480 | BEDSIDE
Identifying warfarin-drug interactions by data mining in administrative registers

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Background: Cardiovascular medications pose many and severe interactions. We hypothesized that explorative searches in registries with data-mining methods might reveal unknown interactions. Therefore, we investigated if an explorative search could reveal already known interactions in warfarin therapy. Warfarin was selected because of its biomarker (INR) and well-known drug-interaction-profile.
Method: Patients with non-valvular atrial fibrillation treated with warfarin and who had a stable INR prior to a novel prescription and at least one measured INR value in the next 45 days were included. Events were defined as an INR value outside the therapeutic range (high INR ≥4.5 or low INR≤1.8) after initiation of a novel drug. Data were split into a training and a test set. Logistic regression with a lasso penalty was set up for prediction. Data were balanced by repetitions of cases and random selection of controls. Important/selected predictors were further analyzed using all data in a logistic regression without penalty or balancing data.
Results: 10.219 patients were included with 2.478 events of high INR and 4.232 events of low INR. Initiation of 331 different medications was investigated. The area under the curve was 0.65 for prediction of high INR and 0.62 for prediction of low INR applying the test set (unseen data). The table illustrates the ten most important drug predictors and all were significant in the subsequent test. Known interactions are marked in red (increased INR) and blue (decreased INR). Yellow indicates interactions known from certain case reports.

	High INR	Low INR
1	amiodaron	dabigatran
2	miconazole	Vitamin K
3	fluconazole	Innohep
4	loperamide	carbamazepine
5	fentanyl	valproic acid
6	metoclopramide	Phenegan
7	chlorzoxazone	dicloxacillin
8	morphin	acetylsalicylic acid
9	amoxicillin	actic acid producing organisms
10	tramadol	miconazole

Important drug predictors

Conclusion: We have demonstrated that drug-drug interactions make detectable patterns, despite that they are already known. Unknown drug-drug interactions in novel drugs may be even more detectable. Data mining may therefore be a

promising supplement in the search for unknown drug-drug interactions in cardiovascular medicine.
Acknowledgement/Funding: Danish Heart Association

P481 | BEDSIDE
Comparison of oral anti-coagulants for stroke prevention in non-valvular atrial fibrillation: a multi-criteria decision analysis

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Background/Introduction: There are five oral anticoagulants available in the United Kingdom for stroke prevention in patients suffering from non-valvular atrial fibrillation (NVAF) with some drug-related variations in clinical profile and non-clinical attributes. Clinical and non-clinical characteristics are sometimes inappropriately considered on an equal footing, risking a misperception of their treatment value among health care decision makers.
Purpose: To compare apixaban, dabigatran, edoxaban, rivaroxaban and vitamin K antagonist (VKA; i.e., warfarin) based on a rigorous and comprehensive analysis of the factors relevant when prescribing oral anticoagulants for stroke prevention in patients with NVAF.
Methods: A multi-criteria decision analysis (MCDA) was developed to compare the five oral anticoagulants. Evaluation criteria were identified through a targeted literature review and expert judgment. The final evaluation model included nine clinical and three non-clinical criteria. The clinical criteria were ranked based on expected changes in clinical implications from the worst to best performing treatment, as demonstrated in clinical trials. These rankings were used to calculate centroid weights for the base-case analysis. An additive model was used to combine treatment performance with centroid weights to estimate the overall value of each oral anticoagulant. Probabilistic and structural sensitivity analyses were performed to assess robustness of the results.
Results: Dabigatran obtained the highest overall value in the base-case analysis (see Figure) and the highest first rank probability (74%) in the probabilistic sensitivity analysis. Rivaroxaban performed worse than the other non-VKA oral anticoagulants, but better than VKA (both with 0% first rank probability). The results were insensitive to changes in model structure.

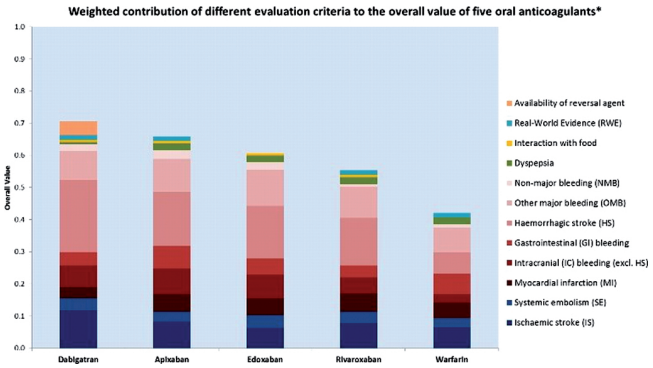

Figure 1. Weighted contribution of different evaluation criteria to the overall value of five oral anticoagulants*. *Overall value varies from 0 (the worst possible performing treatment in the range of performance assessed) to 1 (the best possible performing treatment).

Conclusions: Considering weights for clinical implications can be of help when making treatment choices for stroke prevention in patients with NVAF. When all the factors that distinguish oral anticoagulants and their relative importance are considered in an MCDA, dabigatran was ranked highest and warfarin lowest.
Acknowledgement/Funding: Boehringer Ingelheim

P482 | BEDSIDE
Uninterrupted ivabradine treatment may provide lasting reduction of persistent sinus tachycardia with preserved airways physiology in lung cancer patients: a 48 months retrospective study

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Background/Introduction: Persistent sinus tachycardia (PST) is often present in patients (pts) with lung cancer (LC), as a result of hypoxia, inflammation, bronchodilators. On the other side, ivabradine, the first selective sinus node If channel inhibitor, is successfully used to reduce tachycardia in stable angina and heart failure. At the best of our knowledge, the literature seems to be poor on treating PST in LC with ivabradine.
Purpose: To investigate the long term impact of uninterrupted ivabradine treatment (UIT) on PST in LC pts.
Methods: We retrospectively analysed 144 consecutive pts with LC, any type, any stage, treated with UIT for PST for 48 months, starting with 01/01/2008. Demography: mean age 55,8±10,1 yrs, male predominance 61,3%. These pts had either contraindication, or intolerance, or insufficient heart rate (HR) reduction with beta-blockers. The comparator group had 288 contemporary pts with the same profile, treated with beta-blockers. In both groups, the dosages were increased as much as getting safely the best efficacy. The study enter date was considered the first cardiology examination after the LC confirmatory diagnosis. The schedule of visits respected the chemotherapy serial, and every visit included ECG and LVEF.
Results: After propensity matching (1:2) the 144 UIT pts were combined with 288 controls. The table illustrates the evolution of HR in the two groups. HR significantly lowered in UIT pts versus control group. The most spectacular decrease of HR with UIT was in the group of pts with HR 111–120 bpm. This effect remained stable in the long term follow-up, while blood pressure, cardiac conduction (ECG), myocardial contractility (LVEF) were not affected. No aggravation of dyspnea, wheezing, or sibilant rales were observed in UIT group.

Results

	UIT	BB
Onset	107.2±9.2	107.6±9.3
6 months	82.7±7.9	98.1±8.9
12 months	81.9±7.6	93.7±7.8
24 months	82.3±6.8	95.2±8.2
36 months	80.7±6.2	94.3±7.8
48 months	79.8±5.1	94.5±8.1

Conclusion: UIT appears to be a safe and feasible long-term therapeutic option for treating PST in LC pts. UIT may be an alternative to beta-blockers in this clinical setting, by reducing the resting HR without impairing nor cardiac parameters, neither airways physiology. However, larger data from prospective randomized trials are needed.

BEST POSTERS IN CORONARY SURGERY

P484 | BEDSIDE
A long-term, propensity score-matched comparison of bilateral internal thoracic artery composite Y/T versus in situ grafting in patients undergoing total arterial revascularization

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Background: Coronary artery bypass graft surgery (CABG) utilizing bilateral internal thoracic arteries (BITA) for total arterial revascularization (TAR) is associated with excellent short and long-term results. It can be performed by constructing a composite Y – BITA - graft or by using the BITAs as in situ grafts.
Purpose: A controversy still exists whether TAR using exclusively composite Y/T BITA grafts provides the same safety and efficacy as in situ BITA grafts with or without the use of additional arterial grafts. We, therefore, compared the early and long-term clinical outcomes between the composite Y/T and in situ BITA grafts in patients undergoing TAR.
Methods: A total of 1065 patients underwent isolated TAR using BITA grafts between January 2003 and July 2010 at a single institution. BITAs were exclusively used as composite Y/T grafts in 214 patients and as in situ grafts with or without other arterial conduits in 851 patients. Comparison of the 2 groups with regard to early and cumulative long-term mortality and major adverse cardiac and cerebrovascular events (MACCE) was performed using incidence rates after propensity score-matching (PSM). To mitigate bias arising from observed covariates as well as model-misspecification, we used PSM as a nonparametric method of preprocessing. The matched cohort consisted of 725 patients; 202 patients with composite BITA Y/T and 523 with in situ grafts.
Results: After matching, no differences were noted between the BITA Y/T and in situ groups with respect to age (62.3±10 vs. 61.7±8.5), gender (85.2% vs. 85.7% males), diabetes mellitus (36.1% vs. 36.1%), left ventricular ejection fraction (55.5±15.7% vs. 56.7±14.0%), triple vessel (72.6% vs. 72.6%) and left main disease (45.1% vs 39.0%). The corresponding 30-day mortality was 0.7% and 0.9% (P=0.6). Late all-cause mortality was 9.9% and 12.2% and MACCE rates were 21.8% and 22.2% for the BITA Y/T and in situ groups, respectively. The survival (log rank P=0.5) and freedom from MACCE (log rank P=0.8) as estimated by Kaplan Meier methods were similar between the 2 groups of patients.
Conclusions: Total arterial revascularisation using BITA as a Y/T or in situ grafts is associated with excellent early and long-term outcomes. BITA Y/T configuration provides similar safety and efficacy to in situ BITAs in patients undergoing TAR.

P485 | BEDSIDE

RESURRECT: Resumption of platelet function after cessation of ticagelor in patients with acute coronary syndrome awaiting coronary artery bypass surgery

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Background: Ticagrelor is an oral, direct, reversible non-competitive P2Y12 receptor antagonist with rapid and consistent onset and offset of action and plasma half-life of 7–12 hours. The time course of recovery of platelet function following ticagrelor cessation in patients presenting with acute coronary syndrome (ACS) and undergoing surgical revascularisation is yet to be determined with current guidelines recommend stopping ticagrelor at least 5 days before coronary artery bypass grafting (CABG). However, a shorter half-life and a twice-daily dosing regimen of ticagrelor suggest that this may be longer than necessary for recovery of platelet function. Earlier surgical revascularisation may result in reduced waiting periods and pre-operative ischemic events in ACS patients.
Purpose: To assess the offset of the anti-platelet effects of ticagrelor in ACS patients undergoing CABG.
Methods: 46 consecutive ACS patients who were commenced on Aspirin (75 to 100 mg) and ticagrelor (180 mg loading and then 90mg twice a day) and were referred for CABG after coronary angiography. Immediately after angiography, ticagrelor was discontinued and inhibition of platelet aggregation (IPA) was assessed daily using the VerifyNow P2Y12 assay. We recorded the number of days before the platelet activity recovered (IPA dropped below 20 percent) prospectively.
Results: The mean age was 62.37 (± 9.28) years, 78.% males. 44% were diabetic. ACS presentations were non ST-elevation myocardial infarction 59%, ST-elevation myocardial infarction 11% and unstable angina 30.%.The mean IPA and P2Y12 reacting units (PRU) from the time of coronary angiography to day 4 are shown in Fig.1. 98% had therapeutic platelet inhibition (IPA>40%) prior to discontinuation. Platelet function recovered by day 3 ($p<0.0001$). with 96.% recording less than 20% residual IPA. No significant rebound was noted.

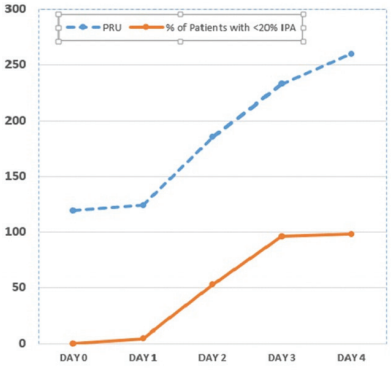

Fig.1 Graph illustrating increase in percentage of the patients achieving platelet function recovery (IPA<20%) with majority achieving this by day 3. Note a corresponding steady rise in platelet reactive units PRU in these subjects.

Conclusion: The offset of the anti-platelet effects of ticagrelor in patients with ACS is achieved by day 3 post discontinuation with restoration of platelet function as assessed by VerifyNow P2Y12 assay, This data suggests an earlier surgical revascularisation strategy than currently recommended in guidelines can be considered.

P486 | BEDSIDE

Long-term clinical outcomes after coronary artery bypass graft versus everolimus-eluting stent implantation in chronic hemodialysis patients

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Background: As optimal coronary revascularization, strategies regarding the long-term clinical outcomes in chronic hemodialysis (HD) patients revascularized by either coronary artery bypass surgery (CABG) or percutaneous coronary intervention (PCI) have been controversial. Recently, PCI with everolimus-eluting stent (EES) has dramatically reduced restenosis even in patients on HD. We comparatively investigated long-term clinical outcomes after CABG and everolimus-eluting stent (EES) in HD patients.
Methods: We compared 138 patients undergoing CABG and 187 treated with EES implantation after 2010 when EES has been clinically available. Primary endpoint was any revascularization. Second endpoint was defined as major adverse cardiac events (MACE) as a composite outcome including revascularization, non-fatal myocardial infarction (MI) or mortality. To adjust the differences of characteristics between two groups, propensity score analysis using a multiple logistic model including all baseline variables was performed, then the score was incorporated into Cox proportional hazards model as a covariate.
Results: Multi-vessel disease was more frequent in CABG group than in EES group (70.3% vs. 51.9%, p=0.0008) and left ventricular ejection fraction was lower in CABG group than in EES group (54±13% vs. 59±14%, p=0.0004). During follow-up period (median 43 months), 95 MACEs (29.2%) including 43 revascularization (13.2%), 14 non-fatal MI (4.3%) and 63 deaths (19.4%) occurred. Kaplan-Meier analysis shows that event free rate from any revascularization at 5-year was higher in the CABG group than in the EES group (89.4% vs. 84.0%, p=0.030). However, freedom rate from MACE was comparable between two groups (69.7% vs. 66.7%, p=0.82). After propensity score-adjustment, adjusted event free rate from revascularization was 91.5% in the CABG group and 78.5% in the EES group [hazard ratio (HR) 0.34, 95% confidence interval (CI) 0.14–0.73, p=0.0055], and adjusted the freedom rate from MACE was 73.1% in the CABG group and 64.8% in the EES group (adjusted HR 0.76, 95% CI 0.47–1.22, p=0.26). Adjusted freedom rates from MI and death were also comparable (97.6% vs. 94.0%, HR 0.43, 95% CI 0.06–1.82, p=0.27 and 77.5% vs. 79.3%, HR 1.22, 95% CI 0.69–1.16, p=0.48, respectively).
Conclusion: Even in the second generation DES era, CABG was still superior for preventing revascularization in chronic HD patients. However, PCI with EES implantation might not have disadvantage for MACE compared to CABG any more.

P487 | BEDSIDE

Adjudicated cause of death in diabetic patients undegoing coronary revascularization

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Background: The cause of death may provide insights into the beneficial effects of coronary artery bypass grafting (CABG) over percutaneous coronary intervention with drug-eluting stents (PCI) in diabetic patients with multivessel coronary artery disease (MV-CAD). To date meta-analyses have only reported all-cause mortality statistics.
Purpose: To evaluate the proportion of adjudicated deaths in the FREEDOM trial attributed to cardiovascular (CV) causes and characterize the proportion of CV deaths caused by fatal myocardial infarction (MI) or sudden death in diabetic patients with MV-CAD undergoing either CABG or PCI.
Methods: The FREEDOM trial randomized 1900 diabetic patients with MV-CAD and demonstrated a significant benefit for CABG over PCI in reducing the 5-year rates of all-cause death, MI and stroke (18.7% versus 26.6%, p=0.005). The cause of death was adjudicated by an independent Clinical Events Committee comprised of cardiovascular and neurology experts. Deaths were classified first as CV versus non-CV and then sub-classified for MI-related and sudden cardiac deaths. Using an intention-to-treat approach, the association of revascularization group and incidence of death within these categories was evaluated.
Results: There were 197 deaths during the 5 year follow-up time, 114 in the PCI group and 83 in the CABG group. There was no difference in the proportion of deaths from a CV cause in the 2 groups (73 deaths (64.0%) in the PCI arm compared to 52 deaths (62.7%) in the CABG group, p=0.88). There were trends for a greater proportion of deaths from both fatal MI (12.3% versus 7.2%, p=0.34) and sudden cardiac death (29.8% versus 18.1%, p=0.07) in the PCI arm. For the combination of fatal MI and sudden cardiac death there was a greater proportion observed in the PCI arm (42.1% versus 25.3%, p=0.02).
Conclusions: PCI patients experienced a greater likelihood of mortality from MI and sudden cardiac death over 5 years of follow-up. The potential role of stent thrombosis and progression of non-target lesions should be studied in diabetic patients after PCI for MV-CAD to fully develop strategies to reduce these types of events. More intensive medical therapy on the horizon may alter the rates of ischemia-related CV deaths.
Acknowledgement/Funding: National Heart, Lung and Blood Institute

BEST POSTERS IN SUPRAVENTRICULAR ARRHYTHMIAS (EXCLUDING AF)

P489 | BEDSIDE

Electroanatomically-estimated localization of superior slow pathway in superior type of fast-slow atrioventricular nodal reentrant tachycardia

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Introduction: Superior slow pathway (sup-SP) with slow conductive properties and an atrial exit near the His bundle is a retrograde limb of the reentry circuit of a novel form of fast-slow atrioventricular nodal reentrant tachycardia (sup-F/S-AVNERT) and is an ablation target to eliminate this tachycardia. However, its localization remains to be not fully elucidated.
Purpose: We investigated a localization of sup-SP in patients (pts) with sup-F/S-AVNRT by using electroanatomical mapping system.
Methods: We enrolled 7 pts (2 men, 69±7 year-old) who obtained successful ablation of the confirmed sup-F/S-AVNRT, resulting in no inducibility of the tachycardia. We measured a distance (mm) between the proximal His bundle electrogram and the successful ablation site (SucABL) that was defined as electroanatomically

estimated length of sup-SP (sup-SP-L), and between SucABL and the tricuspid annulus (TA) (SucABL-TA).
Results: The diagnosis of atrial tachycardia (AT) was excluded by a V-A-V activation sequence immediately after ventricular induction in all patients, including double atrial responses in 5 pts, or termination by ventricular pacing without atrial capture in 1 pt. The diagnosis of AV reentrant tachycardia was excluded by development of AV block during the ongoing tachycardia in 1 pt or ventriculoatial dissociation during ventricular pacing of the tachycardia in other 6 pts. Successful ablation at an earliest atrial site of activation with an A/V ratio of 1.6±0.6 (0.9–2.9) and SucABL-TA interval of 13.2±.8 (6.8–23.3) was obtained in the right-sided perinodal region in 4 pts and in non-coronary cusp of Valsalva (NCC) in other 3 pts, and at 11, 12 or 1 o'clock around TA in left anterior oblique projection in 1, 3 and 3 pts, respectively. sup-SP-L was 9.5±6.8 (4.7–24.7). Ablation in NCC failed to eliminate the tachycardia in 2 pts.
Conclusions: Sup-SP appears to originate from compact AV node and extend superiorly along the TA, but its length and distance relative to the TA is individually variable. Only sup-SP coursing just below the NCC, anteriorly an adjacent to the TA can be ablated in NCC. Interestingly, sup-F/S-AVNRT incorporating sup-SP that extends laterally may apparently mimic AT originating from the TA.

P490 | BEDSIDE
Cooling dynamics: a new predictor of long-term efficacy of atrioventricular nodal reentrant tachycardia cryoablation

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Background: Catheter ablation of the slow pathway is the most effective treatment for atrioventricular nodal reentrant tachycardia (AVNRT). Cryoenergy, compared to radiofrequency, has been reported to be safer and equally effective, but is affected by a higher incidence of long-term AVNRT recurrences.
Purpose: The aim is to confirm the safety and efficacy of AVNRT cryoablation and to identify potential predictors of long-term recurrences.
Methods: 241 patients undergoing AVNRT cryoablation were included and followed. Baseline patients' and procedural characteristics were retrospectively analyzed to identify predictors of arrhythmic recurrences.
Results: Among 241 patients, 239 (99.2%) experienced acute effective cryoablation of the slow pathway, and no procedure-related complications were reported. After a follow-up of 44.9±31.7 months, 28 (11.7%) patients presented AVNRT recurrences. Among electrophysiological parameters, a higher pre-ablation (p=0.05) and post-ablation anterograde Wenckebach point ($p<0.01$), a shorter post-ablation atrioventricular node refractory period (p=0.04) and persistence of the Kay sign (p=0.03) were associated with higher incidence of long-term recurrences. Considering cooling dynamics, a longer time to reach temperature $\leq$ -70°C (p=0.03) and a higher minimal temperature during ablation (p=0.04) related to recurrences. Patients without residual markers, at procedure end, of dual AV node physiology (AH jump, single atrial echo beat, Kay's sign) reported a lower recurrence rate (p=0.05) compared to those without. At multi-variate analysis, a longer time to -70°C was the strongest independent predictor of long term recurrence (OR 1.75, 95% IC 1.01 - 3.03, p=0.04).
Conclusion: AVNRT cryoablation is a safe and effective procedure. The long-term recurrence rate is however still around 10%. An ablation approach directed to the complete elimination of dual AV node physiology, along with assessment of tissue's cooling dynamics, hold the potential to improve long-term AVNRT cryoablation efficacy.

P491 | BEDSIDE
Clinical management and risk stratification of ventricular pre-excitation in asymptomatic paediatric patients

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Background: Sudden cardiac death (SCD) can be the first clinical manifestation of ventricular pre-excitation (VP) in previously asymptomatic individuals. The risk of developing fatal arrhythmic events in paediatric age is poorly defined and the identification of high risk pts is still matter of debate.
Purpose: Our aim is to describe the clinical history and stratify the arrhythmic risk in children with VP discovered on routine ECG observed by a paediatric cardiology outpatient service.
Methods: Paediatric pts referred to our Division with VP incidentally found on ECG from 2002 to 2015 were included in the current analysis. Risk evaluation was done in pts older than 8 yrs with permanent VP. The median follow-up period was 3 yrs (range 0.1–12.4).
Results: We enrolled 78 pts, 52 M and 26 F (median age at time of diagnosis 4 yrs, range 2 d-16 yrs); in 24/78 (31%) VP was found before the first year of life (median age 30d, range 2d-218 d). At the time of diagnosis, 69% of pts were younger than 8 yrs. Minor congenital heart disease was found in 10 pts (13%); 3 pts (4%) had basal intraventricular septal thinning with paradoxical movement; 5 pts (6%) had a family history of rhythm disorders. During the follow-up no SCD or potentially fatal arrhythmia occurred in the overall population. VP disappeared spontaneously in 20/78 pts (26%, median age 1.3 yrs, range 27 d-17.5 yrs). In 18/20 cases VP disappeared spontaneously before age 8. Twenty-two of 58 pts (38%) with permanent VP referred palpitations during the follow-up, but only in 5 cases a supraventricular tachycardia was documented. Twenty-three of 48 pts with VP and older than 8 yrs underwent non-invasive risk evaluation (median age 13.5 yrs, range 8.2–23.7 yrs): 15/23 pts (65%) were considered at low risk according to the results of Holter ECG and/or exercise testing; 2/23 pts (9%) were considered at high risk; the remaining 6/23 pts had not yet completed the evaluation. Based on the results of non-invasive evaluation and/or due to the presence of symptoms, 25/48 pts (52%) with VP and older than 8 yrs underwent an electrophysiological study (EPS) and/or catheter ablation at a median age of 12 yrs. Successful ablation was performed in 18/25 pts (72%); 7 pts were not considered for ablation because at low risk according to EPS results. No clear prevalence of any specific accessory pathway (AP) localization according to EPS or predicted using ECG was found (28% posterior-midseptal AP, 15% right anteroseptal AP, 15% right-sided AP, 4% epicardial AP, 17% left lateral AP, 21% undetermined AP).
Conclusions: Among paediatric pts with incident finding of ventricular pre-excitation only a minority exhibits a high risk profile that deserve subsequent invasive investigation and less than half of the pts referred symptoms over a mid-term follow up. Moreover our data suggest no need for risk stratification in children younger than 8 yrs.

P492 | BEDSIDE
The action of angiotensin-converting enzyme inhibitors on the tissue-plasminogen activator levels in patients with atrial flutter and no structural heart disease. The action of angiotensin-con

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Introduction: Previous studies have demonstrated that Atrial flutter (AFl) considered also as a high risk factor for hypercoagulability, irrespective of underlying structural heart diseases or aetiology.
The aim of this study was to evaluate 1) whether the tissue-plasminogen activator secretion is reduced in AFl patients without structural heart disease indicative reduced fibrinolytic activity which is probably an additional risk of thrombogenicity and 2) whether angiotensin-converting enzyme (ACE) inhibition favorably alters the fibrinolytic balance probably regulated by bradykinin.
Bradykinin is a potent stimulator of tPA secretion in endothelial cells, however the effect of bradykinin during AFl in the abscence of structural heart disease has not been studied.
Methods: One hundred twenty -five patients with AFl and no structural heart disease were randomly assigned to two groups;63 patients were treated with the ACE inhibitor (ACE inhibitor group) tandolapril and 62 were not treated with the ACE inhibitors (non-ACE-inhibitor group). All patients underwent an electrophysiology study for ablation procedure and they were been catheterized for taking blood samples from the aorta and coronary sinus simultaneously. We measured the tPA activator levels and the plasminogen activator inhibitor-1 (PAI-1) levels. We performed TEE in all patients.
Results: The tPA antigen levels at the Ao were similar to those in CS in both groups but in the non ACE inhibitor group were significantly lower than that in ACE inhibitor group ($p<0.0001$). The level of PAI-1 in either the Ao or the CS did not differ between the two groups. The TEE detected thrombus formation in 16 patients (13%) in non ACE inhibitor group and in none patient in ACE inhibitor group
Conclusions: The AFl in patients without structural heart disease is associated with reduced levels of the net tPA without any change in PAI-1 levels. This might be an additional risk for thrombus formation. The ACE inhibitor stimulates the tPA release without causing any change in PAI-1 levels probably through the bradykinin pathyway.

BEST POSTERS IN GENETICS AND GENE THERAPY

P494 | BEDSIDE
Personalized gene therapy targeting cardiac stem cells in patients undergoing LVAD implantation with Duchenne cardiomyopathy: a feasibility in vitro study

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Background: Duchenne Muscular Dystrophy (DMD) is an X linked recessive disorder mostly due to truncating mutations of the Dystrophin gene. Heart failure (HF) is emerging as the most relevant clinical challenge. Among the therapeutic approaches used, systemic antisense oligonucleotides (ASO) induce the skipping of one or more exons of DMD mRNA and restore the expression of the protein.

While ASO are efficient in skeletal muscle, the restoration of DMD in heart appears insufficient for a phenotypic improvement.
Purpose: The aim of this project was to develop an ex vivo gene therapy approach to restore the expression of dystrophin in cardiac stem cell (CSC) of DMD patients, obtained during LVAD implantation.
Methods: 4 consecutive patients with DMD undergoing LVAD implantation were enrolled; the LV core was collected and used for CSCs isolation. CSCs were characterized by FACS. Vectors driving the expression of specific ASOs were constructed and tested in SH-SY5Y cells and CSCs. ASOs were stabilized by placing the mouse U7 sequence at the 3' end. The production of lentiviral vectors for permanent infection of CSC was performed.
Results: CSCs expressed c-kit and markers of mesenchymal origin (CD90, CD105). Population doubling time of CSCs averaged 26.5 hours. Telomere length averaged 7.1 kbp. Telomerase activity was present in all cell lines. Based on the mutations found, we developed vectors driving the expression of ASOs against exon 50 and 55 of the DMD gene. In both SH-SY5Y and CSCs, our antisense sequences allowed to obtain the proper skipping of one or the other exons both by conventional PCR and sequencing analysis. Myocytes developed from CSCs obtained from DMD patients expressed after skipping the Dystrofin protein together with protein specific of myocytes such as beta MHC, a-SA, troponin I and T.
To further confirm the differentiation potential, confocal Ca2 imaging was performed in differentiated and undifferentiated CSCs after skipping. Extracellular application of KCl (100 mM) induced intracellular Ca2 transients in the 83% of differentiated cells while, no significant transients were observed in undifferentiated CSCs. These transients, likely due to depolarization-induced activation of voltage-gated Ca2 channels had mean peak amplitude, expressed as $\Delta F/F$ ratio, equal to 4.6±0.7, and a mean time-to-peak of 23±1 s. To evaluate the contribution of L-type voltage-gated Ca2 channels (Cav1) cells were perfused with KCl and in the presence of nifedipine (5 μM). Nifedipine significantly reduced the mean amplitude of KCl-evoked Ca2 transients by 59±7% ($p<0.0019$). This effect was significantly reversed by blocker washout (3.5±0.7 $\Delta F/F$).
Conclusions: Our results indicate that CSCs from DMD patients retain significant growth reserve and regenerative capacity in vitro. Moreover, specific exons can be skipped in CSCs, supporting the feasibility of this personalized approach to treat advanced HF in DMD patients.

P495 | BENCH
Selenoprotein T protein- or gene-therapy improves cardiac function and remodeling in rats with heart failure

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Background: Selenoprotein T (SelT) is a thioredoxin-like protein, which is abundantly but transiently expressed in the heart only during the embryonic development, suggesting that SelT plays a limited role during adulthood. However, data from our laboratory show that cardiac SelT expression increases after myocardial infarction (MI). This suggests that SelT may play a yet unrevealed role in cardiovascular diseases but SelT's potential protective role is unknown. Thus, we sought to investigate the cardioc effects of increasing SelT protein to supranormal levels via either protein- or gene-therapy in chronic heart failure (CHF).
Methods: CHF was induced by coronary artery ligation (CAL) in Wistar rats. Protein-therapy consisted in SelT administration by osmotic minipumps (15 μg/kg/day, IP, administered for 1 month starting 7 days after CAL) while gene-therapy consisted in a single intravenous injection of rAAV9-SelT (1×10^{11} virus-genome copies, 7 days after CAL). Left ventricular (LV) remodeling and perfusion were determined by echocardiography at 1 or 3 months. Moreover, cardiac hemodynamics were assessed by LV pressure-volume loops.
Results: After 1 month, SelT administration tented to reduce LV dilation (LV diastolic diameter: sham: 6.2±0.2; CAL: 9.0±0.3, $p<0.05$ vs. sham; CAL+SelT: 8.4±0.2 mm, $p=0.07$ vs. CAL), restored cardiac output (sham: 186±10; CAL: 156±7, $p<0.05$ vs. sham; CAL+SelT: 198±5 ml/min, $p<0.05$ vs. CAL). In parallel, SelT improved LV elastance (sham: 21.3±1.9; CAL: 14.2±0.6, $p<0.05$ vs. sham; CAL+SelT: 18.1±0.1 relative volume units/mmHg, $p<0.05$ vs. CAL), compliance (sham: 0.91±0.17; CAL: 2.37±0.19, $p<0.05$ vs. sham; CAL+SelT: 1.62±0.09 relative volume units/mmHg, $p<0.05$ vs. CAL).
rAAV9-SelT administration resulted in a significant increase in cardiac SelT expression as soon as 3 weeks post-injection. After 3 months, SelT reduced LV dilation (LV diastolic diameter: CAL: 10.8±0.4; CAL+rAAV9-SelT: 9.9±0.2 mm, $p<0.05$ vs. CAL), restored cardiac output (CAL: 153±6; CAL+rAAV9-SelT: 178±7 ml/min, $p<0.05$ vs. CAL). In parallel, SelT improved LV elastance (CAL: 11.0±1.0; CAL+rAAV9-SelT: 15.3±0.5 relative volume units/mmHg, $p<0.05$ vs. CAL), compliance (CAL: 2.84±0.24; CAL+rAAV9-SelT: 1.28±0.20 relative volume units/mmHg, $p<0.05$ vs. CAL).
Conclusion: Although the underlying mechanisms remain to be elucidated, our results obtained with either protein- or gene-therapy clearly show that increasing SelT protein to supranormal levels reduces CHF-induced cardiac dysfunction. These results suggest that SelT might be a promising therapeutic option in the treatment of CHF.

P496 | BENCH
Zebrafish models for ARVC8 analysis and drug discovery

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Introduction: Desmoplakin is one the most abundant desmosomal proteins in cardiac and epithelial tissues. In humans, dominat mutations in the desmoplakin gene (DSP) cause Arrhythmogenic Right Ventricular Cardio-myopathy 8 (ARVC8), a dominant cardiomyopathy, frequently involved in juvenile sudden death. Current ARVC models are based on cell lines and transgenic mice. In this context, it has been shown that suppression of DSP expression leads to a reduction in canonical Wnt signaling, suggesting that this pathway could be a molecular target for ARVC therapeutic intervention. In order to address this issue, the present study aims to evaluate the pathogenic mechanisms of DSP mutations in vivo, using zebrafish (Danio rerio) as an innovative model for this disease. In zebrafish, the desmoplakin gene is present with two isoforms, dspa and dspb, both orthologous to the single DSP in humans.
Purpose: The purpose of this study is the generation and the phenotypic characterization of transient ARVC8 zebrafish models using a morpholino-mediated knock-down strategy. In addition, by taking advantage of zebrafish pathway reporter lines, we aim to verify if Wnt signaling and/or other molecular cascades might be involved in ARVC8 pathogenesis. The final goal is the assessment of our ARVC8 model as a suitable tool for molecularly-targeted drug discovery.
Methods: To evaluate the expression of dspa and dspb during zebrafish embryonic development and adulthood, we used whole-mount in situ hybridization (WISH) and semi quantitative RT_PCR. Knockdown of zebrafish dspa and dspb genes was obtained by a morpholino (MO)-based antisense strategy. Specifically, we injected anti-dspa and anti-dspb MO oligos in both wild types and pathway-specific lines reporting the activity of Wnt, Bmp, TGFbeta, FGF, Shh, Notch, CREB, Hippo and Hypoxia signaling.
Results: We found that both dspa and dspb are expressed during zebrafish embryonic development, while the molecular analysis of cDNAs from different adult tissues demonstrates that both dspa and dspb are highly expressed in heart and skin, with dspa more strongly detectable compared to dspb. MO-mediated knock-down of both dspa and dspb leads to delayed development, microcephaly, pericardial edema and, particularly in dspb knock-down embryos, decreased heart rate. TEM analysis of cardiac and skin tissues under dspa+dspb simultaneous knock-down shows reduced and disorganized desmososmes. As far as concerns the analysis of previously mentioned signaling pathways, we observed a specific reduction of Wnt signaling responsiveness in the cardiac region of both dspa and dspb knock-down embryos (Fig. 1).

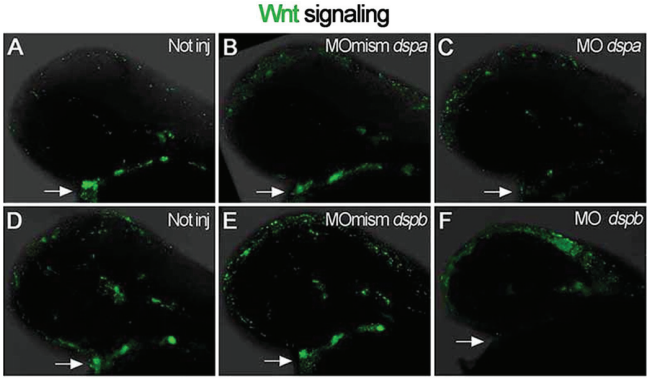

Fig. 1: Analysis of Wnt signaling under MO-mediated dspa and dspb deficiency.
dspa (C) and *dspb* (F) deficient embryos show specific reduction of Wnt signaling responsiveness (green signals) compared to not injected (A,D) or injected (B,E) controls. All pictures show lateral views of embryonic heads at 2 days post-fertilization, in lateral view, anterior to the left. White arrows indicate the cardiac region.

Conclusion: Our results show that transient knock-down of zebrafish desmoplakin genes is able to phenocopy some ARVC8 features, such as cardiac and cutaneous desmosomal defects, heart rate alteration and Wnt signaling reduction, pointing to zebrafish as a suitable ARVC8 model for in vivo screening of molecularly-targeted drugs.
Acknowledgement/Funding: Veneto Region Sanitary Research Project RP-2014-00000394 and UniPD Strategic Project STPD113ZKJ

BEST POSTERS IN HOT TOPICS IN HEART FAILURE 2

P498 | BEDSIDE
Genotype-phenotype correlations: association between mutation status and left ventricular reverse remodeling in idiopathic dilated cardiomyopathy

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Background: Despite recent DNA sequencing technologies have increased the yield of genetic analysis in individuals affected by Dilated Cardiomyopathy (DCM), genotype-phenotype correlations are still poorly understood, whereas the possible association between mutated genotypes and therapeutic response remains completely unknown.
Purpose: To explore the genetic landscape of a highly selected DCM cohort, assessing the main clinical features of different genotypes ant the possible relation with left ventricular reverse remodeling (LVRR).
Methods: Globally, 152 DCM patients have been studied by Next Generation Sequencing (NGS). According to NGS results, patients were grouped in different "gene-clusters" with functionally homogeneous genetic background. LVRR was defined by a LV ejection fraction (LVEF) increase $\geq$10 points associated with a decrease in indexed LV end-diastolic diameter (LVEDDI) $\geq$10% at a median follow-up of 24 months.
Results: A disease-related mutation was identified in 84% of patients (57% considering only pathogenic and likely pathogenic variants): 28 (18%) TTN; 7 (5%) Lamin A/C; 24 (16%) Structural Cytoskeleton-Z Disk genes; 17 (11%) Desmosomal genes; 7 (5%) MYBPC3; 18 (12%) Motor Sarcomeric genes and 26 (17%) Other genes. Baseline clinical features were largely similar between different gene clusters. A significant relationship was found between gene clusters subgroups and LVRR, with a low observed LVRR rate in Structural Cytoskeleton-Z Disk genes mutation carriers (12%, $p<0.05$ Vs all the subgroups). Of note, Structural Cytoskeleton-Z Disk genes mutation carrier status was independently and inversely associated with LVRR when adjusted for clinical predictors of LVRR (OR 0.131; 95% CI 0.035–0.490; p=0.003).
Conclusions: NGS confirmed a high genetic diagnostic yield in DCM. A specific "gene-clusters" classification based on functional similarities in different genes might be helpful in the clinical management of genetically determined DCM. In our population, structural Cytoskeleton-Z Disk genes mutations were independently associated with a reduced LVRR at follow-up.

P499 | BEDSIDE
Contemporary trends of hospitalizations for acute decompensated heart failure in the US from 2008 to 2012

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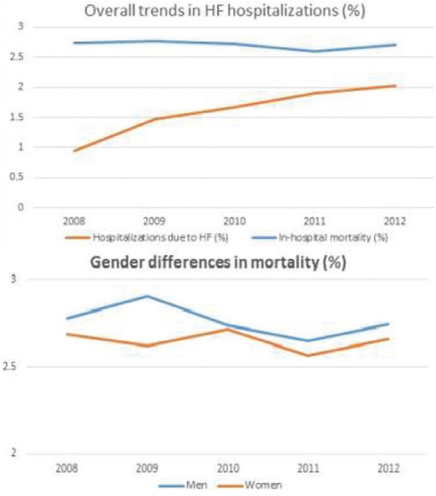
Background: Acute decompensated heart failure is a leading cause of inpatient admissions and is associated with major economic burden. Contemporary trends of hospitalizations for acute heart failure in the United States are not well studied.
Purpose: We aimed to study recent nationwide trends of acute heart failure hospitalizations in the United States using a large national administrative database. We also assessed gender differences in admissions attributed to acute heart failure during the same period.
Methods: We utilized Nationwide Inpatient Sample (NIS) database which is a 20% stratified sample of discharges across the United States except federal institutions. Patients admitted with primary diagnosis of acute systolic or diastolic heart failure during years 2008–2010 were included in the analysis. Linear and logistic regression analyses were performed and trends were adjusted for major comorbidities and previously validated Elixhauser comorbidity index. Patients with a diagnosis of chronic heart failure were excluded.
Results: Overall acute heart failure hospitalizations doubled from 2008 to 2012 (0.95 vs 2.0%, $p<0.001$). In-hospital mortality did not change significantly across years and remained around 2.7% (p=0.29). From 2008 to 2012, there was a statistically significant increase in hospital costs (8.3% increase, $p<0.001$) although the mean length of hospitalization decreased significantly (mean difference 0.24 days, $p<0.001$). Women were significantly less likely to be hospitalized for heart failure (AOR 0.82, $p<0.001$) but had lower adjusted in-hospital mortality (AOR 0.89, $p<0.001$) compared to men. The gender differences in hospitalizations and mortality did not change across years (p=0.70).
Conclusions: Hospitalization rates for acute heart failure have increased significantly among US adults from 2008 to 2012. The in-hospital mortality has remained unchanged; however, the total cost of hospitalization has significantly increased. Women are less likely to be hospitalized for heart failure but have a lower in-hospital mortality.



HF trends

P500 | BEDSIDE
Gender differences in hemodynamics and adverse events predict survival on mechanical circulatory support: insights from the EUROMACS registry

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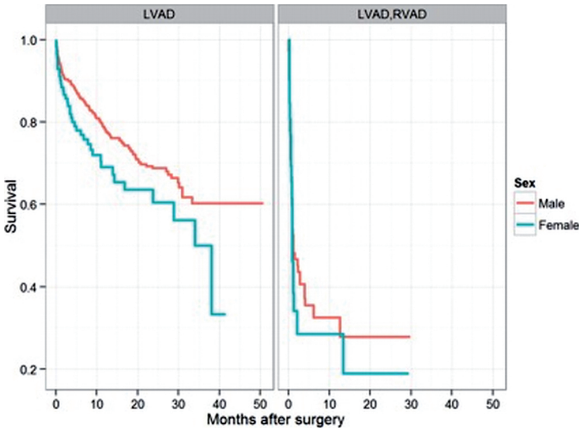
Background: In contrast to the growing use of implantable ventricular assist devices (VAD), gender aspects in preoperative hemodynamics and adverse event rates are not well described. The aim of the study was to identify gender-specific predictors for survival on bi- (BVAD) and left ventricular (LVAD) support.
Material and methods: Multi-center data of 967 patients (median age 55 years, 151 women [74.8% LVAD, 7.3% BIVAD, 17.2% temporary RVAD]) from the EUROMACS (European Registry for Patients with Mechanical Circulatory Support) registry were retrospectively analysed for gender-specific differences in the perioperative course. After a median follow-up of 1.26 years, 309 deaths (N=62 in women) were reported. We performed Cox Regression analyses to show the extent to which hemodynamic variables and adverse events associate with survival in both sexes.
Results: Significantly more male patients (84%) received VAD support. At the time of VAD implantation, women were more often (51.7% compared to 41.6% men) in critical cardiogenic shock (INTERMACS profile 1). Women had a higher prevalence of arrhythmias (P=0.031) and needed more additional right ventricular support (P=0.0094), although no differences in preoperative right ventricular (RV) function were seen for both gender. The survival of female patients on LVAD support was significantly worse (P=0.024) (Figure). Cox regression analyses showed, that preoperatively highly reduced RV function was associated with a 4.9-fold higher mortality in women (95% Confidence Interval [CI] 1.76, 13.38; in men: 3.2-fold, CI 1.95, 5.08). In addition, women with perioperative RV failure had a 4.8-fold (95% CI 2.42, 9.45) increased mortality risk (in men: Hazard Ratio [HR] 6.40, 95% CI 3.79, 10.80). Male patients with cerebral bleeding, ischemic stroke or arterial (non-cerebral) thromboembolism had a 3.1-fold (95% CI 0.76, 12.39) higher mortality risk (in women: HR 1.27, 95% CI 0.17, 9.18). No association was seen for arrhythmias, pulmonary artery pressure and LV function. The associations remained significant after multivariable adjustment for age, body mass



Kaplan-Meier survival curves

index, diabetes, systolic blood pressure, chronic obstructive pulmonary disease, and symptomatic peripheral and carotid artery disease.
Conclusions: Women and men differ in perioperative hemodynamics and adverse events after VAD implantation. RV failure and neurological complications were shown to independently predict survival in both sexes.

P501 | BEDSIDE
Pattern of late gadolinium enhancement predicts fatal arrhythmias in patients with non-ischemic cardiomyopathy

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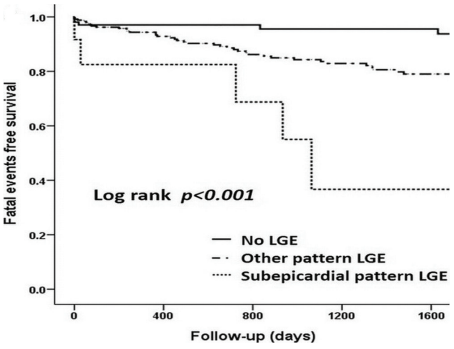
Background: Left ventricular late gadolinium enhancement (LV-LGE) by cardiac magnetic resonance (CMR) imaging has been associated with adverse clinical outcomes in patients with non-ischemic cardiomyopathy (NICM), but does not show consistent correlation with arrhythmic events.
Purpose: This study evaluated impact of the LGE characteristics on arrhythmia risk in patients with NICM.
Methods: A total of 365 consecutive patients (54±15years) with angiographically proven NICM who underwent CMR imaging were enrolled in this study. All patients were followed up for the following outcomes: fatal arrhythmias, including sustained ventricular tachycardia; appropriate implantable cardioverter-defibrillator intervention; ventricular fibrillation and sudden cardiac death.
Results: During 44.3±36.4 months of follow-up, 48 (13.1%) patients experienced fatal arrhythmias. LV-LGE was identified in 261 patients (71.5%). 88 (33.7%) patients had 2≥ pattern of LV-LGE observed. The patients with LV-LGE had a higher incidence of fatal arrhythmias (18.4% vs. 4.8%, p=0.001). In multivariate analysis, subepicardial pattern of LV-LGE (hazard ratio 4.25, 95% confidence interval 1.24–14.52, p=0.02) was independent predictors of fatal arrhythmias.



Event-free survival for fatal arrhythmia

Conclusion: LV-LGE in patients with NICM is not uncommon. The subepicardial pattern of LV-LGE was independent predictor of fatal arrhythmias, suggesting that specific patterns of LV-LGE are closely related to the severity of events.

BEST POSTERS IN THE ONGOING CHALLENGE TO FIND THE "PERFECT" BIOMARKERS

P503 | BEDSIDE
Predictive value of low testosterone concentrations regarding coronary heart disease and mortality in men and women: evidence from the FINRISK study

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Introduction: The volume of evidence that links low testosterone levels with coronary heart disease (CHD) and mortality has steadily grown during the last two decades. Nevertheless, the vast majority of studies suffer from small sample sizes and methodological limitations. In this study, we investigated the potential role of low serum testosterone levels with respect to future CHD events and mortality in the FINRISK study.
Methods: The serum levels of testosterone were measured from samples collected at baseline in the population-based FINRISK97 study including 7,671 subjects (3,710 male, 3,961 female), using a commercially available immunoassay
Results: During a median follow-up of 13.8 years, a total of 779 deaths from any cause, and 395 incident CHD events were registered. Testosterone levels were clearly higher in men than in women (median 17.15 (±9.20) nmol/L vs. 1.15 (±0.69) nmol/L; p<0.001). Age-adjusted baseline testosterone levels were similar in cases and non-cases (men: 15.80 vs 17.01 nmol/L; p=0.69, women: 1.14 vs 1.15 nmol/L; p=0.92). Surprisingly, in men testosterone levels were not correlated with age (R= 0.03; p=0.16). Pearson analyses revealed weak, however statistically significant correlations of testosterone levels with HDL-cholesterol levels (R= 0.22, p<0.001), body-mass-index (BMI) (R= -0.23; p<0.001), waist-to-hip-ratio (WHR) (R= -0.21; p<0.001) in men, and slightly with age (R=0.04; p=0.034) in women.
Kaplan-Meier analyses did not show an association of low testosterone levels with incident CHD or mortality. In accordance, adjusted cox regression also documented that testosterone levels were not predictive for incident CHD or mortality neither in men (HR 1.02; p=0.79 for lowest versus highest quartile regarding CHD and HR 1.06; p=0.67 regarding mortality), nor in women (HR 1.13; p=0.56 for lowest versus highest quartile regarding CHD and HR 0.99; p=0.80 regarding mortality).
Conclusions: Our study shows that low testosterone levels are not predictive for mortality or future CHD -neither in men, nor in women.

P504 | BEDSIDE
Troponin I and cardiovascular risk prediction in the general population

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Biomarkers may contribute to improved cardiovascular risk estimation. The value of troponin assessment for improving prediction of disease beyond established risk scores remains uncertain.
Our purposes were to evaluate the distribution of troponin I concentrations in population cohorts across Europe, to characterize the association with cardiovascular outcomes, to determine the predictive value beyond the variables used in the ESC SCORE, to test a potentially clinically relevant cut-off value, and to evaluate the improved eligibility for statin therapy based on elevated troponin I concentrations retrospectively.
Based on the Biomarkers for Cardiovascular Risk Assessment in Europe (BiomarCaRE) project we analysed individual level data from 10 prospective population based studies including 74738 participants. We investigated the value of adding troponin I levels to conventional risk factors for prediction of cardiovascular disease by calculating measures of discrimination (C-index) and net reclassification improvement (NRI). We further tested the clinical implication of statin therapy based on troponin concentration in 12956 individuals free of cardiovascular disease in the JUPITER study.
Troponin I remained an independent predictor with a hazard ratio of 1.37 for cardiovascular mortality, 1.23 for cardiovascular disease, and 1.24 for total mortality. The addition of troponin I information to a prognostic model for cardiovascular death constructed of ESC SCORE variables increased the C-index discrimination measure by 0.007 and yielded a NRI of 0.048, whereas the addition to prognostic models for cardiovascular disease and total mortality led to lesser C-index discrimination and NRI increment. In individuals above 6 ng/L of troponin I, a concentration near the upper quintile in BiomarCaRE (5.9 ng/L) and JUPITER (5.8 ng/L), rosuvastatin therapy resulted in higher absolute risk reduction compared to individuals below 6 ng/L of troponin I, whereas the relative risk reduction was similar.

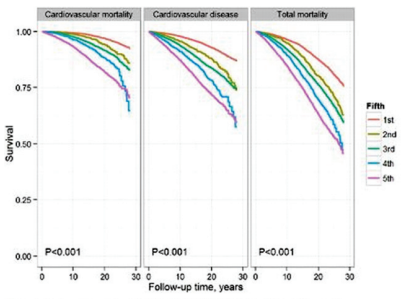

Figure Survival curves according to fifths of the troponin I distribution in the study population
The p-value given in the survival curves is for the logrank test. The troponin I quintiles, computed in the overall population via linear quantile mixed models, are 2.5, 2.8, 5.4 and 5.9 ng/L. The number of cohorts contributing to the figure decreases gradually over the 28 years, and includes only the Glostrup cohort at the end of follow-up. The number of persons at risk at 27 years of the follow-up according to troponin I fifths in increasing order is: 1288, 162, 669, 30, 155 for cardiovascular mortality and total mortality, and 1201, 145, 601, 26, 136 for cardiovascular disease.

In individuals free of cardiovascular disease, the addition of troponin I to vari-

ables of established risk score improves prediction of cardiovascular death and cardiovascular disease.
Acknowledgement/Funding: European Union Seventh Framework Programme; Medical Research Council London; Abbott Diagnostics

P505 | BEDSIDE
Cyr61, a novel biomarker of acute coronary thrombotic occlusion improves risk stratification beyond the GRACE score when combined in a multimarker approach in patients with acute coronary syndromes

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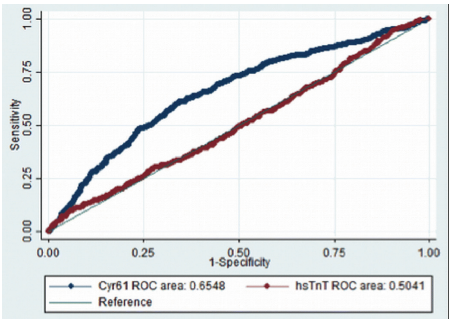
Background: Cystein-rich angiogenic inducer 61 (Cyr61) is a secreted member of the matricellular CCN family. Cyr61 expression is increased at sites of inflammation and wound repair modulated by hypoxia and growth factors. The latter events reflect the pathogenesis of acute coronary thrombus formation. At present, no biomarker of acute coronary thrombotic occlusion exists in ACS patients.
Methods and materials: Consecutive ACS patients referred for coronary angiography to four Swiss university hospitals were enrolled into the SPUM-ACS Biomarker Cohort between 2009 and 2012. Gene expression profiling was performed on mRNA isolated from coronary thrombi and peripheral blood mononuclear cells (PBMC) from individual ACS patients. Based on angiographic data the presence of coronary thrombus in the culprit lesion was assessed. Primary/secondary adjudicated endpoints at 30 days and 1 year were all-cause mortality and the composite of all-cause mortality and recurrent myocardial infarction (MI) as used in the GRACE score. Baseline concentrations of Cyr61 were measured in serum in duplicates using an enzyme-linked immunosorbent assay (EIA-5108, DRG Instruments, Marburg, Germany). A concentration of 344.07 pg/mL was used as a cut point based on measurements in healthy probands. High-sensitivity troponin T (hsTnT), high-sensitivity CRP (hsCRP) and NT-proBNP (Roche Diagnostics, Mannheim, Germany) were used as reference biomarkers.
Results: Cyr61 was markedly induced (66-fold increase) in coronary thrombus compared with PBMC. Among 1834 patients recruited within <24 hours after pain onset, 1225 could be analysed for diagnostic potential and 1734 to determine the prognostic potential of soluble Cyr61. Median Cyr61 concentration was highest in the acute phase (0–6 hour interval to blood draw: 707.2 pg/mL) versus prolonged intervals (6–12 hours: 461.9 pg/mL and 12–24 hours: 493.3 pg/mL). Diagnostic accuracy for presence of coronary thrombus was significantly higher for Cyr61 (AUC 0.66) compared with hsTnT (AUC 0.50; p-value<0.001). Multivariate analysis identified Cyr61 as an independent predictor of all-cause mortality at 1 year (hazard ratio 2.99 (1.37–6.55), p=0.006) and the composite of all-cause mortality or MI at 1 year (hazard ratio 1.85 (1.14–2.99), p=0.012) when combined with the GRACE score, hsTnT, hsCRP and NT-proBNP, respectively. Prognostic accuracy of the GRACE score to predict all-cause mortality at 1 year (c-statistic 0.665) was significantly improved when adding Cyr61 to the model (c-statistic 0.696; p=0.0042). Risk prediction of the composite of all-cause mortality or MI at 1 year was also significantly improved when adding Cyr61 to the model compared with the GRACE score alone (c-statistic 0.634 vs. 0.619; p=0.023).



Diagnostic accuracy: coronary thrombus

Conclusions: This is the first study which identifies Cyr61 as a novel soluble biomarker in ACS. Cyr61 appears to reflect a distinct pathophysiology and adds independent incremental information to current risk stratification tools.
Acknowledgement/Funding: Swiss National Science Foundation (SPUM 33CM30-124112)

P506 | BEDSIDE
Cardiac biomarkers and left ventricular hypertrophy in relation to outcomes in patients with atrial fibrillation: experiences from the RELY trial

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Background: Both cardiac biomarkers and left ventricular hypertrophy (LVH) by electrocardiography (ECG) are related to the risk of stroke and death in patients with atrial fibrillation (AF).
Methods: We investigated the associations between and compared the prognostic value of LVH by ECG and the cardiac biomarkers in plasma samples obtained at baseline in 5275 anticoagulated patients with AF included in the Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) trial. Levels of hs-troponin-T (TnT), NT-proBNP and GDF-15 were determined by Roche Elecsys assays.
Results: LVH was present in 1257 patients. During a median follow-up of 2.0 years, 148 patients developed a stroke and 325 died. LVH was significantly (p<0.0001) associated with higher levels of all biomarkers in multivariable analyses adjusting for baseline characteristics – geometric mean ratio for TnI 1.79 (1.68–1.91), TnT 1.43 (1.37–1.50), NT-proBNP 1.37 (1.31–1.44) and GDF-15 1.11 (1.07–1.15). The levels of all biomarkers were significantly associated with stroke and death after adjustment for baseline characteristics. For stroke the HR (CI) of the highest vs lowest tertile were for hs-TnT 1.73 (1.11–2.71), for NT-proBNP 1.28 (0.87–1.88) and for GDF-15 2.25 (1.41–3.60) (all p<0.05). For death the HR (CI) of the highest vs lowest tertile were for hs-TnT 3.83 (2.71–5.41) for NT-proBNP 2.29 (1.72–3.04) and for GDF-15 2.82 (2.04–3.88) (all p<0.0001). These associations were unchanged by adding LVH to the models. LVH did not remain significantly associated with stroke or death after adjustment for the biomarker levels.
Conclusions: Levels of cardiac biomarkers are significantly associated with LVH. The prognostic value of biomarkers concerning stroke and death are not affected by LVH while LVH provides no prognostic information in the presence of cardiac biomarkers.
Acknowledgement/Funding: RE-LY trial was funded by Boehringer Ingelheim and ROCHE Diagnostics provided GDF-15 pre-commercial assay free of charge

BEST POSTERS IN TRICUSPID VALVE DISEASE

P508 | BEDSIDE
Impact of tricuspid regurgitation in patients undergoing aortic valve replacement

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Background: The presence of Tricuspid Regurgitation (TR) is a common finding in patient undergoing aortic and/or mitral valve surgery. The impact of untreated TR on survival in patients undergoing aortic valve replacement (AVR) is not clearly defined.
Purpose: Aim of our study is to evaluate the evolution and clinical impact on a long term follow-up (FU) of TR in patients who underwent AVR.
Methods: We analyzed our Institutional database identifying all consecutive patients who underwent AVR for aortic valve stenosis or regurgitation as primary disease, with or without associated coronary artery by-pass surgery or surgery on the thoracic aorta, from January 2001 to December 2012. Patients were divided in three groups according to the presence of preoperative TR: none (0+), mild (1+) and moderate (2/3+); no patients presented severe TR (4+). We analyzed the early evolution of TR and its impact on the survival at long term FU.
Results: Five-hundred-seventy-nine patients were analyzed. Mean FU time was 5.75 years (IQR 3.24–8 years). Preoperative TR was absent in 278 patients (48%), mild in 417 patients (72%) and moderate in 64 patients (11%). At discharge: in 0+ group 164 patients (59%) remained stable, 96 patients developed a 1+ TR (35%) and 18 patients developed a 2/3+ TR (6%). In 1+ group 78 patients (19%) reduced TR to 0+, 300 patients remained stable (72%) and 39 patients developed a 2/3+ TR (9%). In 2/3+ group 50% of patients reduces TR, 13 patients (20%) reduced TR to 0 and 19 patients reduced TR to 1+ (30%) while 32 patients remained stable (50%); these differences are significant (p<0.001).
Patients in the 2/3+ group were significantly older (p<0.001), with higher incidence of associated mitral regurgitation (p<0.001), higher incidence of aortic regurgitation (p<0.009), higher incidence of moderate and severe pulmonary hypertension (PH) and biatrial dilatation (p<0.001).

At long-term FU we observed a significantly higher mortality for patients in 2/3+ group (p<0.001).
Multivariate analysis revealed a significant trend toward increased risk of death for patients presenting progressively worse TR (1+: HR 1.64, CI 1.13–2.37; 2/3+: HR 2.61, CI 1.55–4.43) (fig. 1; panel B).

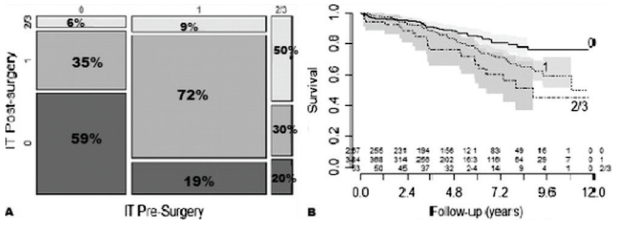

Figure 1

Conclusions: The great majority of patients immediately after surgery present an immediate reduction of TR degree. Patients who presents an unchanged moderate TR after surgery have a less favourable long-term survival. AVR and concomitant tricuspid valve surgery should be carefully evaluated with a specific patient approach considering the presence of associated risk factors as indicators of a more advanced ventricular disease that could benefit from a more extensive treatment.

P509 | BEDSIDE
Should we reduce current thresholds for annuloplasty in functional tricuspid regurgitation associated with rheumatic valve disease?

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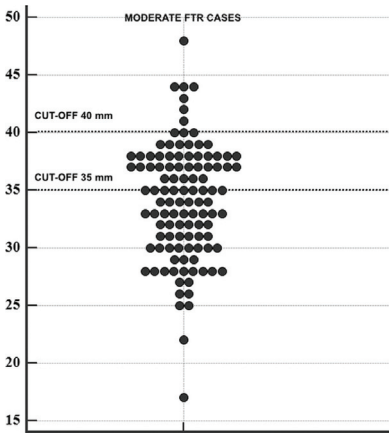
Background: Significant tricuspid annulus (TA) dilatation seems to be the underlying mechanism of severe functional tricuspid regurgitation (FTR) but this could be present even in non-severe FTR. While general agreement exists for tricuspid annuloplasty in severe TR, guidelines only recommend TV surgery in mild and moderate FTR associated with significant TA dilatation (≥40 mm or ≥21mm/m^2). It is well known that more than one third of patients with previous non-severe FTR will develop it lately after surgery.
Objectives: The aims of the present study were (1)to assess TA dilatation associated with the presence of severe FTR, (2) to determine the proportion of non-severe FTR with significant TA dilatation, and (3) to evaluate if current guidelines criteria properly classify patients for surgery in this specific population.
Methods: 109 patients with rheumatic heart disease in absence of previous valve replacement and FTR were prospectively included. The optimal diameters cut-off points for significant TA dilatation identification were calculated and compared with current guidelines thresholds.
Results: Mean age: 68±10 years; 80% women. FTR was divided into three groups: mild (N: 41), moderate (N: 43) and severe (N: 25). An absolute cut-off point of 35 mm and 21 mm/m^2 (adjusted for body surface area) were the diameters with better diagnostic performance. Sensitivity, Specificity and AUC are shown in Table 1. 56% of non-severe FTR had significant TA dilatation. Applying 40 mm threshold, only 2% patients with moderate FTR would be selected for surgery. Proposed 35 mm cut-off value, reclassifies surgical indication in 53% of cases (95% CI, 37%-53%; p<0.001) in comparison with current guidelines. No patient with mild TFR was selected for surgery with either of the two criteria.
Conclusions: Although 21mm/m^2 seems to be reasonable criteria for the selection of patients for surgery, current 40 mm threshold underestimates significant TA dilatation. We strongly suggest a cut-off point ≥35 mm and the need to adjust for body surface area for improving selection of patients with non-severe TFR that should be referred to annuloplasty.

Optimal diameters cut-off points

Tricuspid annulus diameter	Sensitivity	Specificity	AUC
35 mm	80%	70%	0.80
21 mm/m^2	80%	63%	0.78

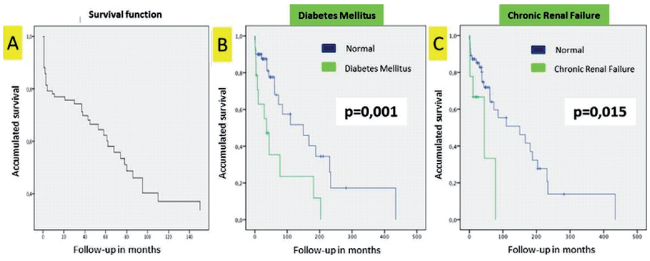


35mm VS. 40mm THRESHOLD IN MODERATE FTR

P510 | BEDSIDE
Tricuspid valve replacement: a safe option for non-reparable valves? A single center 20-year experience

A. Carbonell San Roman, L.M. Rincon Diaz, E. Casas Rojo, J.L. Moya Mur, J.M. Monteagudo Ruiz, A. Gonzalez Gomez, A. Garcia Martin, M. Valverde Gomez, M. Plaza Martin, S. Fernandez Santos, J.M. Garrido, J. Roda, J.L. Zamorano Gomez. *Hospital Universitario Ramón y Cajal, Madrid, Spain*

Introduction and aim: Surgical correction of tricuspid valve pathology is often limited to non-reparable valves, as tricuspid valve replacement (TVR) has been associated with elevated morbidity and mortality. Our aim was to analyze the frequency and nature of major cardiovascular (CV) events after TVR and associated predictive factors.
Methods: Ninety-six patients with previous TVR were included over a 20-year period. Meticulous revision of their clinical history to obtain demographic and clinical data was performed, with recording of events such as prosthetic valve thrombosis, stroke, major hemorrhage, heart failure or CV death. Follow-up was completed by telephonic contact.
Results: Mean age was 61.0±13.2 years at the time of surgery being 56.2% women, with 51.5% of biological prosthesis implanted. There were a total of 52 events including PVTh, stroke, major hemorrhage, heart failure and CV death, of which 38 (39.6%) deceased during a mean follow-up of 54.9±72.23 months. Overall, 30-day combined end-point rate was 12%. The survival function is shown in graph A, being the event-free survival 75% after the first year, 55% after 5 years and 35% 10 years after surgery. Patients with diabetes and chronic renal failure had a significantly lower event free survival (Graphs B and C). At mean follow-up of 54.9 months, Cox regression analysis identified diabetes, chronic renal failure and the biological prosthesis as predictors of events, with an estimated HR for DM of 4.7 [CI 95% 1.8–12.0], 2.15 [CI 95% 0.5–9.1] for chronic renal failure and 4.1 [CI 95% 1.4–11.3] for biological prosthesis. Neither the number of surgery nor the presence of other valvulopathies were found to be predictive factors.



Graphs A, B and C

Conclusions: TVR continues to be a high risk procedure with elevated mortality and risk of other cardiovascular events but identification of patients at most risk with adequate patient selection seems determinant in survival.

P511 | BEDSIDE
Clinical significance of tricuspid regurgitation in degenerative valvular heart disease

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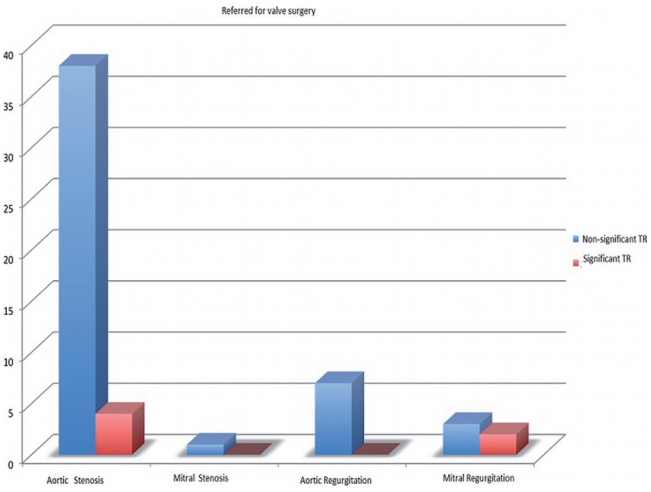
Introduction: In the past decades, due to the increasing aging of the population in developed countries, degenerative etiology has replaced rheumatic disease as the most common etiology of valvular disease (VD). The prevalence of functional tricuspid regurgitation (TR) and its prognostic implications are scarcely understood. The aim of this study was to study the presence and degree of TR in patients with severe degenerative aortic or mitral valve disease and analyze its association with their symptomatic status and indication for surgery.
Methods: We prospectively included 123 consecutive patients (81±8 years, 59% female) with severe degenerative mitral or aortic valve dysfunction referred for an echocardiogram (from October 2013 until September 2014). Demographic and echocardiographic variables related to the presence of TR, quantification of its severity and anatomic and functional right ventricular evaluation of this population were collected. We analyzed the association of TR with the indication for surgery by means of the likelihood ratio test.
Results: The most prevalent VD was aortic stenosis accounting for 76% of the

patients, followed by aortic regurgitation (11%). 69% of the patients were in sinus rhythm. The vast majority of the patients had either none TR (22%) or mild TR (57%). In 21% of the patients, the degree of TR was moderate or severe and considered significant.The annular tricuspid dimension measured in 4Ch apical view was 30±5 mm. Regarding to right ventricular evaluation, 23% patients had right ventricular systolic dysfunction, studied by TAPSE, S' wave or Tei index. Mean right ventricular systolic pressure was 46±16 mmHg. Mean right atrial area was 18±6 cm^2, In 46% of the patients an indication for valvular surgery was stablished. The association between the degree of TR and indication of valve surgery was not statistically significant (likelihood ratio test). However, this association was significant in those patients with severe mitral regurgitation (p=0.048).



Prevalence of functional TR

Conclusions: A significant functional TR in patients with degenerative mitral or aortic valve disease is less prevalent compared to other etiologies. Also, we found that the finding of significant TR does not seem to correlate with the need of valve surgery in the whole cohort. However, in the subgroup of patients with severe mitral regurgitation, the presence of significant TR may be a marker of more advanced state of disease and determine an earlier therapeutic intervention or closer surveillance in those patients. An additional study will be needed to explore the prognostic implication of functional TR after cardiac surgery.

BEST POSTERS IN EXPERIMENTAL STUDIES ON IMAGING OF MYOCARDIAL ISCHAEMIA

P513 | BENCH
CMR-LGE in acute phase of ischemia-reperfusion measures microvascular damage (leakage) rather than infarction

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Background: In acute myocardial infarction (AMI), late gadolinium enhancement (LGE) on cardiac magnetic resonance (CMR) imaging is thought to represent the necrotic region. However, prior histopathological studies have focused on LGE several days or months after AMI. Microvascular leakage is a key pathological feature of AMI, however, an imaging method to detect microvascular leakage has not been established.
Purpose: To test the possibility that LGE in the early phase of AMI represents microvascular leakage within the ischemic zone rather than infarct size.
Methods: Mice were subjected to ischemia (I) by coronary artery occlusion for 1 hour followed by reperfusion (R) for 24 hours. Infarct size was measured using a dual-staining method. To determine microvascular leakage, another batch of mice were subjected to IR and then injected with Evans blue (EB, 20 mg/kg i.v.) as a capillary permeability tracer 3 hours prior to sacrifice. Hearts were perfused to remove blood in the coronary vasculature and then serially sectioned for histological measure of regions with EB stain (microvascular leakage). Further, some animals with IR received both injections of EB (20 mg/kg) 3 hours and gadolinium-DTPA contrast Magnevist (938 mg/kg) 30–40 min prior to sacrifice. Mice were then killed by anaesthetic overdose and CMR imaging was taken within 4 hours. Using a 9.4T CMR scanner, serial cardiac images for LGE were acquired (data matrix 192×384, 9~12 axial slices, 0.8 mm thickness). After CMR, the heart was harvested, perfused, and transversely sectioned into 7–8 sections at 0.8 mm in thickness and histological images were taken digitally for histological analysis. The areas of CMR-LGE or images with BE staining at each section were quantified and the correlation was analyzed.
Results: In mice (n=10) 24 hours after AMI, the infarct size determined by TTC staining was 61±1% of the risk zone. There was more extensive EB staining corresponding to 75±2% area of the risk zone that significantly exceeded the region of necrosis (n=8, P<0.05). Areas of CMR-LGE (Figure A, arrows) were highly correlated with microvascular leakage identified by EB staining (Figure B, r=0.95, P<0.0001, n=28 sections from 4 hearts).

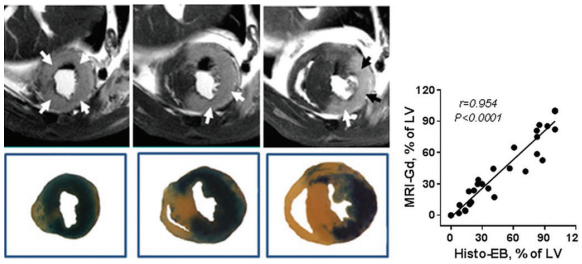

Figure 1

Conclusions: In the early phase of AMI, CMR-LGE represents a prolonged retention of magnevist in the interstitium of the jeopardized myocardium corresponding to the area of microvascular leakage, which is greater than the extent of myocardial necrosis. CMR-LGE based detection of microvascular leakage provides a new diagnostic tool for microvascular damage complementing to the "no-reflow" phenomenon.
Acknowledgement/Funding: NHMRC of Australia

P514 | BEDSIDE
Why does exercise in cold air increase susceptibility to myocardial ischaemia?

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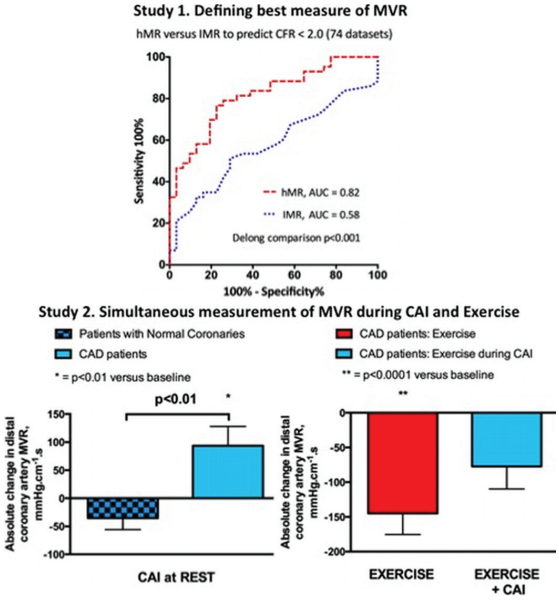
Background: Cold air inhalation (CAI) during exercise increases cardiac mortality. The pathophysiology remains unclear, but may reflect adverse changes in coronary microvascular resistance (MVR). However, there is currently no gold-standard invasive measurement of MVR.
Purpose: We compared the diagnostic accuracy of two novel invasive measurements of MVR measured in the cardiac catheter laboratory to predict microvascular dysfunction: the Doppler-derived hyperaemic microvascular resistance (hMR) and the thermodilution-derived index of microcirculatory resistance (IMR). We then used the best invasive measure of MVR to quantify changes during CAI at rest, dynamic exercise at room temperature and dynamic exercise during CAI.
Methods: 56 patients (61±10 years) undergoing cardiac catheterization for stable coronary artery disease (CAD) or acute myocardial infarction (AMI) were recruited. Simultaneous intracoronary pressure, Doppler flow velocity and thermodilution were carried out in 74 unobstructed vessels (post PCI or FFR >0.8), at rest and during hyperemia. Three independent measures of microvascular function were assessed, using predefined dichotomous thresholds: 1) CFRmean, the average value of Doppler- and thermodilution-derived coronary flow reserve (CFR), and cardiovascular magnetic resonance derived: 2) Myocardial Perfusion Reserve Index (MPRI) and 3) Microvascular Obstruction (MVO).
In a further 55 patients undergoing coronary angiography (61±9 years: 45 with significant stable CAD, 10 with normal coronary arteries), baseline and peak



Doppler-derived MVR were respectively measured before and after 5 minutes of either:
a) CAI at rest (–15°C, via facemask).
b) Cycling (supine ergometry with incremental workload) at room temperature.
c) CAI during cycling.
Results: hMR correlated with IMR (rho=0.41, p<0.0001). hMR had better diagnostic accuracy than IMR to predict CFRmean (area under curve, (AUC) 0.82 vs. 0.58, p<0.001, sensitivity/specificity 77/77% vs. 51/71%) and MPRI (AUC 0.85 vs. 0.72, p=0.19, sensitivity/specificity 82/80% vs. 64/75%). In AMI patients, the AUCs of hMR and IMR at predicting MVO were 0.83 and 0.72 respectively (p=0.22, sensitivity/specificity 78/74% vs. 44/91%).
CAI at rest increased MVR in CAD patients (rest 576±48 versus peak 643±54 $mmHg \cdot cm^{-1} \cdot s$, p<0.01) but not in patients with normal coronary arteries (612±54 versus 550±44 $mmHg \cdot cm^{-1} \cdot s$, p=0.41). Cycling at room temperature in CAD patients decreased MVR (baseline 579±41 versus peak 434±35 $mmHg \cdot cm^{-1} \cdot s$, p<0.001). However, the addition of CAI during exercise in CAD patients severely blunted the MVR reduction by 47% (baseline 573±44 versus peak 495±45 $mmHg \cdot cm^{-1} \cdot s$, p=0.12).
Conclusions: 1. hMR was a better predictor of microvascular dysfunction than IMR. 2. In CAD patients CAI caused adverse changes in MVR at rest and during exercise. CAI may impede coronary vasodilatation and ventricular relaxation, rendering the heart more susceptible to ischemia.
Acknowledgement/Funding: Supported by British Heart Foundation Fellowships to RW (FS/11/90/29087) and the Biomedical Research Centre at St Thomas' Hospital

P515 | BENCH
Fluorescent indocyanine green imaging enables in vivo and ex vivo quantification of myocardial infarct size

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Introduction: The triphenyltetrazolium chloride (TTC) assay is commonly used for ex vivo quantification of infarct size (IS); however, the results are reliable only after >90 min of reperfusion. Here we describe a new method of IS measurement based on the phenomenon of selective accumulation of fluorescent dye, indocyanine green (ICG), in the irreversibly injured ischemic-reperfused area after its intravenous administration.
Purpose: The study was aimed at validation of ICG-based technique of IS quantification both in vivo and ex vivo with TTC staining used as gold standard.
Methods: Male Wistar rats weighing 250–300 g were anesthetized, mechanically ventilated and subjected to 30-min myocardial ischemia followed by either 30 or 120 min of reperfusion in ICG and ICG+TTC groups, respectively. ICG was infused intravenously for 10 min at a dose of 0.25 mg/ml starting from 25th min of ischemia. The intravital video recording was performed in ICG group during ischemia-reperfusion. Anatomical area at risk size and IS were determined in ICG+TTC group with Evans blue and TTC staining, respectively. Near infrared imaging of heart slices was carried out using a laser-induced fluorescence detection system (λ=808 nm).
Results: Video recording demonstrated bright fluorescence of the epicardial surface of the heart corresponding to the area of ischemia-reperfusion 30 min after ICG administration. The area at risk averaged 34.7±3.7%. IS was not different when determined using traditional TTC assay and ICG fluorescent labeling (58.3±7.4% and 62.4±11.5%, respectively, p>0.05).
Conclusions: This study shows that ICG accumulates in area of irreversible ischemia-reperfusion injury as early as 30 min after reperfusion. Fluorescent ICG imaging can be used for both in vivo delineation and ex vivo quantification of IS. The accuracy of IS measurement with ICG is not inferior to that of TTC staining protocol.
Acknowledgement/Funding: This study was supported by the Russian Science Foundation, Project 14-15-00473

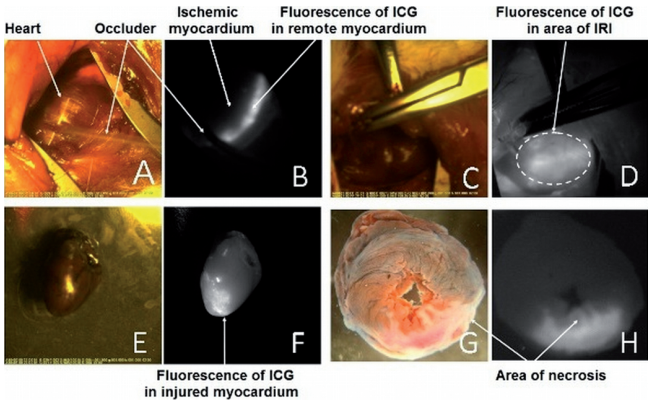

Figure 1. Intravital and post-mortem visualization of ischemic-reperfused area of the heart with ICG and TTC. A, B: perfusion defect immediately after ICG administration; C, D: Intravital epicardial ICG fluorescence; E, F: epicardial ICG fluorescence in the excised heart; G, H: transverse heart slices stained with TTC and ICG obtained after 120 min of reperfusion.

P516 | BENCH
Experimental validation of contrast enhanced SSFP MR imaging to measure myocardium at risk

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Background: Accurate assessment of myocardium at risk (MaR) after acute myocardial infarction (AMI) is important to calculate myocardial salvage. Contrast-enhanced steady-state free precession (CE-SSFP) is a recently developed cardiac magnetic resonance (CMR) method for assessment of MaR up to one week after AMI which has been used in three large cardioprotection trials so far (1–3). The purpose of this study was to validate CE-SSFP for determination of MaR in an experimental porcine model using myocardial perfusion SPECT (MPS) as a reference standard.
Methods: Eleven pigs were subject to 35–40 minutes of left anterior descending artery occlusion followed by four hours of reperfusion. A technetium-based perfusion tracer was administered intravenously ten minutes before reperfusion. In-vivo and ex-vivo CE-SSFP CMR imaging was performed followed by ex-vivo MPS imaging. MaR was expressed as % of left ventricular mass (LVM).
Results: There was a good agreement between MaR by ex-vivo CMR and MaR by MPS (r2=0.92, p<0.0001, bias: 1.3±2.4% LVM, Fig 1A-B) and between ex-vivo and in-vivo CMR (r2=0.91, p<0.0001, bias -0.8±2.7% LVM, Fig1C-D).

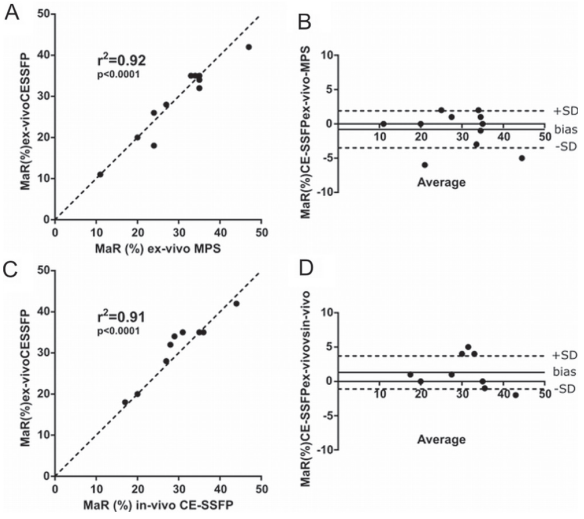

Figure 1

Conclusion: Contrast enhanced SSFP MR imaging can be used to measure MaR with high accuracy and precision in an experimental setting.
Acknowledgement/Funding: Swedish Heart Lung Foundation

POSTER SESSION 1

MULTI-MODALITY IMAGING

P517 | BEDSIDE
Fusion of coronary computed tomography angiography with single-photon emission computed tomography: long-term prognostic value

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Background: Cardiac hybrid imaging fusing single-photon emission computed tomography (SPECT) myocardial perfusion imaging with coronary computed tomography angiography (CCTA) offers information on coronary anatomy and myocardial perfusion for the diagnosis of coronary artery disease (CAD). However, studies on its prognostic value are scarce. Hence, we assessed the long-term prognostic value of cardiac hybrid imaging
Methods: All patients were classified into three groups according to the hybrid imaging findings: 1) stenosis by CCTA and matching reversible SPECT defect; 2) unmatched CCTA and SPECT finding; 3) normal finding by CCTA and

SPECT. Endpoints were: all-cause death or nonfatal myocardial infarction (MI) (hard events) and a composite of major cardiac events (MACE: death, MI, unstable angina requiring hospitalisation, coronary revascularizations). Kaplan-Meier method identified survival free of MACE and Cox's proportional hazard regression determined independent predictors for cardiac events.
Results: Of a total of 428 patients, 14 patients were lost to follow-up and 39 patients were excluded due to early revascularization (<30 days). Thus, the final study population included 375 patients. During a median follow-up period of 6.8 years, a total of 160 MACE occurred in 109 patients (29%), including 45 deaths (12%) and 19 nonfatal MI (5%). Overall, we recorded 78 late revascularisations (63 PCI and 15 CABG). Cardiac hybrid imaging revealed a normal finding by both imaging methods in 216 patients (58%), while a matched defect was found in a total of 46 patients (12%) and an unmatched finding in 113 patients (30%).
Patients with normal findings on hybrid imaging had an excellent event-free survival (Figure 1). By contrast, outcome was progressively worse in patients with unmatched and matched findings. This was true for all-cause death ($p<0.001$; Fig. 1A), for hard events ($p<0.001$; Fig. 1B) as well as for the composite of all MACE ($p<0.001$; Fig. 1C). Finally, the annual death rate was highest in patients with a matched hybrid finding (4.6%), and significantly lower in patients with unmatched (2.9%) and normal findings (0.8%, both $p<0.001$). The highest annual event rate for hard events was noted in patients with matched finding (7.0%). Event rates were lower in patients with unmatched (3.7%) or normal findings (1.2%) ($p<0.001$). The respective values for MACE rate were: 21.8%, 9.0% and 2.4%, respectively ($p<0.001$). A corresponding matched hybrid image finding proved to be an independent predictor for MACE. However, it was not an independent predictor of hard events.

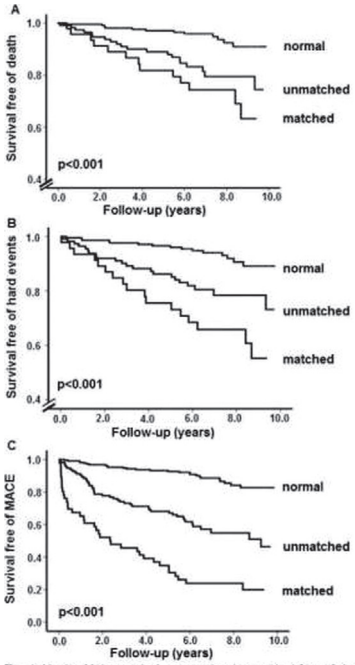

Fig. 1: Kaplan-Meier survival curves showing survival free of death (A), hard events (B) and MACE (C) in the different patients group (matched, unmatched and normal)

Conclusions: This study expands the knowledge on the prognostic value of cardiac hybrid imaging to a follow-up period of up to 10 years. The results identified a matched finding as a strong long-term predictor of MACE, while a normal finding confers an excellent long-term prognosis, allowing improved risk stratification in patients with known or suspected CAD.

P518 | BEDSIDE
Feasibility and reproducibility of hybrid 18F-FDG PET/MRI in the progression of early subclinical atherosclerosis (PESA) study

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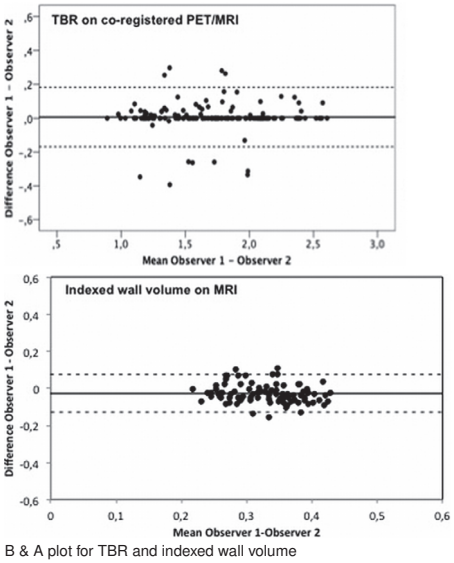
Background: Although hybrid technology using 18F-fluordeoxyglucose positron emission tomography and magnetic resonance imaging (18F-FDG PET/MRI) can provide in vivo molecular and anatomical information, data are limited regarding multi-territorial evaluation of atherosclerosis.
Purpose: To assess the feasibility and reproducibility of 18F-FDG PET/MRI to characterize plaque burden, composition and inflammation in subclinical atherosclerosis.
Methods: A total of 938 asymptomatic participants with extensive atherosclerosis (age 48.0±4.3 years, 84% men) from the PESA (Progression of Early Subclinical Atherosclerosis) study underwent 18F-FDG PET/MRI of the carotid arteries, aorta, and ilio-femoral arteries 30 min after 18F-FDG injection (FDG dose 293±10.5 MBq, radiation dose 5.6±0.2 mSv). Arterial FDG uptake was evaluated on co-registered PET/MRI images using target-to-background ratios (TBR). Atherosclerotic burden was evaluated on T1-weighted MR images (indexed wall volume) and plaque characterization on T1- and T2- weighted MR images (lipidic, fibrous, mixed). Reproducibilities of FDG uptake and atherosclerotic burden/composition were quantified in 15 PESA participants using intraclass correlation coefficients (ICC), kappa and Bland & Altman analysis.
Results: A total of 842 (89.7%) 18F-FDG PET/MRI studies were available for final analysis (5.9% of which were incomplete, mainly lacking carotid imaging). FDG circulation time was 106.0±14.9 min for the ilio-femoral PET and 133.0±19.5 min for the carotid-aortic PET. Plaque composition analysis showed a Kappa value of 0.57. ICC of multi-territorial TBR was excellent (0.98; 95% CI of 0.97–0.98). ICC of multi-territorial indexed wall volume was good (0.89; 95% CI of 0.84–0.93). Bland & Altman plots showed good agreement for all explored territories, with mostly narrow confidence intervals (Figure).



B & A plot for TBR and indexed wall volume

Conclusions: Hybrid 18F-FDG PET/MRI of multi-territory subclinical atherosclerosis in a single setting is feasible and highly reproducible, as demonstrated in the largest cohort ever reported for vascular PET/MRI, allowing multiparametric characterization of plaque burden, composition and inflammation.
Acknowledgement/Funding: The PESA study is co-funded equally by the Spanish National Center for Cardiovascular Research (CNIC), Madrid and Banco de Santander, Madrid.

P519 | BENCH
Multimodality intravascular molecular imaging of inflammation and endothelial permeability independently predicts plaque progression over time

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Background: Little is known how changes in coronary atherosclerotic plaque biology relate to plaque burden over time, and whether intravascular imaging of plaque biomarkers can independently predict plaque progression. This experimental study evaluated the ability of serial intravascular near-infrared fluorescence (NIRF) imaging of molecular changes during plaque progression in coronary-sized arteries.
Methods: Atherosclerosis was induced by balloon-injury in the aorta of 14 cholesterol-fed rabbits. Serial intravascular ultrasound (IVUS) and dual-modality intravascular NIRF - optical coherence tomography (OCT) imaging was performed in aortas of 14 cholesterol-fed rabbits after balloon catheter injury. After injection of a NIRF molecular imaging agent of plaque inflammatory protease activity (ProSense VM110; n=7), or impaired plaque endothelial permeability (indocyanine green (ICG); n=7), we measured concentrations of NIRF imaging agent using OCT-based distance correction. Subsequently, plaque burden was assessed by assessing plaque size with IVUS. After in vivo imaging, the findings were sub-

stantiated by ex vivo fluorescence reflectance imaging, fluorescence microscopy, and histological analysis.
Results: The analysis of 1,811 cross-sectional plaque images revealed that the difference in quantified NIRF plaque signal from 8 to 12 weeks strongly correlated with IVUS plaque burden at these time points (ProSense VM110: r=0.774; ICG: r=0.572; p<0.0001). The correlation continued to be significant on multivariate analysis adjusted for IVUS lumen area, remodeling index and plaque burden (p<0.001). Additional multivariate analyses demonstrated that baseline NIRF signal at 8 weeks predicted the magnitude of plaque progression, even after adjustment for baseline plaque burden (p<0.001 for Prosense VM110, p=0.004 for ICG). The histological assessment demonstrated NIRF agent uptake in lipid-rich, inflamed atheroma.
Conclusion: This study demonstrates that multimodality intravascular imaging of molecular biomarkers representing plaque inflammation and permeability independently correlate with future plaque burden. Integrated in vivo NIRF-OCT analysis may offer not only a unique, translatable approach with potential to image high risk pathophysiology in human coronary atherosclerosis over time, but also a platform for rapid drug testing of biological effects of anti-atherosclerotic treatments.

P520 | BEDSIDE
Multimodality imaging based scoring system predicts clinical resolution in recurrent pericarditis

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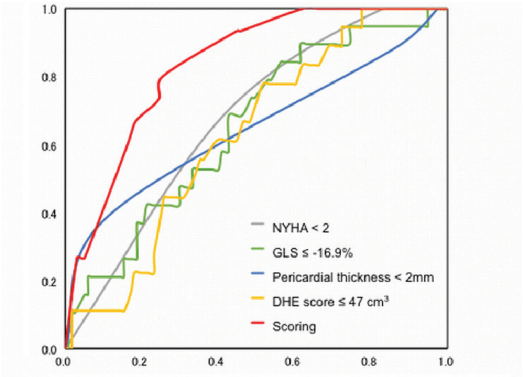
Background: Recently, studies have investigated the use of strain imaging and pericardial delayed hyperenhancement (DHE) on cardiac magnetic resonance imaging (CMR) to predict clinical outcomes in constrictive pericarditis patients. However, there is lack of data on the utility of strain and DHE imaging in patients with recurrent pericarditis (RP).
Purpose: The aim of this study is to develop a multimodality prognostic score and evaluate its performance in predicting clinical outcome in patients with RP.
Methods: This is a retrospective study of 137 RP patients who underwent DHE imaging, echocardiography and had a clinical follow-up for more than six months. Pericardial inflammation was quantified using pericardial DHE sequence on CMR by contouring the pericardium, selecting normal septal myocardium as a reference region, and then quantifying the pericardial signal that was >6 SD above the reference. Pericardial thickness was evaluated on black blood sequence by CMR. Baseline clinical symptoms, laboratory inflammatory markers, and echocardiographic parameters were also collected. Left ventricular global longitudinal strain (GLS), global circumferential strain (GCS), radial strain (RS), and right ventricular longitudinal strain were measured by 2-dimensional speckle tracking echocardiography. Our primary outcome was clinical resolution defined as freedom from off all anti-inflammatory therapy without recurrence and normalizations of ultrasensitive C-reactive protein (us-CRP) and westergen sedimentation (WSR) rate for a period of at least three months at the end of the follow-up period.
Results: During a median follow-up period of 19 months (interquartile range 13 to 27 months), 19 (14%) patients showed clinical resolution. The mean age of our patients was 45±14 years, with 50% females. In logistic regression analysis, NYHA class (Odds ratio [OR] 0.34; 95% confidence interval [CI]: 0.11 to 0.81; p=0.013), GLS (OR 0.81; 95% CI: 0.67 to 0.98; p=0.026), quantitative pericardial DHE score (OR 0.98; 95% CI: 0.96 to 0.99; p=0.032), and pericardial thickness (OR 0.35; 95% CI: 0.13 to 0.88; p=0.023) were identified as predictor of clinical improvement. Based on the 4 predictor variables, prognostic score were created.



	AUC	Sen.	Spec.	PPV	NPV
NYHA <2	0.66	69%	58%	21%	92%
GLS ≤ -16.9%	0.65	89%	38%	19%	96%
DHE ≤ 47 cm^3	0.63	78%	48%	19%	93%
Pericardial thickness <2 mm	0.50	39%	89%	35%	90%
Scoring >2 *	0.83	93%	55%	24%	98%

*Scoring: NYHA <2 =1; GLS ≤ -16.9% =2; DHE ≤ 47 cm^3=1; pericardial thickness < 2mm =1
ROC curve for variables and scoring associated with clinical resolution.

Prognostic: Score was formed by assigning one point each for NYHA class I, Pericardial Thickness <2mm, DHE quantification ≤47 cm^3. Two points were assigned to GLS ≤ - 16.9%. Prognostic score showed improved global Chi-square (p<0.001) and area under the receiver operating characteristic (ROC) curve (Figure). Event rate (clinical resolution) increased as the prognostic score increased in RP patients: 0% for a score of 0/1; 3% for 2; 15% for3; 28% for 4; 57% for 5 (P<0.001).
Conclusions: In RP patients, a new multi-modality imaging based prognostic scoring showed incremental prognostic value in stratifying patients with better outcome.

P521 | BEDSIDE
Multi-modality imaging in cardiac aTTR familial amyloidosis: agreement between echocardiography, MRI and DPD-scintigraphy

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Background: Echocardiography, MRI and diphosphonate (DPD) scintigraphy are the three main imaging techniques to identify cardiac involvement in transthyretin (ATTR) amyloidosis. Each one provides specific diagnostic and prognostic informations, with specific limitations. We sought to evaluate a multimodality imaging strategy in this setting.
Methods: Patients referred for aTTR Familial Amyloidosis underwent multimodality imaging (echocardiography, 1.5T MRI and 99mTc-DPD scintigraphy) for the diagnosis of cardiac amyloidosis. Patients with pacemaker or severe kidney failure had no MRI and were analyzed with echocardiography and DPD scintigraphy (n=17). We defined 3 groups: 1/pts with agreement between all imaging modalities consistent with cardiac amyloidosis (PA-ATTR group); 2/pts with an agreement between imaging modalities consistent with the absence of cardiac amyloidosis (PA-normal); 3/ pts with no agreement between imaging modalities (NA).
Results: Seventy seven consecutive pts were included, mean age was 52 years [44–70] and 59% were males. TTR mutation was Val30Met in 67%, and 12% had acquired aTTR from previous domino liver transplantation; 30 pts had a positive echocardiography, 37 positive MRI and 36 positive DPD scintigraphy. Imaging modalities were in agreement in 50/77 pts (65%: 30 PA-ATTR and 20 PA-normal), whereas they were not in 27/77 pts (NA, 35%). Compared with PA-ATTR patients, NA pts were younger (68 [64–72] years vs. 46 [41–64], had lower BNP levels (149 [94–248] pg/ml vs. 40 [25–102]) and thinner interventricular septum (17 [14–20] mm vs. 12 [10–14]), all p values <0.0001). The two main causes for the absence of agreement were isolated positivity of MRI (n=10) and isolated negativity of DPD scintigraphy (n=6). Compared with PA-ATTR pts, those with isolated MRI positivity were younger (41 [39–44] years vs. 68 [64–72], p<0,001), more frequently women (80% vs. 26%, p=0,002), had thinner interventricular septum (9 [8–11]mm vs. 17 [14–20], p<0,0001), lower BNP levels (26 [24–36] vs. 149 [92–249], p<0,0001) and less diffuse late gadolinium enhancement pattern (10% vs. 66% patients, p<0.0001). Whether these abnormalities are related to early stages of the disease or to false positives will be determined by further follow up. As compared with PA-ATTR pts, those with isolated negativity of DPD scintigraphy had acquired aTTR from domino liver transplantation in all but one case (83% vs. 6% patients; p=0.02).
Conclusions: In aTTR amyloidosis, the agreement between echocardiography, cardiac MRI and DPD scintigraphy in the setting of cardiac amyloidosis diagnosis was observed in 65% of patients. Those without agreement between the three techniques had distinct patterns: isolated positivity of the MRI, which could correspond to early stages of cardiac amyloidosis or be false positives; patients with acquired ATTR amyloidosis due to domino liver transplantation had often false negative DPD scintigraphy.

P522 | BEDSIDE
intravascular ultrasound versus multidetector computed tomography for annular sizing during transcatheter aortic valve replacement

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Background: Multidetector computed tomography (MDCT) is crucial for sizing the aortic annulus and selecting a transcatheter heart valve (THV). Contrast media use with MDCT limits its application in patients with renal failure. IVUS does not require contrast media, but has not been investigated for annular sizing.
Objectives: We compared intravascular ultrasound (IVUS) with (MDCT) for sizing of the aortic annulus and predicting paravalvular aortic regurgitation (PVR) after transcatheter aortic valve replacement (TAVR).
Methods: IVUS of the aortic annulus was performed in 50 patients during TAVR and the annulus location was determined at the level of basal attachments of the

aortic valve cusps. At this level, the aortic annular measurements were compared with those of MDCT.
Results: The aortic annular area and diameters measured by IVUS were not significantly different from those of MDCT (446±87 mm^2 and 23.8±84 mm vs. 466±84 mm^2 and 24±2.1 mm, respectively; P>0.05). Receiver operating characteristic analyses showed that the differences between THV area and annular areas measured by IVUS and MDCT were predictive of ≥ mild PVR (areas under the curve [AUC] 0.79 and 0.81, respectively; P<0.001),

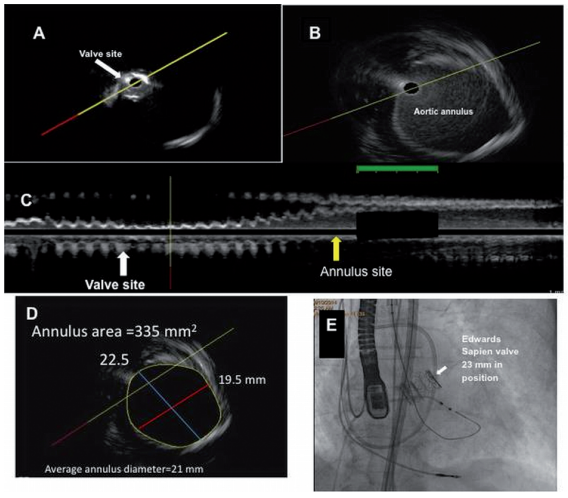

Fig. 1

Aortic valve annulus measurement by IVUS

Conclusions: The aortic annular measurements and the prediction of PVR by IVUS were not significantly different from those of MDCT. IVUS can be utilized in lieu of MDCT for sizing the aortic annulus in patients with renal failure, or in those with suboptimal MDCT images undergoing TAVR.

P523 | BEDSIDE
Multi-modality cardiac imaging provides a practical way for comprehensive differentiation of cardiac tumors: retrospective systemic review of a histopathologically verified case series

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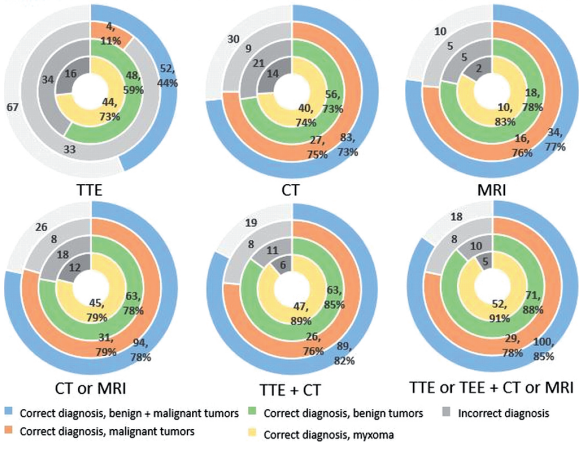
Introduction: We clinicians often meet a series of cardiac tumors occasionally in daily clinical practice. But differential diagnosis is not always straightforward, and sometimes, this clinical conundrum might be challenging and hard to solve even allowing for meticulous imaging evaluation.
Purpose: We examined whether multi-modality imaging work-up was really helpful to differentiate cardiac tumors in histopathologically confirmed cases.
Methods: Regardless of its malignant potential, all pathologic reports of surgically treated or biopsy-proven patients were systematically reviewed. Imaging studies of pathologically confirmed cases were retrieved and rechecked to test the diagnostic power of each imaging modalities such as transthoracic echocardiography (TTE) or transesophageal echocardiography (TEE), computed tomography (ECG-gated CT or not), magnetic resonance imaging (MRI), and positron emission tomography (PET-CT). Pre-procedural imaging findings and their corresponding reports were reassessed to test their predictive ability. Examination reports were considered to be correct only if pathologic reports had been agreed well to their working diagnoses.

Figure. Imaging modalities and their combinations for proper working diagnosis



Results: From January 2007 to July 2015, a total of 124 patients were treated and surgically confirmed for their cardiac tumors in Seoul National University Hospital. TTE was checked for 119 patients and 33 for TEE, 113 for CT and 44 for MRI. 85 patients had benign diseases and 39 patients (31.5%) were diagnosed as malignant cardiac tumors. Presumptive diagnosis before surgery or biopsy procedure was given for 120 patients, and 106 cases (88.3%) had correct answers. Among these patient, 97 cases were solely diagnosed by imaging clues, but previous pathologic reports or treatment history were needed for the remaining 23 patients. Predictive power of mult-modality imaging study was somewhat more obvious in benign tumors, but this difference was not statistically significant (87.7% for benign vs. 78.4% for malignant tumors respectively, χ^2 1.69, p=0.194). Diagnostic power was a bit lower in TTE or TEE imaging than CT or MRI, and more patients were able to be received proper working diagnosis by comprehensive imaging work-up rather than single echocardiographic evaluation (82.4%, 83.3%, 82.9% by TTE + CT, TTE + MRI, TTE + CT + MRI study, respectively). PET-CT was very useful mainly for 24 malignant tumor cases in a total of 26 PET-CT exams.
Conclusion: For cardiac tumors, additional predictive power of multi-modality imaging was useful for more accurate preoperative diagnosis and proper patient management.

P524 | BEDSIDE
Serial changes in coronary atheroma burden and composition in relation to on-treatment plasma levels of proprotein convertase subtilisin/kexin type 9 (PCSK9) following high-intensity statin therapy

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Background: Proprotein convertase subtilisin/kexin type 9 (PCSK9) is a secreted protein implicated in the degradation of the hepatic LDL-receptor. Statins are known to increase plasma PCSK9 levels. While agents that inhibit PCSK9 markedly reduce circulating LDL-cholesterol (LDL-C), the association of plasma PCSK9 levels with changes of coronary plaque burden and composition in patients receiving statin therapy remains unknown.
Objectives: To assess volumetric and compositional changes of coronary atheroma in relation to on-treatment PCSK9 levels in patients with ST-elevation myocardial infarction (STEMI) receiving high-intensity statin therapy.
Methods: In the IBIS-4 study, 82 STEMI patients underwent serial, 2-vessel intravascular ultrasound (IVUS) and radiofrequency (RF)-IVUS of the non-infarct-related arteries at baseline and following 13-month treatment with rosuvastatin 40mg. The present analysis includes 44 patients (80 arteries) with available serial measurements of plasma PCSK9 levels.
Results: The majority of patients (88.6%) were not taking statin at baseline. At 13 months, median LDL-C decreased from 3.27 to 1.99 mmol/L, HDL-C increased from 1.14 to 1.23 mmol/L, and PCSK9 levels increased from 283.1 (235.4 to 362.7) to 388.1 (277.8 to 550.2) ng/ml (p<0.001 vs. baseline for all). Regression of percent atheroma volume (-0.99%, -1.84 to -0.14; p=0.024) did not correlate with baseline (p=0.83) or follow-up levels of PCSK9 (p=0.41). Serial changes of RF-IVUS-defined plaque components consisted of an increase in percent necrotic core volume (p=0.006), increase in dense calcium content (p<0.001) and reduction in percent fibrous (p<0.001) and fibro-fatty tissue content (p=0.04). On-treatment levels of PCSK9 correlated with percent fibrous tissue content (p=0.026) and inversely with necrotic core content at follow-up (p=0.06), but not with serial changes in any of the RF-IVUS tissue components.
Conclusions: In this observations study of STEMI patients treated with high-intensity statin therapy, on-treatment levels of PCSK9 did not correlate with changes in atheroma burden or RF-IVUS-defined plaque composition. Although PCSK9 is an important therapeutic target for reduction of atherogenic lipoprotein concentrations, on-treatment levels of the biomarker do not appear to reflect serial changes in coronary atherosclerosis in statin-treated patients.

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Complex assessment of vulnerability markers associated with neoatherosclerotic plaques in patients with in-stent restenosis using cardiac CT, OCT and VH-IVUS

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Introduction: In-stent restenosis (ISR) is traditionally associated with neointimal hyperplasia. However, the term of "neoatherosclerosis" has been recently introduced to characterize the development of new atheromatous process within the implanted stent. The extent in which this neoatherosclerosis is an unstable condition is not known in present, therefore in this study we aimed to assess the correlations between Cardiac Computed Tomographic Angiography (CCTA) markers associated with unstable plaques, such as a very low CT density of the restenotic tissue, and Optical Coherence Tomography (OCT) or Intravascular ultrasound (IVUS) markers of vulnerability in patients with ISR.
Material and methods: We included 28 patients with 36 coronary bare metal stents, having at least one symptomatic ISR as defined by >50% stenosis inside

the implanted stent identified by both CCTA and coronary angiography, 6 months to 1 year after stent implantation. In total, 30 ISR lesions were screened and analyzed, including qualitative and quantitative analysis of the restenotic tissue by CCTA, OCT and virtual histology IVUS (VH-IVUS). Patients were divided in: group 1 - 21 cases in whom CCTA qualitative analysis identified the presence of dark spots representing areas with very low plaque density inside the restenotic tissue, and group 2 - 9 cases without dark spots inside the restenotic tissue.
Results: OCT analysis identified a significantly lower thickness of the fibrous cap in gr. 1 (35.5 μm vs 94.5 μm, p<0.0001). By OCT, restenotic tissue presented a heterogenous aspect in 80,95% of cases in gr.1 vs 22.22% of cases in gr.2, (p=0.004), an irregular shape in 76.19% vs 33.33% of cases (p=0.04), and a multilayered appearance in 85.71 vs 44.44% (p=0.03) of patients. The presence of microvessels was recorded in 80.95% vs 22.22%, p=0.004. Rupture of the neointima was significantly associated with a lower density plaque (76.19% in gr 1 vs 11,11% in gr 2, p=001). VH-IVUS plaque quantification identified a significantly larger necrotic core in patients with low density neoatheroma (44.5% vs 21.2%, p<0.0001). Multivariate analysis identified the presence of a low density plaque by CCTA (OR 3.2) and a>40% necrotic core (OR=2.4) as the most powerful predictors for plaque rupture.
Conclusions: An area with very low CT density within the restenotic tissue, visualized as a dark spot, is associated with a significantly lower thickness of the fibrous cap and with a higher risk for plaque rupture, thus representing a new potential marker for noninvasive assessment of plaque vulnerability in patients with ISR.

P526 | BEDSIDE
Multimodality imaging in ICD implantation decision making: 123-iodine metaiodobenzylguanidine imaging and cardiac magnetic resonance imaging

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Background: According to guidelines, implantable cardioverter defibrillator (ICD) is recommended in prevention of sudden cardiac death (SCD) in heart failure (HF) patients (pts). Guidelines have several limitations because ICD indication is based mainly on left ventricular ejection fraction (EF). Recently, 123-iodine metaiodobenzylguanidine imaging (123-I MIBG) seems to identify, independently from EF, pts at high risk of SCD (heart/mediastinum (H/M) ratio<1.6 and summed score (SS)>26).
Purpose: Our aim is to assess the role of 123-I MIBG combined with cardiac MRI to predict malignant ventricular arrhythmias (VA) in HF pts.
Methods: We enrolled 69 pts, consecutively admitted to our hospital with diagnosis of HF and EF≤35%, NYHA class II and III, who underwent 123-I MIBG imaging and cardiac MRI. Summed score of 26 was used as cut-off to identify high risk (group 1) versus low risk pts (group 2). Late gadolinium enhancement (LGE) and number of segments with scar were evaluated in the 2 groups. All pts underwent to ICD implantation. We assessed VA events at 18months follow-up.
Results: 21 pts were included in group 1 and 48 pts in group 2. All baseline characteristics were similar in the two groups. The percentage of the pts with LGE was 70.9% in group 1 vs 39.1% in group 2 (p=0.023). At 18 months follow-up VA events in group 1 were 19.05% vs 4.17% in group 2 (p<0.037). Moreover VA events were recorded greater in pts with both SS>26 and LGE compared to pts with only SS>26 (46.7% vs 19.6%, p=0.046).

Table 1. Patients characteristics

	Group 1 SS >26 (n=21)	Group 2 SS ≤26 (n=48)	P value
H/M	1.47±0.24	1.63±0.27	0.015
Hypertension (%)	76.19	66.7	–
Diabetes mellitus (%)	23.81	16.67	–
Ischemic CM (%)	65.02	28.30	0.003
Idiopatic DCM (%)	34.98	68.90	0.003
EF (%)	26.05±5.66	28.79±6.30	–
LGE (%)	70.9	39.1	0.037
Malignant ventricular arrhythmias	4 (19.05%)	2 (4.17%)	0.037

SS, summed score; H/M, heart mediastinum ratio; CM, cardiomyopathy; DCM, dilated cardiomyopathy; EF ejection fraction; LGE, late gadolinium enhancement.

Conclusion: Our results seem to confirm that 123-I MIBG uptake and LGE are associated with the occurrence of life-threatening VA in HF pts independently from EF. The use of integrated imaging could be a useful tool in the future to increase the specificity of the pts selection for ICD therapy.

P527 | BEDSIDE
Agreement analisys of different three-dimensional transoesophageal echocardiographic modalities and cardiac CT scan in aortic annulus sizing for transapical heart valve implantation

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Background: In the selected subgroup of people with severe symptomatic aortic stenosis at high risk or with absolute contraindication for conventional surgery, Transcatheter Aortic Valve Implantation (TAVI) procedure is actually the gold standard. Aortic annulus dimension is critical in the assessment of patients undergoing transapical aortic valve implantation (TA-AVI). Computed Tomography CT scan) is the current reference imaging method for aortic annulus sizing. Utilizing a virtual ring method CT-scan has shown the highest accuracy in determining size of the aortic annulus and in particular its crossi sectional area (CSA).
Purpose: Our aim was to test agreement in CSA values obtained by three-dimensional transesophageal echocardiograpy (3DTEE) and CT-Scan in patients undergoing TAAVI.
Methods: Seventy-three patients (80±5 yo, 38 Females) underwent pre-TAAVI 3DTEE. Annulus size by 3DTEE was determined by 3 methods: direct annular planimetry, virtual ring CSA (assessed at the level of the most basal attachment points of all three aortic cusps joined by a virtual ring) and computation from two axial diameters. Linear regression, variation coefficients (VC) intra-class correlation coefficients (ICC) and concordance correlation coefficients (CCC) were used to test agreement with MDCT measures obtained at level of virtual basal ring.
Results: 3D-TEE derived CSA calculated either by virtual ring or computed methods was lower than that measured at CT (p=0.003 and p=0.04 respectively) whereas negligible difference was obtained by the direct annulus planimetry method (p=0.31). Planimetry also provided the highest agreement with CT according to R2, ICC or CCC. Procedures were uneventful with no significant aortic regurgitation.
Conclusions: Pre- TAAVI CSA assessment using the direct annulus planimetry method by 3DTEE has optimal agreement with CT-Scan, without the well known risks related to the use of contrast.

P528 | BEDSIDE
The impact of hybrid coronary CT angiography and adenosine stress CT perfusion imaging on referral for catheterization and subsequent revascularization in patients with new-onset chest pain

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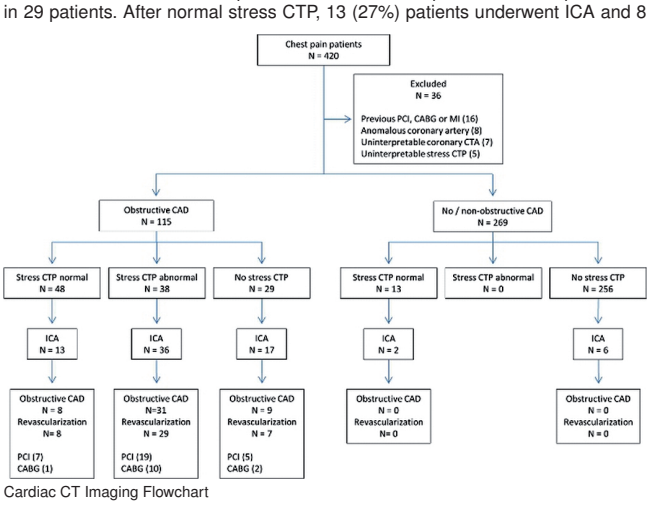
Background: Compared with functional imaging, a diagnostic strategy based on coronary CTA leads to more ICA's and revascularizations, predominantly without knowledge about ischemia or improving prognosis. Stress CTP may serve as an ICA gatekeeper for patients with ≥50% stenosis at coronary CTA.
Purpose: The aim of this study was to assess the impact of a cardiac CT imaging protocol consisting of coronary artery calcium (CAC) score and coronary computed tomography angiography (CTA), added with adenosine stress computed tomography perfusion (CTP) in case of ≥50% stenosis, on the downstream performance of invasive coronary angiography (ICA) and revascularization in patients presenting with new-onset stable chest pain.
Methods: 384 patients with new-onset stable chest pain were enrolled in the cardiac CT imaging protocol. Patients with lesions ≥50% stenosis on coronary CTA underwent subsequently stress CTP. Perfusion scans were considered abnormal if a defect was observed in ≥1 segment. Downstream performance of ICA and revascularization was assessed within 3 months.
Results: In total, 115 patients showed ≥50% stenosis on coronary CTA; the stress CTP was normal in 48 patients, abnormal in 38 patients and not performed in 29 patients. After normal stress CTP, 13 (27%) patients underwent ICA and 8



Cardiac CT Imaging Flowchart

(17%) underwent revascularization. After abnormal stress CTP, 36 (95%) patients underwent catheterization and 29 (76%) revascularizations were performed. No or non-obstructive CAD was observed in 269 patients among whom 8 underwent catheterization; none underwent revascularization. The rate of finding ≥50% stenosis at ICA was 65%.

Conclusions: The cardiac CT imaging protocol consisting of CAC score and coronary CTA, added with stress CTP in case of ≥50% stenosis effectively serves as a gatekeeper to ICA and revascularization for patients with new onset chest pain. In patients with ≥50% stenosis, stress CTP could direct clinical decision making regarding downstream ICA and subsequent revascularization.

Acknowledgement/Funding: Supported by a research grant from the Interuniversity Cardiology Institute of the Netherlands (ICIN, Utrecht, The Nethe

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Low ratio of serum eicosapentaenoic acid to arachidonic acid is associated with intraplaque cholesterol crystals: an optical coherence tomography study

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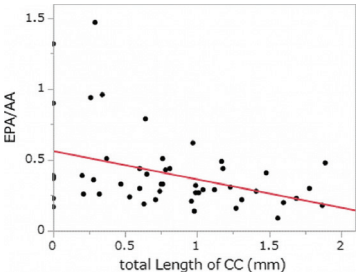
Background: It has been reported that macrophage phagocytosis of cholesterol crystals (CC) contributes to coronary plaque destabilization by stimulating the nucleotide-binding domain and leucine-rich repeat containing protein 3 (NLRP3) inflammasome pathway. Recent studies demonstrated that omega-3 fatty acids inhibit NLRP3 inflammasome activation. Few reports are available on relation between CC located in coronary plaque and serum omega-3 fatty acid (Eicosapentaenoic acid: EPA) levels.

Purpose and methods: We evaluated culprit lesions of 50 patients with stable angina pectoris (age 67±1 y; 14 female) who underwent pre-percutaneous coronary intervention (PCI) optical coherence tomography (OCT) imaging. Exclusion criteria include the following: patient who underwent plain old balloon angioplasty before OCT finding, poor OCT image quality, patient who has no blood test of ratio of serum eicosapentaenoic acid to arachidonic acid (EPA/AA). We counted number of CC, measured max length and total length of CC, and evaluated the correlation between CC and patient characteristics including coronary risk factors, medications, blood test of low density lipoprotein (LDL), high density lipoprotein (HDL), glycated hemoglobin (HbA1c), smoking habits, EPA, and AA.

Results: EPA showed a negative correlation with number of CC (P=0.032, r=–0.303), max length of CC (P=0.033, r=–0.301), total length of CC (P=0.009, r=–0.362). In addition, EPA/AA also have a negative correlation with number of CC (P=0.048, r=–0.281), max length of CC (P=0.014, r=–0.344), total length of CC (Figure, P=0.005, r=–0.385). CC was significantly longer in current smoker group compared to those in non-smoker group (0.37±0.04 vs. 0.54±0.07 mm; P=0.028).



Relationship between EPA/AA and CC

Conclusion: Low serum EPA level and a low EPA/AA was associated with Cholesterol Crystals in the plaque.

P530 | BEDSIDE

Accuracy and inter-changeability in left ventricular quantification by multi-modality imaging: a systematic review and meta-analysis

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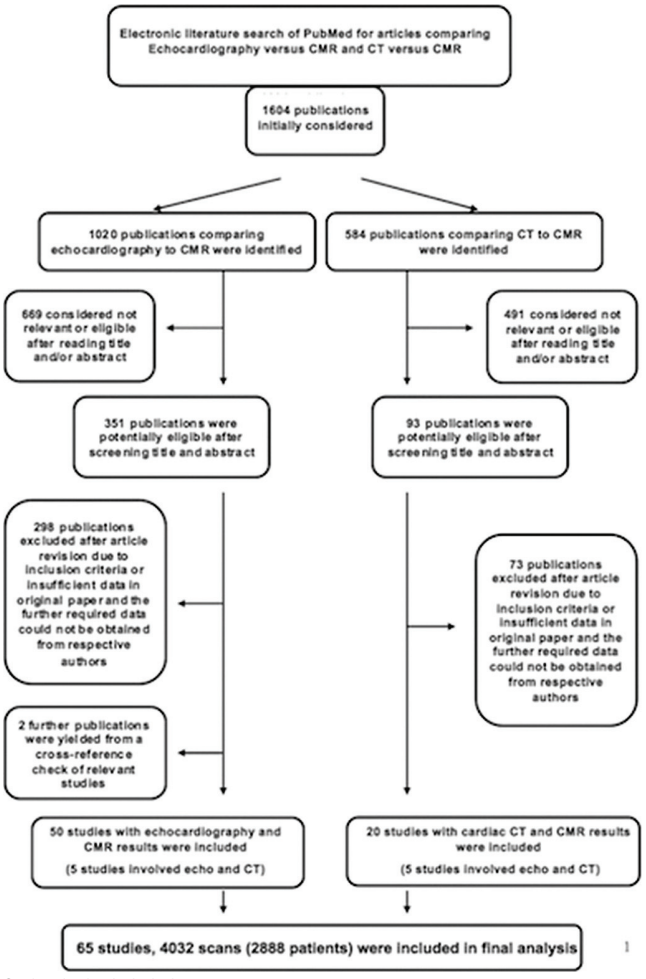
Background: Left ventricular (LV) quantification is crucial for decision-making and patient outcome. Cardiac magnetic resonance (CMR) is the gold standard for ventricular volumetric and functional estimation. Patients during lifetime undergo different tests for evaluation and follow-up. Although two-dimensional echocardiography is still the most adopted, various modalities are available and their inter-changeability remains under-investigated.

Purpose: We undertook a systemic meta-analysis to assess accuracy and absolute bias in LV quantification of all the commonly available non-invasive imaging modalities: non-contrast and contrast two-dimensional echocardiography (2DE, CE-2DE), three-dimensional echocardiography (3DE), and multi-detector computed tomography (MDCT) were compared to CMR.

Methods: Studies published over 20 years were included if reporting LV echocardiographic (2DE, CE-2DE, 3DE), or MDCT measurements compared to CMR. We evaluated LV end-diastolic volume (LVEDV), end-systolic volume (LVESV) and ejection fraction (LVEF). Only modern CMR (SSFP cine sequences) was considered as gold standard. Studies involving small sample size and unusual cardiac geometry were excluded.

Results: 1604 articles were initially considered: 65 were included (total of 4032 scans, 2888 subjects). Compared to CMR, significant biased underestimation of volumes with 2DE was seen (LVEDV –33.30 ml, LVESV –16.20 ml, p<0.0001). This difference was reduced but remained significant with CE-2DE (LVEDV –18.05, p<0.0001) and 3DE (LVEDV –14.41, p<0.001) while MDCT values were



Study selection for inclusion

Abstract P530 – Table 1. Summary of meta-regressione of differences observed by each method. Mean differences compared to cardiac magnetic resonance

Imaging modality	LVEDV (ml) [95% CI]	Overall P value	I2 P value	LVESV (ml) [95% CI]	Overall P value	I2 P value	LVEF (%) [95% CI]	Overall P value	I2 P value
2D-Echocardiography	–33.30	<0.0001	87%	–16.20	<0.0001	73%	–0.78	0.29	72%
Volumes N=1579, LVEF N=1683	[–43.18, –23.44]		p<0.0001	[–21.36, –11.04]		<0.0001	[–2.24, 0.68]		<0.0001
2D-Echocardiography with contrast	–18.05	<0.0001	0%	–7.84	0.02	0%	–1.23	0.27	0%
Volumes N=283, LVEF N=283	[–6.39, –9.7]		p=0.45	[–14.46, –1.22]		p=0.99	[–3.42, 0.95]		p=0.71
3D-Echocardiography	–14.41	<0.0001	28%	–6.62	0.0002	0%	0.14	0.79	0%
Volumes N=1159, LVEF N=1104	[–19.00, –9.81]		p=0.08	[–10.11, –3.13]		p=0.94	[–0.90, 1.19]		p=1
Multi-detector computed tomography	–1.20	0.43	0%	–0.13	0.91	0%	0.89	0.11	0%
Volumes N=790, LVEF N=780	[–4.19, 1.80]		p=0.86	[–2.44, 2.18]		p=0.94	[–0.20, 1.99]		p=0.78

Abbreviations: LVEDV = Left ventricular end-diastolic volume; LVESV = left ventricular end systolic volume, LVEF = left ventricular ejection fraction. Values are mean [95% confidence interval].

similar to CMR (LVEDV –1.20, p=0.43; LVESV –0.13, p=0.91). However, excellent agreement for echocardiographic LVEF evaluation (2DE LVEF 0.78%–1.01%, p=0.37) was observed, especially with 3DE (LVEF 0.14%, p=0.88).
Conclusions: Comparing all the commonly available imaging modalities to CMR as reference standard, 3DE had the highest accuracy in LVEF estimation. 2DE and 3DE-derived LV volumes were significantly underestimated, while CT showed excellent volumetric accuracy.

P531 | BEDSIDE
Can intracoronary pressure measured with a pressure wire predict spasm provocation?

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Background: Spasm provocation testing is an important procedure used to diagnose vasospastic angina (VSA). Spasm provocation tests are sometimes rushed because of unexpected spasm provocations and unstable hemodynamics resulting from prolonged coronary spasms. Thus, it is useful to predict the presence of spasm provocation during spasm provocation tests. This study investigated whether provoked spasms can be detected based on the intracoronary pressures assessed using a pressure wire.
Methods: Spasm provocation tests using a pressure wire were performed on 70 (36 males and 34 females) patients with a mean age of 68 years who were suspected of having VSA. For testing, the pressure wire was optimally placed in the distal portions of the right coronary artery (RCA) and left anterior descending coronary artery (LAD). The pressure ratio of the distal lesion to the proximal lesion (Pd/Pa) was continuously monitored during the test. A spasm was defined as >90% narrowing of the epicardial coronary arteries as observed on angiography during an acetylcholine (ACh)-induced spasm provocation test (low doses: 30 μg for RCA and 50 μg for LAD, high doses: 50 μg for RCA and 100 μg for LAD), accompanied by characteristic chest pain and/or ST-segment deviation on electrocardiography.
Results: Spasm provocation tests were performed in 64 RCA vessels and 70 LAD vessels. The pressure wire was successfully inserted into the distal portion of 55 RCA vessels (86%) and 67 LAD vessels (96%). Among these 122 vessels, a spasm was not induced in 49 vessels (Group N) and was induced in 25 vessels following low ACh doses (Group L) and in 49 vessels after high Ach doses (Group H). The baseline Pd/Pa was the lowest in Group L (0.94±0.01, p<0.05), while Pd/Pa was lower in Group H than Group N (0.96±0.01 vs. 0.98±0.01, respectively, p<0.05). Pd/Pa at low ACh doses was significantly lower in Group H (0.90±0.01) than Group N (0.96±0.01, p<0.001). The receiver-operating characteristic analyses showed that the cut-off delta Pd/Pa as measured from baseline to low ACh doses for spasms provoked by high ACh doses was 0.05 (sensitivity 74%, specificity 79%).
Conclusions: These findings suggest that using pressure wires during spasm provocation tests may effectively detect spasm provocations, especially at high ACh doses.

P532 | BEDSIDE
Fusion multimodality continuity equation for aortic valve area estimation and its impact on aortic stenosis severity reclassification

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Purpose: Measurement of left ventricular outflow tract (LVOT) area using two-dimensional (2D) transthoracic echocardiography (TTE) assumes a round LVOT. In this study we aim to compare measurements of LVOT area by TTE and multidetector computed tomography (MDCT) and assess their impact on the aortic valve area (AVA) estimated by the continuity equation.
Methods: We studied 52 patients (P) with severe aortic stenosis defined by TTE estimated AVA<0.6cm^2/m^2 who underwent evaluation for transcatheter aortic valve implantation (age 81±5 years; 54% female; mean transaortic gradient 49±14 mmHg; left ventricular ejection fraction 59±14%; stroke volume index 39±14 mL/m^2).
According to flow (stroke volume index <35 or ≥35 mL/m^2) and gradient (mean transaortic gradient ≤40 or >40mmHg), we classified patients into 4 groups: G1= normal flow-high gradient (n=24), G2= low flow-high gradient (n=17), G3= normal flow-low gradient (n=6) and G4= low flow-low gradient (n=5).
We estimated LVOT area and TTE-AVA by the continuity equation using conventional 2D TTE parameters. MDCT parameters included maximum systolic LVOT area, ratio of maximum to minimum LVOT diameter (eccentricity index), and aortic planimetry (AVAp).
We then used the LVOT area, measured on MDCT, as part of the continuity equation, to generate a fusion multimodality AVA: (MDCT LVOT area × LVOT VTI) / Aortic valve VTI.
Results: LVOT area measured by MDCT was notably larger than TTE derived LVOT area (4.31±0.99 cm^2 Vs 3.28±0.66 cm^2; p<0,001). Correlation between LVOT areas was moderate (r=0.48, p<0.001). Mean TTE LVOT diameter was 2.04±2.0 cm, which correlated better with MDCT LVOT minimum diameter (1.93±2.7 cm; r=0.52, p<0.001) than with MDCT medium (2.32±2.7 cm; r=0.49, p<0.001) or maximum (2.83±3.3 cm; r=0.47, p<0.001) diameters. LVOT mean eccentricity index was 1.47±0.14. No correlation was found among the eccentricity index and the difference between MDCT LVOT area and TTE LVOT area (p=0.25).
Fusion multimodality AVA was significantly higher than TTE-AVA (0.80±0.24 cm^2 Vs 0.62±0.20 cm^2; p<0,001) with a good correlation between AVAs (r=0.74; p<0.001). Fusion AVA was not different from AVAp (0.85±0.22 cm^2, p=0.18) obtained by MDCT. Using fusion AVA, a total of 9 P (17%) would be reclassified from severe to moderate aortic stenosis [4 P (20%) from G1, 2 P (33%) from G3 and 3 P (60%) from G4]. Applying a correction factor of 1.33 (derived from the mean ratio of MDCT LVOT area/TTE LVOT area) we estimated a corrected TTE-AVA (0.83±0.27 cm^2) which was similar to fusion AVA (p=0.36) and AVAp (p=0.60).
Conclusions: MDCT imaging suggests an eccentric LVOT in most P, leading to an underestimation of LVOT area and AVA on 2D TTE. Incorporating MDCT LVOT area into the continuity equation results in higher AVA values, allowing 17% of P to be reclassified as moderate aortic stenosis. Fusion multimodality AVA, corrected TTE-AVA and MDCT AVAp held similar AVA values.

P533 | BEDSIDE
Correlation between the parameters of myocardium deformation and the results of endomyocardial biopsy in recipients at the stage of subclinical heart transplant rejection

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Background: The acute rejection of a heart transplant is characterized by histological changes such as infiltration of inflammatory cells, edema, haemorrhages, necrosis, which cause the disfunction of contractility and lusitropy (myocardial relaxation).
Purpose: The aim of our research is to carry out the correlation analysis of the noninvasive markers of the heart transplant rejection and the results of the endomyocardial biopsy, as well as drawing the conclusions about early predictors of the transplant rejection.
Materials and method: The heart recipients were examined by means, endomyocardial biopsy, the method of speckle-tracking echocardiography.
In accordance with cellular rejection diagnostics criteria of International Society for Heart and Lung Transplantation Registry (1990 Stanford classification and 2004 Working Formulation ISHLT) and humoral rejection criteria (2004 Working Formulation ISHLT and 2013 review of criteria) we have picked out: group No. 1 (n=150) – the samples of biopsy without signs of cellular and humoral rejection (AMR0 ACR0); group No. 2 (n=65) – the samples of biopsy with the transplant rejection of the first degree; group No. 3 (n=35) – the samples of biopsy with the transplant rejection of the second degree; group No. 4 (n=12) – the samples with the humoral transplant rejection.
Results: While analysing the results by means of the speckle-tracking echocardiography: in group No. 1 the global peak systolic strain (GLPS LV) – (–17,54±3,71%), radial systolic strain (Rad S LV) – (19,68±7,12%), circular systolic strain (CirS LV) – (21,17±6,77%), twisting – (14,4±4,56%); in group No. 2 was marked the reduction of GLPS LV – (–10,52±1,8%); Rad S LV – (25,3±4,7%), CirS LV – (18,5±8,78%), (twist)- (12,58±1,6%) don't have significant anomalies; in group No. 3 decreased GLPS LV – (6,44±1,8%), CirS LV (–16,3±4,9%), twist (7,58±1,6%);
While conducting the correlation analysis between the parameters of deformation and heart mechanics (GLPSLV,%) and the components of biopsy specimen (CD 3,CD 20, CD 68) in groups No. 1, 2, the factor of correlation makes up 0.73, 0.96, 0.01 accordingly; between CD 3, CD 20, CD 68 and the parameter GLPS LV % in groups No. 1, 2 makes up 0.54, 0.86, 0.26 accordingly. The factor 0.3 is the evidence of the presence of correlation, the factor 0.7 and > is the evidence of the good correlation connection.
Conclusion: The results obtained in the process of the analysis show the correlation between the parameters of deformation and histological changes in infiltrate of biopsy specimen in heart transplant recipients. The global peak systolic strain of the left ventricle (GLPSLV) can be regarded as the diagnostic criterion at early stages of rejection.

P534 | BEDSIDE
Cardiac fusion imaging with computed tomography and Doppler echocardiography in the assessment of right ventricular outflow tract obstruction in patients with adult congenital heart disease

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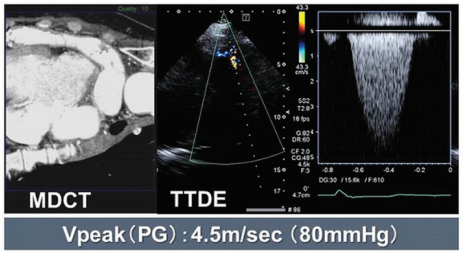
Background: Echocardiographic visualization of right ventricular outflow tract (RVOT) in patients with adult congenital heart disease (ACHD) is sometimes difficult and misleading because of the poor image quality after surgery or with abnormal position of the heart.
Recently, an innovative imaging technique has been developed to display in real time a virtual multi-planar reconstruction obtained from contrast-enhanced multidetector-computed tomography (MDCT) corresponding to the same cross-

sectional image from echocardiography (Smart Fusion, Toshiba). The aim of this study is to assess the usefulness of this fusion imaging in the assessment of RVOT obstruction (RVOTO) / pulmonary stenosis (PS) in a patient with ACHD.
Methods: Smart fusion imaging obtained in 37 patients with ACHD who underwent TTE and MDCT within a week from January 2015 to December 2016, were analyzed in this study. Of those, 6 patients (4 women, 33±12 years, 5; after Rastelli procedure, 1; after RVOT reconstruction) with suspected RVOTO/PS were included in this study. The location of RVOTO/PS, peak pressure gradient was evaluated with/without fusion imaging.
Results: Fusion imaging was safe and feasible in all patients with ACHD. Identification of precise location of RVTO/PS was difficult because of poor image quality in all 6 patients without fusion imaging. This integrated fusion imaging combined with Doppler echocardiography provided precise location of RVOTO/PS in all 6 patients, and also revealed significantly higher RVOT pressure gradient in 2/6 patients (Case 1; peak gradient 52→81 mmHg, Case 4: 81→100 mmHg), resulted in reclassification of RVOTO/PS severity in 1 patient (Case 1; moderate → severe).)

Assessment of RVOTO/PS using Smart Fusion Imaging (SFI); precise location and grade.

Case	Age	Sex	Diagnosis (RVOT)	RVOT peak V Echo only	RVOT peak V SFI+	RVOT peak PG Echo only	RVOT peak PG SFI+
1	40	F	cTGA (after Rastelli)	3.6	4.5	52	81
2	47	M	TGA (after Rastelli)	3.7	3.7	53	54
3	46	F	TGA (after Rastelli)	1.8	1.7	13	12
4	15	F	TOF (after Rastelli)	4.5	5	81	100
5	23	F	PA (after Rastelli)	3.1	3.1	39	39
6	25	M	TOF (after RV reconstruction)	1.7	1.7	12	12

Case 1; 40 y.o. woman, s/p RVOT reconstrcuction (Rastelli)



Assessment of RVOTO/PS using SFI

Conclusion: Combined with Doppler echocardiography, this novel cardiac fusion imaging is clinically useful for the assessment of precise location and severity of RVOTO/PS.

P535 | BEDSIDE
Intima-media thickness in the brachial artery predicts subclinical coronary atherosclerosis determined by MDCT

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Background: Coronary artery calcification (CAC) measured by CT reflects subclinical coronary atherosclerosis and is an excellent maker of future cardiovascular events. Brachial intima-media thickness (IMT) which measured simultaneously with flow-mediated dilatation (FMD), as a vascular endothelium test, is reported to be associated with coronary risk factors. Although carotid intima-media thickness (IMT) was associated with CAC, clinical significance of the brachial IMT remains unclear.
Purpose: To investigate the association of CAVI and subclinical atherosclerosis markers including CAC.
Methods: A total of 346 patients without prior coronary artery disease (mean age 65 years, 57% men) who underwent CT and FMD were analyzed. The measurements of IMT and FMD in the brachial artery were performed with specialized machine (Unex Co. Ltd.). CAC was defined by Agatston score.
Results: Of all, brachial IMT and FMD were 0.33±0.07 mm and 5.5±2.6%, respectively. 246 patients (71%) had CAC (Agatston score>1). FMD was related to brachial IMT (r=-0.259, p<0.001), age (r =-0.353, p<0.001), LDL cholesterol (r=0.155, p=0.012), CAC score (r=-0.107, p=0.046) and estimated glomerular filtration rate (r =0.128, p=0.040). Brachial IMT was related to age (r =0.312, p<0.001), CAC score (r =0.231, p<0.001) and LDL cholesterol (r =-0.193, p=0.002).When patients were divided to three groups according to CAC score; group1=0, group2>0, <100, group3>100, FMD and brachial IMT were increased in a stepwise fashion (trend for p<0.001, p<0.001, respectively).Univariate logistic analysis showed that severe coronary calcification (CAC >100) was significantly associated with IMT (OR=1.06, p=0.01), FMD (OR=0.82, p<0.001), and age>60 (OR=5.82, p<0.001). The ROC curve analysis of IMT for discriminating patients with CAC >100 showed that the sensitivity 89.3% and specificity 39.3% at the cut off value of 0.30mm (AUC: 0.637, p<0.001). Multivariate logistic analysis demonstrated that both increased IMT and lower FMD was significantly associated with CAC>100 (OR=1.752, p=0.026) after adjustment of conventional risk factors.
Conclusion: The measurement of brachial IMT in addition to FMD, less invasive test than CAC measurement, could be of use for the risk assessment of patients at high risk for cardiovascular diseases.

P536 | BEDSIDE
Coronary flow reserve on left anterior and posterior descending artery during stress echocardiography: an addictive prognostic value in patients without wall motion abnormalities

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Introduction: The combined evaluation of wall motion and Coronary Flow Reserve (CFR), particularly on left anterior descending artery (LAD), seems to improve prognostic value of stress echocardiography in patients with known or suspected coronary artery disease (CAD). However, the effective role played by the evaluation of CFR on left posterior descending artery (LPD) is not completely defined.
Purpose: The aim of this study was to determine the prognostic value of combined evaluation of CFR on left anterior and posterior descending artery in patients with normal wall motion on stress echocardiography.
Methods: A total of 674 patients with known or suspected CAD were enrolled from October 2011 to January 2041 at the Cardiology Division of our hospital. They underwent high-dose dipyridamole (0.84 mg/kg in 6 minutes) stress echocardiography with Wall Motion Score Index calculation (WMSI) and CFR evaluation. Follow-up was made through phone contact, with a median follow-up time of 14 months.From the final analysis were excluded: 119 patients not traceable at follow-up; 76 who underwent myocardial revascularization for a wall motion abnormality; 95 because the evaluation of CFR was possible only on a single vessel. We then evaluated 384 patients (266 men, mean age 62±11), in whom we could determine CFR both on LAD and LPD and with a normal WMSI.Primary endpoints were death for cardiovascular events, acute coronary syndromes, onset of angina or a new demonstration of inducible ischemia during follow-up.
Results: Patients were divided into 3 groups according to CFR: normal (CFR ≥2.5), borderline (CFR 2.0–2.5) and pathological (CFR ≤2.0).We first evaluated CFR on LAD: the prevalence of primary endpoints was higher in pathological (16 of 77 patients, 20.7%) than in borderline (7/76, 9.2%) and normal group (15/161, 9.3%) (p=0.03).The same analysis was made for CFR on LPD: a single event occurred in 45 patients in the normal (2.2%), 7/61 in the borderline (11.4%) and 11/39 in the pathological group (28.2%) (p=0.002).To better define the prognostic value of CFR on LPD, we divided patients with normal CFR on LAD in 3 subgroups: there were only 2 adverse events in 130 patients (1.5%) with normal CFR on both vessels, 7 events in 49 patients (14.2%) with borderline and 4 events in 13 patients (30.7%) with pathological CFR on LPD (p<0.001 for both these subgroups compared to the normal one).
Conclusions: CFR on LPD is a further significant prognostic factor in patients with normal WMSI on stress echocardiography: those with a pathological and also with a borderline value have a higher incidence of cardiac adverse events compared to those with a normal CFR.Therefore, the evaluation of LPD combined to LAD needs to be carefully assessed during stress echocardiography, in order to determine a better prognostic stratification and to find patients who need a closer follow-up and a stricter control of cardiovascular risk factors.

P537 | BEDSIDE
Prognostic value of high proximal left coronary artery flow velocity detected by transthoracic Doppler echocardiography in patients with angina pectoris

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Background: Evaluation of lesions in the proximal left coronary artery (pLCA) is valuable in determining disease prognosis. Transthoracic Doppler echocardiography (TTDE) may be used to detect coronary flow velocity (CFV) of pLCA (Figure A), the result of which is associated with the severity of the pLCA lesion. We hypothesized that high CFV at pLCA would be associated with poor prognosis. The aim of this study was to investigate the prognostic value of CFV at pLCA in patients with angina pectoris.
Methods: We prospectively enrolled consecutive 108 patients with high CFV and scheduled intervention for pLCA within one month after TTDE (group 1). For comparison, 108 age- and sex-matched patients with high CFV without scheduled intervention (group 2) and 108 control patients with low CFV (group 3) were included. CFV at pLCA was measured using the pulsed Doppler method. High CFV was defined as averaged diastolic peak velocity of ≥48cm/s (a previously validated external cut-off) and low CFV as averaged diastolic peak velocity of ≤20cm/s. A Framingham risk score was calculated for all patients. The primary outcome of interest was cardiac death, and patients were followed-up over 4.4 years. Cox multivariable regression analysis was used to assess the association with the primary outcome. Net reclassification improvement (NRI) was used to assess the incremental benefit of disregarding high CFV (group 2) to the Framingham risk score for predicting outcome.
Results: In total, 21 cardiac deaths were observed. Framingham risk score and disregarding high CFV were significantly associated with the primary outcome. The Kaplan–Meier curves showed a significantly higher incidence of the primary

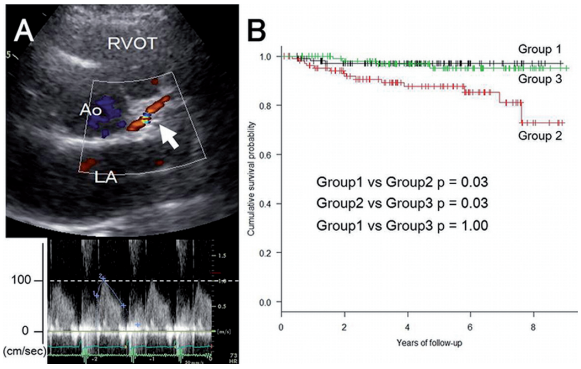

Figure 1

outcome in group 2 than in the other groups (group 1: 3%, group 2: 13% and group 3: 4%; p<0.01) (Figure B). Disregarding high CFV was independently associated with the primary outcome after adjustment of the Framingham risk score [Hazard ratio = 3.72 (95% confidence interval: 1.49–9.29), p<0.01]. Furthermore, addition of disregarding high CFV to the Framingham risk score led to a significant reclassification improvement (continuous NRI = 0.71, p<0.01).
Conclusion: Disregarding high CFV at pLCA is associated with poor outcome in patients with angina pectoris, independent of and incremental to clinical risk score. This association may be modified by appropriate intervention.

P538 | BEDSIDE
Intra-renal ultrasonographic blood flow parameters as early diagnostic predictors of contrast-induced acute kidney injury following coronary angiography

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Purpose: The aim of the study was to evaluate clinical utility of ultrasonographic indices of intra-renal blood flow as early diagnostic predictors of contrast-induced acute kidney injury (CI-AKI) following coronary angiography/percutaneous coronary interventions (CA/PCI).
Methods: This prospective observational study covered 95 consecutive patients (69.5% men; median age 65 (59; 71)) with either stable angina (43.2%), or non-ST-elevation acute coronary syndrome (56.8%) who underwent coronary angiography (44.2% referred for direct PCI and 14.7% for elective surgical revascularization). Ultrasonographic parameters of renal blood flow in arcuate/interlobular arteries, including peak systolic (PSV) and end-diastolic velocity (EDV), augmentation index (AI), acceleration time (AT), renal resistive index (RRI) and pulsatility index (RPI), were acquired directly before and 1 hour after the procedure. The absolute difference between post- and pre-procedural values was calculated (Δ). CI-AKI was defined as ≥50% relative or ≥0.3 mg/dl absolute increase of serum creatinine concentration at 48 hours after procedure.
Results: CI-AKI occurred in 9 patients (9.5%). CI-AKI occurrence was linked to significantly higher pre- (0.69 vs. 0.62, p=0.005) and post-procedural RRI (0.76 vs. 0.67, p=0.003) and greater pre- (1.54 vs. 1.36, p=0.017) and post-procedural RPI levels (1.72 vs. 1.45, p=0.0002), as well as post-procedural AT (107.0 vs. 77.8 ms, p=0.019), but lower post-procedural EDV (0.11 vs. 0.15 m/s, p=0.006). Although ΔRRI and ΔRPI did not differ between groups, patients with CI-AKI had greater ΔAT (43.5 vs. 17.8 ms, p=0.016) and more negative ΔAI (–0.99 vs. –0.56 $m/s^2$2; p=0.025) than other study participants. Logistic regression analysis revealed that renal resistive index at 1 hour (OR=1.49 per 0.01; p=0.005) belonged to independent predictors of CI-AKI development (AUC=0.96, p<0.0001). Receiver operating characteristic (ROC; Figure 1) curve analysis revealed that post-procedural RRI >0.73 (sensitivity- 88.9, specificity- 83.7%; AUC=0.88, p<0.0001) and RPI value >1.68 (sensitivity- 77.8%, specificity- 88.4%; AUC=0.86, p<0.001) accurately predicted CI-AKI onset.

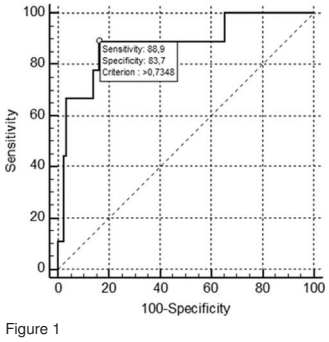

Figure 1

Conclusions: High RRI and RPI values may serve as early indicators of CI-AKI development. Intra-renal blood flow characteristics are altered in the direct period preceding CI-AKI.
Acknowledgement/Funding: Conflict of interest: Grant for scientific research in the field of cardio-nephrology funded by Polish Cardiac Society

P539 | BEDSIDE
Assessment of post-systolic shortening and early systolic lengthening in addition to peak systolic strain can improve diagnostic accuracy of non-stress echocardiography in single-vessel LAD stenosis

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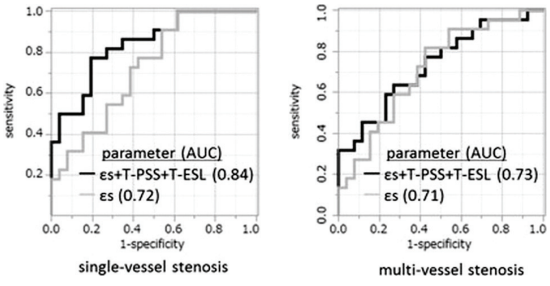
Background: Post-systolic shortening (PSS) and early systolic lengthening (ESL) are subtle myocardial deformation observed in the myocardium with contractile dysfunction. There have been few reports that show the usefulness of the assessment of such deformation in addition to the conventional contractile parameter for diagnosing coronary artery disease (CAD) by non-stress echocardiography.
Purpose: We sought to determine whether the assessment of PSS and ESL in addition to peak systolic strain could improve diagnostic accuracy of non-stress echocardiography in patients with left anterior descending artery (LAD) stenosis.
Methods: Patients with clinically suspected CAD but without visual wall motion abnormalities by echocardiography at rest were enrolled in this study and 44 patients with significant LAD stenosis (>50%) by quantitative coronary angiography (single-vessel stenosis, n=22; multi-vessel stenosis, n=22) and 26 patients without significant stenosis of any vessel were analyzed. Non-stress speckle tracking echocardiography (GE Vivid E9) was performed before angiography and the absolute value of longitudinal peak systolic strain (εs), time to PSS (T-PSS, time from aortic valve closure to peak PSS) and time to ESL (T-ESL, time from onset of the R wave to peak ESL) were measured in 11 segments perfused by the LAD. Diagnostic accuracy for each parameter and the combination were calculated as the area under curve (AUC) of the ROC curve analysis.
Results: In patients with single-vessel LAD stenosis, εs was significantly lower, and T-PSS and T-ESL were significantly longer compared to patients without stenosis in the apical anterior segment (εs: 17.0±6.7 vs. 22.3±6.6%, p<0.05; T-PSS: 57.8±70.0 vs. 10.8±54.9 ms, p<0.05; T-ESL: 27.9±26.1 vs. 8.0±16.7 ms, p<0.05). The AUCs of εs, T-PSS, and T-ESL for detecting stenosis were 0.72, 0.71, and 0.73, respectively; however, that of the combination of each parameter tended to be improved up to 0.84 (Figure). In contrast, T-PSS in patients with multi-vessel stenosis was significantly longer compared without stenosis but T-ESL did not change significantly and the combination did not improve diagnostic accuracy (Figure).



Conclusion: The assessment of PSS and ESL in addition to peak systolic strain could improve diagnostic accuracy of non-stress echocardiography in patients with single-vessel LAD stenosis.

P540 | BEDSIDE
Is TEE needed before hospital discharge after Bentall surgery. A monocentric study on 198 consecutive patients from 2010 to 2014

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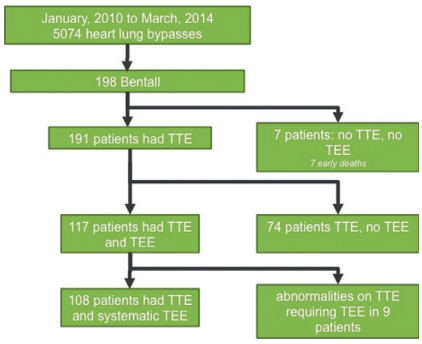
Background: Whether transoesophagial echocardiography (TEE) should be systematically performed (without clinical indication beyond reference imaging) prior to hospital discharge after Bentall surgery remains unclear.
Purpose: We took advantage of this practice in our institution to evaluate its benefit.
Methods: All the patients who had undergone Bentall procedure in our hospital from January, 2010 till March, 2014 were inclued. For each patient, we collected from the various reports the transthoracic echocardiography (TTE) and TEE data and the clinical events.
Results: One hundred ninety eight patients had undergone Bentall procedure

during this period. Post-operative TEE was performed in 117 patients (59.1%) including 9 abnormalities observed on TTE (a vibrating element on the new prosthetic valve, suspicion of peritubular complication in 2 patients, aortic regurgitation in 6 patients). In 108 patients TEE was systematic, i.e. performed without clinical indication beyond reference imaging (including no questioning on TTE). Patients with and patients without systematic TEE were identical, except more frequent endocarditis as an indication for surgery in patients with systematic TEE.
Systematic TEE did not reveal any finding that prior TTE had not shown. The most frequent findings on TTE or TEE were images of peri-aortic hematoma which sometimes led to performing a CT-scanner. This imaging did not change the care of the patients in our population.



Flow chart

Conclusions: Our study does not support performance of TEE after Bentall surgery during in hospital course in the absence of a specific indication. A reference imaging using TEE of preferably a CT-scanner should probably preferably be proposed remotely of the early postoperative period after cicatrisation.
Acknowledgement/Funding: Fédération Française de Cardiologie

ECHO-DOPPLER, OTHER

P541 | BEDSIDE
Prediction of outcome in patients with chronic ischemic cardiomyopathy

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Background: Cardiac magnetic resonance imaging (CMR) has been established as a powerful predictive tool of mortality. However, application is limited by availability and various contraindications. This study evaluated the predictive value of layer specific myocardial deformation analysis as assessed by strain echocardiography for cardiac events in patients with chronic ischemic left ventricular dysfunction in comparison to CMR.
Methods: 390 patients (mean age 63±4 years, 69% male, left ventricular ejection fraction (LVEF) 41±7%) with chronic ischemic cardiomyopathy were prospectively enrolled and underwent strain echocardiography and CMR within 3±1 days. LVEF, wall motion score index and circumferential (CS), longitudinal (LS) and radial strain (RS) for total wall thickness and for three myocardial layers (endocardial, mid-myocardial and epicardial) were determined by echocardiography. The extent of total myocardial scar (TMS) was determined by CMR. Follow-up was obtained for a mean of 4.9±2.2 years. Cardiac events were defined as readmission for worsening of heart failure, ventricular arrhythmias or death by any cause. The incremental value of LVEF, strain parameters and TMS to relevant clinical variables was determined in nested Cox models.
Results: There were 133 (34%) cardiac events. Baseline clinical data associated with outcome were age (hazard ratio (HR) 1.27, p=0.04), diabetes mellitus (HR 1.52, p=0.001) and renal insufficiency (HR 1.77, p=0.001) by multivariate analysis. The addition of LVEF, global and endocardial strain parameters and TMS increased the predictive power, but endocardial CS (HR 1.52, $p<0.01$) caused the greatest increment in model power (χ^2=39.2, $p<0.001$). An endocardial CS <-20% was found to be the optimal predictor of prognosis.
Conclusions: Endocardial CS is a powerful predictor of cardiac events and appears to be a better parameter than LVEF, TMS by CMR or other strain variables by echocardiography.

P542 | BEDSIDE
Left atrial global longitudinal strain is useful for predicting pulmonary capillary wedge pressure in patients with heart disease

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Background: Predicting pulmonary capillary wedge pressure (PCWP) accurately in patients with heart disease remains a challenge. We hypothesized that left atrial global longitudinal strain (LAS) might provide useful information for accurately predicting PCWP in patients with heart disease.
Purpose/Methods: In order to clarify the utility of LAS for predicting PCWP, we studied 67 patients with heart disease who exhibited a sinus rhythm (mean age: 69±12 years) using transthoracic Doppler echocardiography (Echo). Thirty-seven patients had ischemic heart disease, 10 had valvular heart disease, and 17 had cardiomyopathy. The patients were divided into 2 groups; i.e., into those with preserved left ventricular ejection fractions (LVEF) (≥50%) (PEF, n=33) and those with reduced LVEF (<50%) (REF, n=34). PCWP was examined in the cardiac catheterization laboratory within 24 hours of the Echo examination. LAS was studied using speckle-tracking Echo in the apical 4-chamber view, and the maximum LAS during ventricular end-systole (Max LAS) and the LAS during late diastole (Late LAS) were obtained. As for Echo variables, mitral inflow velocity and mitral annular velocity in early diastole (E and E', respectively) and late diastole (A and A', respectively), and left atrial volume and left ventricular volume in end-systole (LAESV and LVESV, respectively) and end-diastole (LAEDV and LVEDV, respectively) were obtained. Then, LVEF, E/A, E/E', E/Max LAS, and E/Late LAS were calculated.
Results: Several variables were significantly correlated with PCWP although there were some differences between the PEF and REF groups. E/A, E/Max LAS, and E/Late LAS exhibited significant positive correlations with PCWP in both groups. The correlation coefficients for these relationships were larger in the REF group than in the PEF group. A significant correlation was observed between E/E' and PCWP in the REF group; however, no such correlation was seen in the PEF group. In a stepwise multivariate regression analysis, E/Late-LAS and E/Max LAS were selected as predictors of PCWP in the PEF and REF groups, respectively. In the PEF group, E/Late-LAS displayed sensitivity and specificity values of 86% and 77%, respectively, for predicting a PCWP of ≥15 mmHg, whereas in the REF group E/Max LAS demonstrated equivalent values of 75% and 100%, respectively.

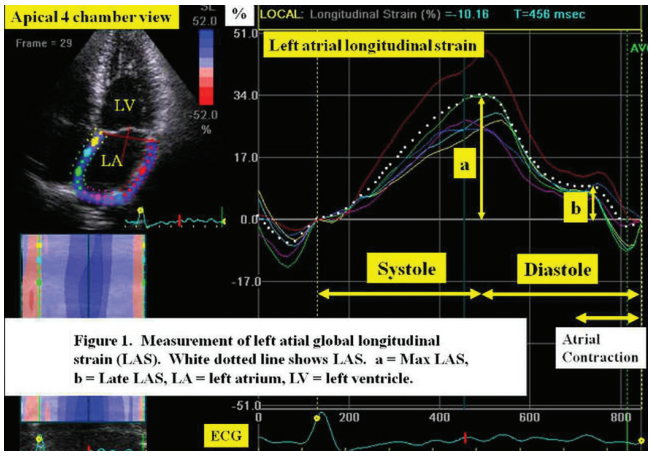

Figure 1. Measurement of left atial global longitudinal strain (LAS). White dotted line shows LAS. a = Max LAS, b = Late LAS, LA = left atrium, LV = left ventricle.

Conclusions: Diastolic left atrial and left ventricular hemodynamics might differ between patients with PEF and REF. LAS appears to provide useful information for predicting PCWP although the optimal predictive variable differs between patients with PEF and REF.

P543 | BEDSIDE
Prediction of left ventricular contractile recovery at rest using tissue Doppler strain and strain rate measurements in patients undergoing percutaneous coronary intervention

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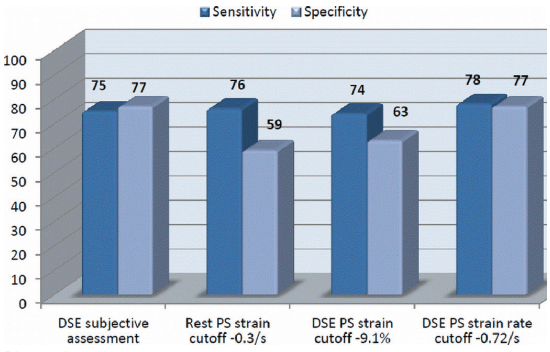
Coronary artery disease is the most common cause of left ventricular dysfunction. The most critical therapeutic option in patients with acute coronary syndrome and ischemic cardiomyopathy remains to be revascularization. In appropriate patients, it may lead to symptomatic, mechanical and prognostic improvement. The objective of viability testing is to predict those who may benefit from revascularization. Dobutamine stress echocardiography (DSE) provides a reasonable insight into myocardial viability with important limitations regarding the qualitative and subjective nature of the test. The addition of deformation analysis have been proposed to provide further quantitative measures. However, the role of deformation analysis at rest in the prediction of contractile recovery is not clear. The aim of the study was to assess the ability of tissue Doppler (TD) deformation analysis at rest to predict left ventricular contractile recovery in patients undergoing percutaneous coronary intervention (PCI).
Subjects and methods: A prospective cohort enrolling 67 ischemic heart disease patients with segmental wall motion abnormality who had successful PCI. Patients were subjected to baseline assessment with resting echocardiography and deformation analysis by TD, Assessment of each segment of the 16 segment

model was performed using a 4 point scoring system, peak systolic strain (PSS) and peak systolic strain rate (PSSR). Low dose DSE subjective wall motion scoring as well as TD PSS and PSSR were assessed in each segment. The study followed up the uneventful patients after 6 months of successful PCI by echocardiography. Segments were divided into two groups: Contractile recovery and no contractile recovery segments, comparisons between groups were done with independent t-test, predictors were tested with logistic regression analysis and ROC curves were formulated.

Results: Of the 319 dysfunctional segment, 155 (49%) showed contractile recovery and 164 (51%) did not. PSS and PSSR at rest were significantly higher in recovered segments compared to segments without recovery (PSS: -7.27±79 Vs. - 6.14±67%, PSSR: - 0.34±0.13 Vs. - 0.24±0.1 /s. p<0.0001 both). By multivariate regression analysis, resting PSSR as well as PSS and PSSR during DSE were significant independent predictors of contractile recovery (p<0.001 each). For predicting segmental contractile recovery, resting PSSR with a -0.31/s cutoff point had 76% sensitivity and 59% specificity (Area Under Curve (AUC): 0.74). DSE subjective wall motion scoring had sensitivity of 75% and specificity of 77%, DSE PSS with a cutoff point of -9.1% had 74% sensitivity and 63% specificity (AUC: 0.77) and DSE PSSR with a cutoff point -0.72/s had 78% sensitivity and 77% specificity (AUC: 0.8).



Diagnostic performance

Conclusion: Resting PSSR is a modest predictor of segmental contractile recovery after PCI while PSSR during DSE has a comparable diagnostic performance to subjective wall motion scoring.

P544 | BEDSIDE
Different transthoracic Doppler signs for successful evaluation of stenotic main coronary arteries

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Background: Qualitative or semi-quantitative evaluation of stenotic main coronary arteries (MCA) by contrast transthoracic echocardiography (TTE) has been reported.

Aim: To detect the potential of different qualitative, semi-quantitative and quantitative TTE signs for successful evaluation of stenotic MCA.

Methods: 173 patients (52±10 years; 149 men) with chest pain and scheduled quantitative coronary angiography (CAG) were evaluated at rest by non-contrast TTE (Vivid 7 GE Healthcare). The left main coronary artery (LMCA), proximal (p), mid (m) and distal (d) parts of the left anterior descending artery (LAD), the circumflex artery (Cx) and the right coronary artery (RCA) were examined. The Doppler signs of coronary stenosis >50% were determined as follows: (1) local Doppler aliasing with the Nyquist limit set at 60 cm/s; (2) maximal peak diastolic velocity (Vpd) >60 cm/s; (3) ratio of "stenotic/prestenotic Vpd" >2.0; (4) stenosis >50% according to flow continuous equation: stenosis, % = 100 × (1 – prestenotic/stenotic VTId), where VTId - diastolic time velocity integral. CAG was performed within 1 week after TTE. Stenosis >50% of diameter reduction was considered as significant.

Results: Good Doppler recording of coronary flow velocity pattern was acceptable for LMCA in 75% of cases, pLAD in 84%, mLAD in 84%, dLAD in 93%, pCx in 35%, mCx in 9%, dCx in 28%, pRCA in 20%, mRCA in 35%, dRCA in 90%. Sensitivity (Sens), specificity (Sp) and diagnostic accuracy (Ac) of different Doppler signs for detecting stenosis >50% are presented in Table 1.

Table 1. Doppler stenotic signs

Doppler signs, number	Assessed segments, %	Sens, %	Sp, %	Ac, %
All MCA (n=1730)				
(1)	56	45	94	87
(2)	55	52	94	88
(3)	50	70*	96	93
(4)	50	77*	97	95
LMCA + LAD (n=692)				
(1)	84	53	94	88
(3)	78	75*	97	94
(4)	78	80*	98	95

Note: *p<0.01 vs (1) and (2) for all MCA and vs (1) for LMCA + LAD.

Thus, TTE is a method for correct evaluation of stenotic LMCA and LAD. Quantitative ratio of stenotic to prestenotic coronary flow velocities is a more sensitive sign for detecting stenosis >50%, than qualitative and semi-quantitative evaluation of maximal coronary flow velocity only.

P545 | BEDSIDE
A new equation for deriving right atrial pressure from right atrial volume in patients with pulmonary arterial hypertension

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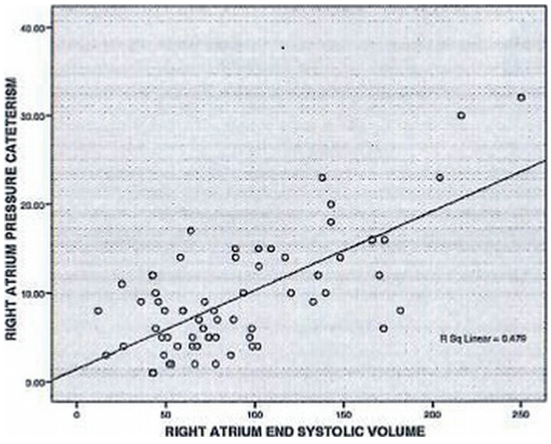
Introduction: Current guidelines recommend that right atrial (RA) pressure is derived from dimensions of inferior vena cava (IVC) and its collapsibility. We have previously demonstrated a pilot association between RA volume and RA pressure (RAP), which was stronger than the association between IVC dimension and RAP but its validity in a larger cohort of patients with pulmonary arterial hypertension remains unknown.

Purpose: We hypothesized that maximum RA end-systolic volume (RAV) is correlated with RAP better than measurements of IVC.

Methods: The current study is a joint collaboration between 2 pulmonary hypertension centers in Bucharest and Thessaloniki. Sixty-seven consecutive patients with pulmonary arterial hypertension were included. All patients underwent echocardiography with measurement of RA volume (aria-length method and disk summation technique in apical 4-chamber view) and IVC dimensions and its respiratory variations divided into three categories, according to current guidelines recommendations: <21 mm with inspiratory collapse, <21 mm without collapse, >21 mm. All patients underwent right heart catheterization with measurement of RAP. Patients with other possible causes of RA enlargement were excluded from the study.

Results: The study population consisted of 67 consecutive patients with pulmonary arterial hypertension, 67.2% females and 32.8% males. Mean RAV was 99.8 mL (range: 12mL-279 mL), while mean RAP was 9.6 mm Hg (range: 1mmHg-32mmHg). Bivariate correlation analysis revealed a strong association between RAV and RAP (r=0.677, p<0.0001) which was stronger than the association between IVC dimension and RAP (r=0.359, p=0.051).

Regression analysis confirmed RAV as a predictor of RAP and the equation for estimating RAP by RA volume is: RAP = 0.089 × RAV + 1.415 (R=0.479).



Conclusion: Our study confirms a superior correlation between RAV measured by echocardiography and RAP measured by right heart catheterization compared with IVC size and respiratory variation. A mathematic formula for estimating RAP may be derived from measuring RAV.

Acknowledgement/Funding: This work was supported by CREDO Project - ID: 49182, financed through the SOP IEC -A2-0.2.2.1-2013-1 cofinanced by the ERDF.

P546 | BEDSIDE
Can 3D echocardiography challenge magnetic resonance imaging in the assessment of right ventricular size and function?

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Background: Magnetic resonance imaging (MRI) is considered as the gold standard for RV size and function assessment but 3D echocardiography could challenge MRI in this field.

Purpose: To compare RV volumes and ejection fraction as calculated from 3D echocardiographic acquisitions by two different new methods with MRI measurements.

Methods: 48 pts (22 PAH, 13 cardiomyopathies, 13 myocardial infarction) underwent both echocardiography including a 3D multicycle acquisition centered on the RV (GE vivid 7 and 9) and MRI in a mean delay of 0.9±1.3 days. Echocardiographic RV EDV and RV ESV (ml) and EF (%) were derived from 1) 3D speckle imaging (3DSI) analysis using an automated tool for the LV adapted to the RV by unselecting segments corresponding to the RV outflow tract, and 2) from volumetric analysis using the newly developed TOMTEC specific tool (TOM). All measurements were made by two different physicians and twice by the same physician. Pearson's correlation coefficients were calculated. Agreement was evaluated using Bland–Altman method. Intra class correlation coefficients (ICC) were calculated for inter- and intra-observer variability.
Results: 3DSI-EDV (65.4±25.8) and TOM-EDV (54.9±19.1) correlated significantly with MRI EDV (89.7±33.1) (respectively r=0.741, p<0.001 and r=0.554, p<0.001). 3DSI-ESV (33.9±20.5) and TOM-ESV (31.8±16.3) correlated significantly with MRI ESV (50.1±35.2) (respectively r=0.873, p<0.001 and r=0.727, p<0.001). Bland-Altman analysis revealed small underestimation of echo-derived volumes as compared to MRI.
3DSI-RVEF (51.2±12.5) and TOM-RVEF (44.1±11.9) correlated significantly with MRI RVEF (48.9±16.1) (respectively r=0.897. p<0.001 and r=0.909. p<0.001). Bland Altman analysis revealed a small but significant underestimation of TOM-RV EF (difference -3.16±7.0, p=0.003) and a good agreement for 3DSI-RVEF (difference 0.13±7.4, ns) as compared to MRI.
All interobserver and intraobserver ICC were between 0.8 and 0.95.
Conclusion: Overall, RV volumes and EF measured either by 3DSI or by TOM correlate well with MRI measurements. Furthermore, their accessibility and good reproducibility makes them potentially very useful in the follow-up of pts. Together with estimated pulmonary pressures and resistance, these echocardiographic parameters of RV size and function could provide interesting insights in the echocardiographic assessment of the cardiopulmonary unit.

COMPUTER MODELLING AND SIMULATION / BIG DATA

P547 | BENCH
Experimental testing of AF septal pacing modeling results

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Introduction: Moving to clinical validation is an essential phase with every model-based result. However, this translation is often not straightforward because animal models differ from human computer models in many anatomic and electrophysiologic ways, while testing on human subjects in clinical studies is often limited by cost and ethical factors. The present study investigated the translation from computer modeling to experimental testing of an atrial fibrillation (AF) termination algorithm based on rapid septal pacing.
Methods: Using a biophysical model of AF based on CT scans from AF patients and atrial membrane kinetics, an algorithm for AF termination was developed: rapid pacing from a ring of electrodes around the septum at 62–70% AF cycle length (AFCL) for 10–30s, followed by stepwise transition to slow pacing at 180% AFCL. This algorithm showed promising results (up to 29% AF termination) in computer simulations. Animal experiments on swine hearts were performed in vitro at the Visible Heart Laboratory and during in vivo acute experiments. Three septal electrode rings were tested using a transseptal approach: Pulmonary Vein Ablation Catheter, Multi-Array Septal Catheter and a decapolar lasso catheter. Rapid stimulation was applied simultaneously to 4 electrodes on the ring (Grass S48 Stimulator, FHC Pulsar 6b Pulse Generator). After AF induction using drugs, the extent of AF capture induced by septal pacing was assessed via decapolar mapping catheters in the right and left (coronary sinus) atria.
Results: In vitro tests validated the electrode-stimulation system and showed that the lasso catheter was the best electrode ring to implement AF septal pacing. Pacing thresholds were 0.6–1.2V and 1.4–2.3 mA in vivo. The impact of septal pacing on AF was harder to study experimentally due to the limited view provided by the mapping catheters compared to computer simulations. Nevertheless, local AF capture could be observed when pacing from the lasso catheter.
Conclusion: The results from animal experiments are promising and will serve as a basis for a clinical study on patients undergoing ablation of persistent AF. AF septal pacing could represent an alternative to drugs and catheter-based ablation for some AF patients.
Acknowledgement/Funding: This study was supported by Medtronic and the TRM Foundation.

P548 | BEDSIDE
Towards a more accurate planning of invasive procedures: finite element simulation of percutaneous pulmonary valve implantation

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Introduction: Percutaneous Pulmonary Valve Implantation (PPVI) is a minimally invasive procedure to treat severe right ventricular outflow tract dysfunction in selected patients. Such innovative procedure represents an optimal field for conducting investigations through patient-specific finite element (FE) simulations to predict stent behavior during the intervention and unravel problems of cardiovascular mechanics. Here we present a virtual cardiac laboratory we recently created to plan interventional procedures.
Methods: Based on CT images, performed in a selected cohort of patients with complex congenital heart disease, the cardiac anatomy was segmented using the a software and subsequently extracted, obtaining an STL-file that in some cases was printed as a 3D plaster model. Also, geometrical models were used to reproduce structural patient-specific PPVI simulations exploiting FE methods: the real FE model of the stent was replicated, discretized into hexahedral elements, and complemented by the description of its mechanical properties [Bosi et al. 2015]; the mesh of the pulmonary trunk was refined and reliable mechanical properties adopted. All simulations were run on a commercial solver.
Results: Models of a cohort of patients with right ventricular outflow tract dysfunction candidated to PPVI were created. Data were sheared with our team of engineers to set up a computer simulation of PPVI release and implantation. We simulated both stent crimping and deployment through balloon inflation. The developed procedure enabled us to simulate the virtual implantation of prosthetic valve selected for each patient-specific right ventricle outflow tract (figure 1a); hence, it allows to assess the impact of stent deployment on the pulmonary trunk wall (figure 1b and 1c) as well as to predict possible distortion of the cardiac anatomy and identify local concentrations of high mechanical stress (figure 1d). Analysis of risk of coronaries compression during the procedure is under investigation.

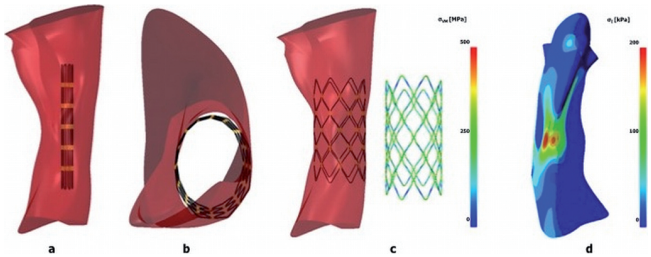

Figure 1

Conclusions: The clinical use of 3D models allows to assess, plan, and simulate interventions necessary in case of complex congenital malformations. These skills are especially important for young doctors and surgeons in training. In our experience, the simulation program for PPVI had been a useful tool to improve patients' selection and to avoid any potential surprise during the procedure in vivo. Multi-center studies should be set up to evaluate the impact of cardiac 3D models on medical decisions, the quality of care, and the patients' outcome.

P549 | BENCH
Hemodynamic modeling of fetal aortic and ductal arches using computational fluid dynamics and 3D/4D spatio-temporal image correlation fetal echocardiography

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Background and objectives: Flow in the aortic and ductal arches plays an important role in the cardiovascular development and maturation in human fetuses and is involved in the pathophysiology of congenital heart defect, e.g. coarctation of the aorta (CoA). We sought to establish a hemodynamic model of the aortic and ductal arches using computational fluid dynamics and 3D/4Dspatio- temporal image correlation (STIC) fetal echocardiography to probe the fluid dynamics in this region and the mechanism and diagnostics of CoA.
Methods: We obtained 3D/4D STIC fetal echocardiographic images of the aortic and ductal arches in 5 normal fetuses. Based on these images, we simulated the hemodynamics using CFD methods and computer aided design (CAD) software. Data of blood flow streamlines, pressures and wall shear stress (WSS) of the aortic and ductal arches were constructed as shown (Figure 1).
Results: Stream-wise swirling secondary flow pattern exists in aorta arch, which forms a pair of symmetric vortexes. There is a pair of crosswise vortexes with similar strength at the junction of aortic and ductal arches. There is relatively uniform distribution and gradual descending pressures along blood flow directions from ascending to descending aorta. WSS is apparently higher at superior wall of ascending aorta, roots of the branch vessels and downstream of the junction of the aortic and ductal arches; while it is significantly lower at superior wall of aortic arch and the junction of aortic and ductal arches.
Conclusions: We established the feasibility of hemodynamic modelling of the aortic and ductal arches in human fetuses using 3D/4D STIC fetal echocardiography and CFD. We determined the patterns of flow streamlines, pressures and WSS in normal human fetuses in these structures. These methodologies may provide powerful tools to understand the fluid mechanics, pathophysiology, and

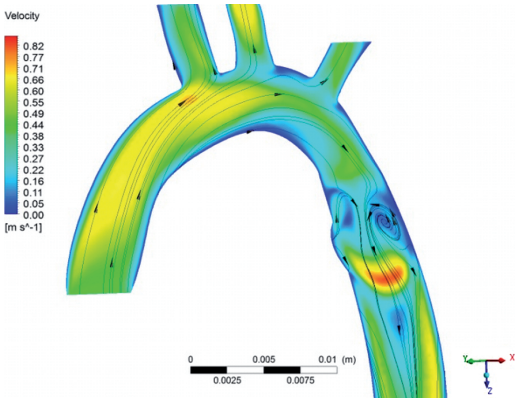

Figure 1. Blood flow streamlines of aortic arch

diagnostics in congenital heart defects of the aortic and ductal arches in human fetuses.

Acknowledgement/Funding: New century support plan of excellent talents in fetal heart (NCET-12-0613)

P550 | BEDSIDE
Non-invasive prediction of acute hemodynamics in cardiac resynchronisation therapy through patient specific modeling

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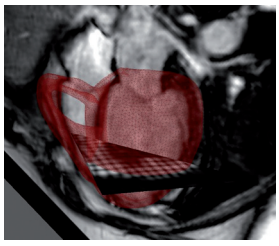
Background: Cardiac resynchronisation therapy (CRT) has been shown to improve cardiac function in patients with dyssynchronous heart failure. However, up to 50% of patients selected for CRT do not respond. It has been shown that hemodynamic measurements of the left ventricle (LV), dP/dtmax or %ΔdP/dtmax, taken during CRT implantation can predict volumetric or clinical response to CRT. While more research is needed, these studies highlight the importance of LV hemodynamics in CRT response. Currently, these hemodynamic metrics are unusable for patient selection as they are only available invasively during CRT implantation.
Purpose: This work is a proof-of-concept to show personalised computational modeling can non-invasively estimate baseline and acute CRT hemodynamics for a specific patient. Computational models can be used to represent the diseased heart and predict changes induced by CRT, including dP/dtmax and %Δ dP/dtmax. We built a personalised model for a CRT patient with left bundle branch block (LBBB) and compared our modeled hemodynamics with invasive measurements taken during the CRT procedure. To further test the model, invasive data was collected at different heart rates (80 bpm and 120 bpm).
Methods: A personalised model for a patient with non-ischeamic LBBB, QRS duration 144 ms, and NHYA Class II is achieved by integrating echo and MRI data, including SSFP, CINE and 3D TAG sequences, into a 3D biventricular model. This computational model combines mechanical and electrophysiological models, parameterised by the patients cardiac anatomy and motion. Once calibrated, biventricular simulations under the baseline dyssynchronous and CRT pacing protocols used in the implantation provide dP/dtmax and thus %Δ dP/dtmax.
Results: We show it is possible to use a personalised computational model to non-invasively predict LV dP/dtmax within 20% error. dP/dtmax, and thus %Δ dP/dtmax are calculated for baseline dyssynchronous and different specific CRT protocols used in implantation, then compared to the invasive LV dP/dtmax, which has a 15% beat-by-beat variability. Additionally, the processing of CRT patient data has been done with this modeling protocol in the time frame of two weeks between clinical assessment and CRT implantation.



Biventricular mesh with MRI data

Conclusions: Personalised computational modeling has the capability to non-invasively predict LV dP/dtmax under baseline and CRT paced conditions for individual patients with error close to measurement error. Additionally, the processing time frame achieved shows that it has the potential to aid in clinical CRT patient selection.

Acknowledgement/Funding: This study is funded by European Union's Seventh Framework Programme, grant no. 611823

P551 | BENCH
Bioinformatics analysis of the gene profile of coronary endothelial cells treated with Grapevine microRNAs: an in vitro study

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Introduction: microRNAs (miRNAs), the most abundant class of small non coding RNAs involved in post-transcriptional regulation of gene expression, exert control over a wide range of cellular functions. Emerging evidences suggest that diet-derived miRNAs might play an active role in human cardiovascular health as nutraceutical compound. However, studies on the potential action of plant miRNAs on cardiac cells are still lacking. Coronary endothelial cells directly modulate performance of the subjacent cardiomyocytes. A detailed understanding of multi-gene regulation by plant miRNAs is no longer feasible with traditional single gene studies but requires large-scale gene expression analysis provided by recent technological advances as bioinformatics.
Purpose: To evaluate the gene profile of cultured murine coronary endothelial cells (MCEC-1) long-term exposed to miRNAs, extracted from selected Tuscany Vitis vinifera grapevine, using a bioinformatics approach.
Methods: miRNAs were extracted from Vitis vinifera berries, cultivar Sangiovese, at full maturity, by a two steps extraction and evaluated for purity and integrity. MCEC-1 were maintained in DMEM-low glucose, supplemented with 10% FBS, and were seeded for 24h. The cells were then transfected with grapevine miRNAs at increasing doses (5, 20, 50 ng) in triplicate. After 48h, the MTT assay was used to evaluate the metabolic activity of MCEC. Untreated cells were used as control. Bioinformatics analysis (psRNA Target) were carried out to detect miRNAs target genes which may changes in response to grapevine miRNAs.
Results: The treatment with higher dose of grapevine miRNAs significantly increased the cell viability compared to untreated cells (percent cell viability: 133.5±8.8). The bioinformatics analysis identified 36 most abundant grapevine miRNAs in mature Sangiovese berries, which potentially target 141 genes in transfected endothelial cells.
Conclusion: We demonstrated, for the first time, that long-term treatment of healthy coronary endothelial cells with grapevine miRNAs modulate cell viability in a dose-dependent manner. We also reported preliminary bioinformatics results regarding the identification of murine genes potentially targeted by grapevine miRNAs. Our results support further investigations on the new role of grapevine miRNAs as nutraceuticals for cardiovascular prevention.
Acknowledgement/Funding: Bando Nutraceutica DD650/2014 Cardio.MiR. San.To

P552 | BEDSIDE
Variability of radiation doses of cardiac imaging tests: data from the RADIO-EVINCI study (RADIation dOse subproject of the EVINCI study)

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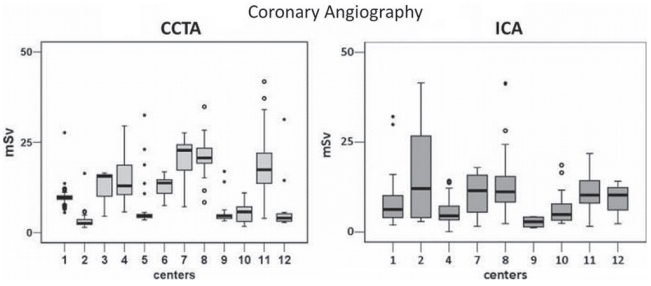
Background: Patients with known or suspected coronary artery disease (CAD) can cumulate significant radiation dose through repeated exposures to invasive diagnostic and percutaneous coronary intervention (CA), myocardial perfusion imaging with SPECT or PET, and coronary computed tomography angiography (CTA).
Aim: To audit radiation doses of CCTA, SPECT, PET and ICA in patients enrolled in a prospective, randomized, multi-centre multi-national study of diagnostic imaging for CAD (EVINCI).
Methods: We reviewed radiation dose data obtained in 1132 consecutive imaging tests (484 CTA, 85 PET, 310 SPECT, 236 CA) performed in 494 patients (age= 58±9 years, 58% males) enrolled in 12 different centers participating to the EVINCI (Evaluation of Integrated Cardiac Imaging for the Detection and Characterization of Ischemic Heart Disease) study who enrolled a total of 695 patients. The effective doses (ED) were calculated in milli-Sievert (mSv) as median, interquartile range (IQR) and coefficient of variation of the mean.
Results: For CCTA (476 exams in 12 centers) median ED was 9.6 mSv (IQR= 13.2 mSv); for SPECT (310 exams in 9 centers) 9.3 (IQR= 2.8); for PET (85 in 3 centers) 1.8 (IQR= 1.6); for ICA (199 in 9 centers) 7.4 (IQR= 7.3). Inter-institutional variability was highest for ICA (100%) and CCTA (54%) and lowest for SPECT (20%). Intra-institutional variability was highest for ICA (121%) and CCTA (115%) and lowest for SPECT (14%).
Conclusion: CCTA and ICA doses vary between and within centers. The variability in nuclear medicine procedures is substantially lower. The findings highlight the need to audit doses, to track cumulative exposures and to standardize doses for each imaging technique.



Acknowledgement/Funding: A grant from the European Union FP7-CP-FP506 2007 project (grant agreement no. 222915, EVINCI)

P553 | BEDSIDE
Intelligent cardiac CT registry: the feasibility of a structured reporting and automated registry generation in the daily routine

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Background: Routine cardiac CT reporting and research data collection require detailed data acquisition and robust data management.
Purpose: We sought to test the feasibility of automated registry generation regarding patients' history, indications, image acquisition parameters and clinical findings in a cardiac CT program of a single center.
Methods: The intelligent cardiac CT registry (iCCTR) is a database generated by an in-house developed structured reporting tool that automatically stores all relevant data points, such as anamnestic data, indications, premedication, CT acquisition parameters, segment based coronary evaluation and clinical recommendation. In addition, the platform automatically calculates the pretest probability of obstructive coronary artery disease (CAD) using the Diamond-Forrester criterion and generates clinical report.
Results: In total 2866 consecutive patients (age 59.5±11.9 years, 41.3% females) were included in the iCCTR between August 2014 and September 2015. All examinations were performed with a 256-slice multi-detector row CT scanner. Suspected CAD was the main indication (60.1%) followed by left atrial angiography (20.3%). Based on the automated pretest probability estimation in patients with suspected CAD 3.4% had high, 90.0% had intermediate, 5.9% had low and 1.7% had very low probability of obstructive CAD. Average effective radiation dose of the cardiac CT was 4.0±1.4 mSv. For premedication 68.3% of the patients received metoprolol, 4.1% ivabradin and 98.5% nitroglycerin. Invasive coronary angiography was recommended in 14.3% and secondary prevention (statin and/or aspirin therapy) in 47% of the cases.
Conclusions: The majority of the patients had an intermediate pretest probability of obstructive CAD and the main indication for cardiac CT was to rule out severe coronary artery stenosis. Invasive coronary angiography was avoidable in the majority of patients. Structured cardiac CT reporting and automated registry generation is feasible using a dedicated software tool in the daily routine and it provides valuable data for quality assurance and scientific research.

P554 | BEDSIDE
Quantifying the residual risk of cardiovascular events in secondary prevention patients with uncontrolled LDL-C receiving statins

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Background: Clinical atherosclerotic cardiovascular disease (ASCVD) and uncontrolled low-density lipoprotein cholesterol (LDL-C) are risk factors for cardiovascular (CV) events. Although LDL-C lowering statin therapy has been shown to reduce the risk of subsequent CV events in patients with ASCVD and elevated LDL-C, residual risk may remain despite statin therapy.
Purpose: To estimate the 5-year, 10-year and lifetime risk for subsequent CV events in clinical ASCVD patients with uncontrolled LDL-c despite receiving statins.
Methods: A Markov model with annual cycles was developed to estimate the risk of subsequent CV events over a lifetime horizon or a shorter period of time among ASCVD patients treated with statins. ASCVD was defined as history of acute coronary syndrome (ACS), other coronary heart disease, ischemic stroke or peripheral arterial disease. In the model, patients could remain stable or progress to subsequent CV events such as ACS, elective coronary revascularization, ischemic stroke, CV death, or to non-CV death. Baseline characteristics and annual transition probabilities were informed by an analysis of CV event rates, performed by medical history and diabetes prevalence, in a large US commercial claims database over a follow-up period of 1 year, and supplemented with published literature for HeFH patients. Transition probabilities changed with age and LDL-C level as informed by published literature. Risks of CV events at 5 and 10 years and over a lifetime projection were generated by the model for subsets of ASCVD patients with and without HeFH at varying levels of LDL-C.
Results: The table summarizes the result obtained with the different high CV risk subpopulations.

Table 1

High CV risk group	Composite CV risk		
	5 year	10 year	Lifetime
HeFH with clinical ASCVD and LDL-C >130 mg/dl (age 55)	47.9%	74.7%	95.0%
Clinical ASCVD and LDL-C >100 mg/dL (age 65)	30.2%	50.8%	78.1%
Clinical ASCVD and LDL-C >70 mg/dL (age 66)	27.5%	46.9%	73.1%

Conclusions: Despite current treatments, our findings suggest significant residual risk of CV events among patients with clinical ASVCD and elevated LDL-C, with highest risk among HeFH secondary prevention patients.
Acknowledgement/Funding: Sanofi and Regeneron

TREATMENT OF HYPERTENSION

P555 | BEDSIDE
Role of pressure, shear, and stretch in endothelial microparticle release: importance in hypertension

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Background: Membrane microparticles are submicron fragments of membrane vesicles shed from various cell types. Circulating endothelial microparticles have been proposed as markers of endothelial injury. However, which mechanical forces contribute to their release is not clear.
Objectives: It was the aim of the present study to investigate the role of mechanical forces, namely shear, stretch, and pressure, in the release of endothelial microparticles.
Methods: In a first series, 41 subjects (50% hypertensives) were recruited. MP subpopulations were discriminated by flow cytometry according to the expression of established surface antigens including CD31+/41-, CD144+, and CD62e+. Besides office and ambulatory 24 h blood pressure measurements, pulse wave analysis was performed to determine central blood pressure, augmentation index (AIX), and pulse wave velocity. Endothelial function (Flow-mediated dilation, FMD), arterial pulsatile stretch (fractional diameter changes, FDC), and wall-shear-stress (WSS) were measured in the same segment of the brachial artery (BA) by ultrasound. In a second series, we took measurements (n=12) in subjects with hypertensive crises (SBP>180 mmHg) before and after 4h and normalization of arterial BP by urapidil. In a third series, microparticles were measured in the cubital vein during reactive hyperemia (n=10).
Results: Univariate inverse correlations were found between CD31+/41-, CD144+, and CD62e+ microparticle levels and WSS in the BA. Furthermore, FDC only correlated with CD144+. Both ambulatory and office systolic blood pressure significantly correlated with CD31+/41-, CD144+, and CD62e+. All microparticle levels inversely correlated with FMD with the strongest being between FMD and CD62e+ ($r=-0.50$; $p<0.001$). In a stratified analysis comparing hypertensives (HT) and normotensives (NT), HT exhibited decreased FMD and increased endothelial MPs levels as compared to NT. Interestingly, hypertension was associated with an increase BA diameter (5.0±0.3 vs 4.5±0.5 mm) and hence with lower WSS (5.3±1.2 vs 3.9±0.6 dyne/cm^2) explaining increased levels of endothelial microparticles in hypertensive. In parallel, hypertensives' FMD was lowered (5.3±1.2 vs. 3.8±1.3%, p=0.001).
In the second series the patients with hypertensive crisis showed a reduced FMD 2.6±0.7%. vs. 3.8±0.7%, p=0.011) at baseline and FMD increased significantly after BP normalization whereas the BA diameter (4.8±0.5 vs. 4.8±0.4 mm) and WSS were not affected (3.6±0.6 mm vs 3.4±0.9 dyne/cm^2). In parallel, endothelial MPs decreased (CD144+: 243±39 vs. 198±42 Ev/ul, p=0.08). Univariate correlations were found between the decrease in SBP and decrease in CD62e+ MPs ($r=0.7$, $p<0.0011$).
Conclusion: Our results suggest that both endothelial injury due to high systolic blood pressure and stretch along with decreased protection by low wall shear stress confers microparticle release in hypertensives contributing to endothelial dysfunction

P556 | BEDSIDE
A novel approach to perform renal sympathetic denervation in moderate to severe chronic kidney disease using carbon dioxide angiography

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Introduction: Chronic kidney disease (CKD) is the commonest cause of sec-

ondary hypertension affecting up to 80% of the patients and >50% have uncontrolled hypertension (≥140/90 mmHg on ≥3 antihypertensive medications). Renal sympathetic denervation (RDN) has been shown to reduce BP in uncontrolled hypertension. Although patients with CKD have high sympathetic drive and as such are most likely to benefit from RDN; all major clinical trials have excluded patients with eGFR<45 for risk of contrast-induced nephropathy associated with renal angiography. In this pilot study we test whether carbon dioxide (CO2) angiography can be used to perform RDN in patients with CKD.

Methods: Patients with moderate to severe CKD (eGFR 15–44 ml/min) and uncontrolled hypertension were included. Written informed consent was obtained from all patients. Anatomical suitability for RDN was confirmed using non-contrast CT reconstruction of renal arteries. Renal angiography was performed using CO2 as the sole contrast agent before proceeding to perform RDN using the Medtronic Symplicity Catheter System. Clinic BP, 24-hour ambulatory BP, renal function and urinary protein excretion was measured at baseline and follow-up.

Results: Eleven patients (8 males) with CKD stage IV and IIIb underwent RDN. The median age was 57 years (interquartile range [IQR]: 49–66). Median (IQR) number of antihypertensives being taken at baseline was 4 (3–4). The baseline and follow-up kidney function and BP indices are summarised in the table below. There was no significant difference in the follow-up serum creatinine or eGFR when compared to baseline (Wilcoxon Test). Procedure-related complications observed include; one patient had flank pain managed with simple analgesics, one patient had groin pain and did not require any analgesics, and another patient had groin haematoma requiring overnight admission but no intervention.

Median (IQR)	Baseline (n=11)	Week 1 (n=11)	Week 4 (n=8)	Week 12 (n=8)	Week 26 (n=7)
Creatinine, μmol/l	200 (147–307)	179 (169–305)	206 (162–281)	200 (158–322)	198 (151–337)
eGFR, ml/min	29 (18–41)	33 (19–36)	27 (21–39)	29 (18–37)	25 (17–34)
Urine ACR, mg/mmol	203 (63–412)	156 (42–316)	150 (17–356)	123 (5–331)	99 (1–370)
Clinic SBP, mmHg	170 (158–180)	169 (158–175)	160 (128–170)	161 (148–183)	164 (149–168)
Day ambulatory SBP, mmHg	159 (149–164)				156 (148–167)

Conclusions: This is the first reported study to perform RDN with the sole use of CO2 as a contrast agent. This pilot study shows that CO2 renal angiography can be used to perform RDN in patients with significant renal impairment with associated improvement in clinic BP and proteinuria.

P557 | BEDSIDE
Results from real-world evidence and randomized controlled clinical studies with the combination of amlodipine and valsartan

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Background: Randomized controlled trials (RCTs) may not always reflect real-world outcomes of medicines. In comparison, real-world evidence (RWE) mimic settings wherein patients with comorbidities, polypharmacy and possibly different compliance levels are exposed to a medicine, thereby assessing its therapeutic benefits in daily clinical practice, thus enhancing and complementing data from RCTs.

Purpose: In this post-hoc analysis, we compared blood pressure (BP) lowering efficacy of amlodipine/valsartan (Aml/Val) combination therapy in RCTs and RWE studies conducted in patients with hypertension.

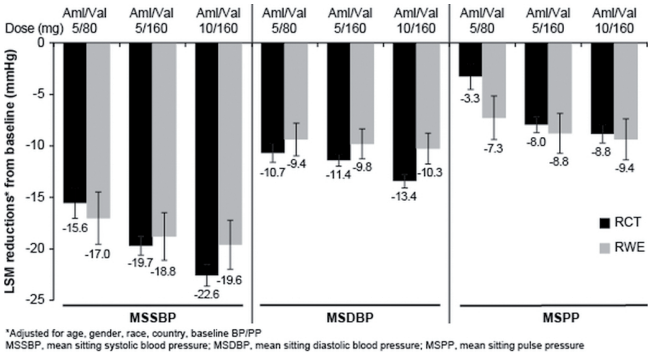
Methods: Data from 23 studies, with 4650 patients from RCTs and 1817 patients from RWE studies, were pooled and analyzed. In these studies, patients with uncontrolled hypertension (>140/90 mmHg) were assigned to either Aml/Val at different doses (5/80, 5/160 or 10/160 mg) or placebo. Only patients without missing data were included. Using a fitted linear mixed-effects model and random factors, interaction of treatment and study design on mean sitting (MS) systolic BP (SBP), diastolic BP (DBP) and pulse pressure (PP) reductions from baseline to 3 months of treatment were compared. For studies with duration >3 months, data were analyzed for the initial 3-month period. In studies with a cross-over design and/or titration, only the initial study period was analyzed (min: 60; max: 90 days of observation).

Results: Patients' baseline and demographic characteristics were comparable between RCT and RWE datasets and within Aml/Val treatment groups (Table). In both RCT and RWE settings, least-squares mean (LSM) reductions in MSSBP/MSDBP and MSPP from baseline were significant ($p<0.05$) across all dosages. Efficacy of Aml/Val in RCTs was not significantly different from its effectiveness in RWE studies (Figure).

Baseline and demographic characteristics

	Randomized controlled trials			Real-world evidence studies		
	Aml/Val 5/80 mg (N=744)	Aml/Val 5/160 mg (N=2467)	Aml/Val 10/160 mg (N=1439)	Aml/Val 5/80 mg (N=367)	Aml/Val 5/160 mg (N=943)	Aml/Val 10/160 mg (N=507)
Age, years	61.3 (11.9)	58.2 (11.1)	55.9 (12.0)	56.2 (13.4)	54.1 (11.2)	57.7 (11.3)
Male, n (%)	406 (54.6)	1282 (52.0)	733 (50.9)	177 (48.2)	571 (60.6)	305 (60.2)
Body mass index, kg/m^2	28.1 (5.2)	29.5 (5.4)	29.3 (5.3)	26.9 (4.7)	29.5 (4.9)	30.4 (5.5)
Mean sitting systolic/ diastolic pressure, mmHg	154.5 (10.9)/ 90.9 (10.2)	153.4 (14.5)/ 93.1 (10.2)	149.7 (12.1)/ 94.5 (6.2)	154.6 (17.2)/ 90.5 (11.4)	160.3 (15.0)/ 96.4 (9.5)	163.4 (18.9)/ 95.8 (12.3)
Mean sitting pulse pressure, mmHg	63.6 (14.6)	60.4 (13.8)	55.2 (12.0)	64.1 (16.2)	63.9 (13.7)	67.6 (14.9)

Data are represented as mean (standard deviation), unless otherwise indicated.



BP and PP reductions from baseline

Conclusion: This post-hoc analysis confirms the effectiveness of Aml/Val (5/80, 5/160 and 10/160 mg) in a real-world environment in Germany and in different countries in the Middle East and Asia. Furthermore, these results proved to be very similar to the clinical efficacy of Aml/Val in RCTs.

Acknowledgement/Funding: The studies included in this post-hoc analysis were funded by Novartis Pharma AG, Basel, Switzerland and Novartis Pharma GmbH, Nuremberg, Germany

P558 | BEDSIDE
Statins and perindopril/amlodipine efficacy in hypertensive patients with hypercholesterolemia

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Objective: The majority of patients with frequently coexisted hypertension and hypercholesterolemia require combination treatment with a statins and antihypertensives.There is evidence of a synergistic blood pressure (BP)-lowering effect of statins added to antihypertensive therapy. The objective of this subanalysis of the PERSPECTIVA study was to assess the impact of statins on antihypertensive efficacy of single-pill combination (SPC) perindopril and amlodipine in hypertensive patients with hypercholesterolemia.

Patients and methods: PERSPECTIVA study included 701 patients with newly diagnosed hypertension or hypertension uncontrolled on monotherapy or free dual-combination therapy (systolic BP ≥140 mmHg and/or diastolic BP ≥90 mmHg). Patients were started on SPC perindopril 5 mg/amlodipine 5 mg (if previously untreated), or switched to SPC perindopril 10 mg/amlodipine 5 mg (if systolic BP ≥140 and <180 and/or diastolic BP ≥90 and <110 mmHg), or SPC perindopril 10 mg/amlodipine 10 mg (if systolic BP ≥180 and <200 and/or diastolic BP ≥110 and/or <120 mmHg). We compared the antihypertensive efficacy of SPC in 226 patients wit hstatin therapy at baseline (statin (+) vs 361 patients without statins (statin (–), over a follow-up period of 60 days.

Results: At day 60, rate of BP control (<140/90 mmHg) was significantly higher in the statin (+) vs statin (–) group: 73% vs 64% respectively (+14%, $p<0.05$). In the statin (+) group, SPC reduced BP significantly in patients previously untreated, or treated with monotherapy, dual therapy, or triple therapy: -38.8/-20, -39.1/-20.1, -38/-19.4, -39.9/-18.3 mmHg respectively ($p<0.001$ vs baseline BP). Treatment was well tolerated with a similar rate of adverse events: 0.9% in the statin (+) vs 2.5% in the statin (–) groups.

Conclusion: In hypertensive patients the addition of a statin to perindopril/amlodipine SPC resulted in significantly better BP control and BP reduction regardless of previous antihypertensive therapy. Furthermore, the combination of statin plus perindopril/amlodipine was well tolerated. This subanalysis of the PERSPECTIVA study supports the synergistic effect of statins and perindopril/amlodipine combination.

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Poor control of blood pressure is associated with increased risk of cardiovascular events in hypertensive patients with atherosclerotic vascular diseases, especially in the elderly

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Background: Optimal control of hypertension is important for secondary prevention in patients with coronary and other atherosclerotic vascular diseases.
Purpose: To determine if poor control of blood pressure (BP) is associated with increased risk of cardiovascular event in hypertensive patients with established atherosclerotic vascular diseases
Materials: Taiwanese Secondary Prevention for Patients with AtheRosCLErotic Disease (T-SPARCLE) Registry is a prospective multi-center cohort conducted since Jan. 2010 in 18 hospitals enrolling patients with established coronary artery disease, cerebrovascular disease, and/or peripheral arterial disease. The patients with hypertension under medical control were included in this study. The BP at enrolment was used to stratify the risk of cardiovascular events thereafter with a mean follow-up of 2 years. Multivariate Cox proportional hazard model was employed to predict the primary outcomes (cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, and cardiac arrest with cardiopulmonary resuscitation).
Results: A total of 1,626 patients were included in this analysis (mean age 66.4±11.4 years old, male n=1,166). The risk of cardiovascular events was significantly higher in patients with diastolic BP ≥100 mmHg (HR 4.81, 95% CI 1.98 - 11.69, P<0.001) or mean arterial pressure (MAP) ≥120 mmHg (HR 4.59, 95% CI 2.10 - 10.07, P<0.001). For elderly patients (≥70 years old, n=645), the hazard ratios were even higher (HR 4.91, 95% CI 1.41 - 17.13, P<0.05 for diastolic BP ≥100 mmHg; HR 6.01, 95% CI 2.20 - 16.41, P<0.001 for MAP ≥120 mmHg). Systolic BP of ≥160 mmHg also served as an independent factor predicting higher risk of cardiovascular events in the elderly (HR 2.55, 95% CI 1.04 - 6.26, P<0.05). For patients <70 years of age, only those with diastolic BP ≥100 mmHg had increased risk with borderline significance (HR 3.67, 95% CI 0.94 - 14.32, P=0.06).
Conclusions: Poor control of BP is associated with increased risk of cardiovascular events in hypertensive patients with atherosclerotic vascular diseases, especially in the elderly. Control of diastolic pressure appears more important than systolic pressure for the secondary prevention in this group of patients.
Acknowledgement/Funding: Funds from the Ministry of Science and Technology, Taiwan ROC, Taiwan Society of Lipids and Atherosclerosis, and Taiwan Society of Lipid Educators

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Factors that exacerbate resistance to the antihypertensive treatment in hypertensive patients with diabetes

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Background: Accumulating evidence supports that reducing blood pressure in hypertensive subjects has a marked cardiovascular protective effect regardless of the drugs employed. However, effective blood pressure control is particularly difficult to achieve especially in patients with diabetes mellitus and combinations of two or more agents are frequently necessary.
Purpose: We investigated factors that exacerbate resistance to the antihypertensive therapy in hypertensive patients with diabetes.
Methods: Hypertensive patients with type 2 diabetes (n=118, 67±9 years, male 44%) were enrolled and step-wise upward-titration of medication was implemented in the following eight steps to reach a target level of home blood pressure <130/80 mmHg: step 1, usual dose of angiotensin receptor blocker (ARB); step 2, usual dose of ARB and calcium channel blocker (CCB); step 3, step1 + high dose of CCB; step 4, high dose of ARB and CCB; step 5, step 4 + diuretic; step 6, step 5 + beta-blocker; step 7, step 6 + usual dose of alpha-blocker; step 8, step 6 + high dose of alpha-blocker. The primary endpoint was the number of antihypertensive medications needed per patients to achieve the target home blood pressure goal. The step number at which the target blood pressure goal was achieved was considered as the number of drugs needed.
Results: All patients reached target blood pressure at step 4.0±1.5. The step number was correlated with age, eGFR, and HbA1c in univariable analysis. However, after adjustment for possible factors, eGFR (r = –0.571), but not HbA1c, was an independent predictor of the medication step number (p<0.0001). Reduction in blood pressure obtained in step 1 (effect of ARB) was positively correlated with eGFR (r = 0.439, p<0.0001) and negatively correlated with age (r = –0.524, p<0.0001), baseline blood pressure (r = –0.211, p<0.05), and baseline pulse pressure (r = –0.245, p<0.05) by multivariable analysis. In contrast, blood pressure reduction in step 2 (caused by addition of CCB) showed positive correlation with baseline pulse pressure (r = 0.232, p<0.05), while other factors did not indicate significant correlation with the blood pressure reduction in step 2.
Conclusions: The number of antihypertensive medications needed for blood pressure control in hypertensive patients with diabetes mellitus was largely dependent on eGFR. Impairment of kidney function may produce resistance to antihypertensive therapy. Factors that build up resistance to ARB may be different from those to CCB.

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Is ARB/CCB combination superior to ARB/HCTZ combination in day-by-day blood pressure variability reduction? a prospective randomized trial

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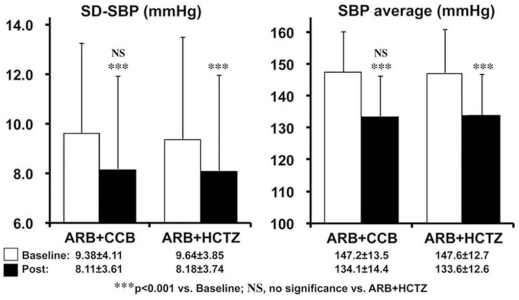
Background: Day-by-day blood pressure (BP) variability (DDV) is an independent risk for cardiovascular events. Although Ca channel blockers (CCBs) have been shown to reduce visit-to-visit BP variability, little is known about the effects of antihypertensive treatment on home BP measurement DDV. An angiotensin II receptor blocker (ARB) combined with a CCB or hydrochlorothiazide (HCTZ) is an established option for combination therapy to achieve target BP.
Purpose: The aim of this study was to determine whether ARB/CCB combination would be superior to ARB/HCTZ combination in DDV reduction.
Methods and results: This prospective, randomized, open-labeled, parallel-group, multicenter trial enrolled 926 outpatients who had not achieved home BP target (<135/85 mmHg) and/or clinic BP target (<140/80 mmHg) despite antihypertensive medications. Patients were randomly assigned to receive a 8-mg candesartan/5-mg amlodipine tablet (ARB/CCB group) or a 8-mg candesartan/6.25-mg HCTZ tablet (ARB/HCTZ group) once every morning. The primary and secondary end-points were morning DDV, assessed by SD of SBP (SD-SBP), and morning SBP average, respectively, after 6-month treatment (Figure).



Conclusions: ARB/CCB and ARB/HCTZ reduced morning DDV and morning SBP to the similar levels. Therefore, strict BP lowering is important for DDV reduction, irrespectively of antihypertensive regimen.
Acknowledgement/Funding: A grant for the science frontier research Promotion Centers and a KAKEN from the Ministry of Education, Science, Sports and Culture, Japan

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Effectiveness of perindopril/amlodipine fixed dose combination in hypertensive patients with coronary artery disease. A panhellenic prospective non-interventional study

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Background/Introduction: Recent ESH/ESC 2013 guidelines recommend the initiation of treatment with a two-drug combination in hypertensive patients with coronary artery disease (CAD). The prompt reduction of blood pressure (BP) in these patients is translated into an improvement in cardiovascular (CV) morbidity and mortality. Moreover, in hypertensive patients with CAD, the use of an angiotensin-converting enzyme inhibitor (ACEi) and calcium antagonist have pleiotropic effects above and beyond BP reduction.
Purpose: The aim of this study was to record the effectiveness, adherence, safety, and tolerability of perindopril/amlodipine fixed-dose combination (FDC) in hypertensive patients with CAD during a 4-month treatment period.
Methods: In this observational study, 1907 hypertensive patients with CAD, who had been recently commenced on perindopril/amlodipine FDC at the treating

physician's discretion, were recruited from 192 non-hospital centers. The data were recorded at baseline, and at 1 and 4 months of treatment. Adherence to treatment was assessed through the 4-item Morisky Medication-Taking Adherence Scale (MMAS-4, recorded at the 2nd and 3rd visit). Patients' total CV risk was assessed through the ASCOT-BPLA risk score model (ASCORE) that evaluates age, sex, smoking, diabetes, previous BP treatment, systolic BP, total cholesterol, high-density lipoprotein–cholesterol, fasting glucose, and creatinine levels.
Results: From 1907 hypertensive patients who were recruited for this study, 7 patients (0.4%) discontinued treatment. According to the ASCORE model, 79.2% of the patients were considered as high or very high CV risk. Mean systolic BP (SBP)/diastolic BP (DBP) values decreased from 156.5±15.0/89.9±9.6 mmHg (1st visit), to 130.8±8.4/78.2±6.4 mmHg on the 3rd visit ($P<0.001$). Patients with higher BP values or high CV risk on the 1st visit showed greater BP reduction ($P<0.001$). At study completion, patients with grade 1, 2, and 3 hypertension showed a SBP/DBP reduction of 19.3/9.4 mmHg, 31.5/13.5 mm Hg and 47.8/22.2 mmHg, respectively ($P<0.001$). Patients with moderate, high, and very high CV risk showed a SBP/DBP reduction of 23.2/11.4 mm Hg, 25.4/11.4 mm Hg and 36.2/15.9 mmHg, respectively ($P<0.001$). The BP reduction observed in these patients was significant, regardless of the previous antihypertensive treatment administrated (P-value nonsignificant for the use, or non-use, of other antihypertensive drug classes/type of drugs). Adherence to treatment was high: 85.7% (1628 patients) of the sample were taking their treatment every day at 4 months. A total of 1607 patients (84.2%) received a constant dose of perindopril/amlodipine FDC throughout the study, of which 45.6% received the lowest dose of 5 mg/5mg.
Conclusions: Perindopril/amlodipine FDC promptly and significantly decreases BP levels, regardless of the previous antihypertensive treatment administrated, with high adherence to treatment.
Acknowledgement/Funding: Servier Hellas

P563 | BEDSIDE
Effect of algorithmized antihypertensive treatment at masked uncontrolled hypertension persistence in uncomplicated hypertensives

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Background: Masked uncontrolled hypertension (MUH) has carries cardiovascular risk comparable to that of sustained hypertension, but effect of antihypertensive treatment on its short-term persistence remains uncertain.
Purpose: To assess MUH persistence in uncomplicated hypertension (UH) during 6 month (M) algorithmized antihypertensive treatment in a real-life longitudinal program.
Methods: Per protocol cohort of PERFECT-BP prospective observational study (No. ISRCTN75706523) included 436 patients (pts) <75 years (57,6±0.5years) newly diagnosed (18,3%) or treated but uncontrolled (<200/120mmHg) UH. Pts and MDs (54 ambulatory cardiologists) were provided with validated oscillometric blood pressure (BP) measurement devices with individually selected and universal cuff correspondingly. At visit 1, pts were given training and written instructions for home BP monitoring (HBPM) and recording (twice per day for 7 consecutive days before each visit at day (D) 7, M1, 2, 3, 6) and were prescribed or switched to perindopril/amlodipine fixed-dose combination (FDC). Step 2 for target office BP (<140/90 mmHg) attainment was FDC uptitration, step 3 – plus indapamid-SR, step 4 – spironolactone, step 5 – moxonidine or doxasosine. Doses of FDC and therapy increasing were at discretion of MDs. Normotension was defined as office BP<140/90 and home BP<135/85mmHg; MUH – as office BP<140/90 and home BP≥135/85mmHg; sustained hypertension – as office BP≥140/90 and home BP≥135/85mmHg; white coat hypertension – as office BP≥140/90 and home BP<135/85mmHg.
Results: At D7 target office BP was attained in 96 (22%), at M1 – in 197 (45,2%), at M2 – in 261 (59,9%) and M3 – in 325 (74,5%; p<0,0001 compared to D7) pts. So, within 3 M of treatment target office BP was recorded at 879 visits with MUH at 270 (30,7%) of them: at D7 – in 47 (49%); M1 – in 73 (37,1%); M2 – in 74 (28,4%); M3 – in 77 (23,7%; p<0,001 compared to D7) pts. At the next visit in the 232 (85,9%) cases, when the therapy has not increased, MUH persisted in 69 (29,7%) pts, converted to sustained hypertension – in 38 (16,4%), to normotension – in 118 (50,9%) or to white coat hypertension – in 7 (3%) pts. By M6 MUH was indentified in 79 (22,3%) from 355 pts with target office BP (p<0,001 compared to D7).
Conclusion: Prevalence of MUH among UH decreased under the influence of 6M algorithmized treatment at 54,5%, but ignoring of the results of HBPM led to persisting of MUH in 29,7% of pts and converting to sustained hypertension in 16,4% of them in the short term period of observation.

P564 | BEDSIDE
Efficacy,safety and treatment adherence with fixed-combination perindopril arginine/amlodipine in patients switched from previous ineffective free combination antihypertensive therapy in real practice

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Objective: The aim of this postmarketing observational study, POTENTIAL, was to assess the antihypertensive efficacy and safety of fixed-dose combination (FDC) perindopril arginine/amlodipine in patients with arterial hypertension uncontrolled by previous free combination antihypertensive therapy, in a real clinical practice.
Material and methods: The patients included in the program (n=1061, 414 men [39%], 647 women [61%]) were followed by 243 physicians in 51 regions of the Russian Federation. The duration of treatment was 3 months. The parameters recorded were systolic and diastolic arterial blood pressure (BP), rate of achievement of BP<140/90 mm Hg, rate of positive responses (BP decrease ≥10 mm Hq) to treatment evaluated by office BP measurement and home blood pressure monitoring (HBPM), adherence to therapy assessed by the adherence scale, and self-assessment of state of health using a visual analog scale. Implementation of the Programme had been approved at a meeting of the Inter-University Ethics Committee, protocol number 09–14 orr 23.10.2014 (Moscow).
Results: After 3 months, target BP was achieved in 90.8% of patients who were switched to perindopril arginine/amlodipine FDC. BP was reduced on average by 33.1/15.0 mm Hg (mean baseline BP: 160.0±11.1/92.7±8.8 mm Hg; mean BP at 3 months: 126.9±8.3/77.7±6.4 mm Hg) ($P<0.00001$). A positive effect of the treatment was observed in 93.1% of patients after 2 weeks and 99.4% of patients after 1 month according to office measurements. According to the results of HBPM, 63.5% of patients achieved BP<135/85 mm Hg at 3 months. Taking the drug at night was associated with a greater reduction in BP. Perindopril arginine/amlodipine FDC therapy significantly improved adherence to treatment, from 43.4±18.3% to 71.8±11.7% ($P<0.00001$). Fifty-three patients (3.92%) dropped out of the program prematurely, including 16 patients (1.1%) who dropped out because of adverse effects.
Conclusion: This study demonstrates the benefit of perindopril arginine/amlodipine FDC use in patients whose BP is insufficiently controlled with a free combination of antihypertensive drugs. Taking the drug in the evening can help to achieve a more pronounced BP reduction.

P565 | BEDSIDE
Comparison between canrenone or hydrochlorothiazide in addition to sartans in hypertensive diabetic patients

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Aim: To evaluate the effects of canrenone compared to hydrochlorothiazide in addition to sartans on glycemia, lipid profile, potassium, aldosterone and renal function in hypertensive, diabetic patients.
Methods: We enrolled 182 Caucasian patients affected by hypertension and type 2 diabetes mellitus. Patients were already in treatment with sartans, at randomization patients were randomized to canrenone, 50 mg once a day, or hydrochlorothiazide 12,5 mg once a day for 12 months. Patients not reaching blood pressure target, were up-titrated to canrenone 100 mg or hydrochlorothiazide 25 mg once a day. We evaluated at the baseline, and after 6 and 12 months, these parameters: systolic (SBP) and diastolic blood pressure (DBP), body weight, body mass index (BMI), fasting plasma glucose (FPG), post-prandial glucose (PPG), fasting plasma insulin (FPI), homeostasis model assessment insulin (HOMA-IR), lipid profile, potassium, plasma aldosterone, urine albumin excretion rate, estimated glomerular filtration rate.
Results: We observed a significant similar decrease of SBP and DBP with both canrenone and hydrochlorothiazide after 6, and 12 months, without differences between groups. Canrenone gave a significant decrease of FPG, PPG, FPI, and HOMA index compared to baseline, while there was a significant increase of the same parameters with hydrochlorothiazide. Moreover, values recorded with canreone were lower compared to the ones recorded with hydrochlorothiazide. No variations of lipid profile were recorded with canrenone, while there was a worsening of total cholesterol and triglycerides with hydrochlorothiazide. Potassium levels were decreased, and uric acid levels were increased by hydrochlorothiazide, but not by canrenone that had a neutral effects on these parameters. We recorded a slight decrease of estimated glomerular filtration rate with hydrochlorothiazide, and an improvement with canrenone. Plasma aldosterone levels were decreased by canrenone and decreased by hydrochlorothiazide.
Conclusion: Despite giving similar blood pressure, canrenone seems to be more effective than hydrochlorothiazide in improving metabolic parameters such as glycemia, insulinemia, uric acid levels, and in improving estimated glomerular filtration rate.

P566 | BEDSIDE
Five-year trends in specific risk factors in hypertensive patients reffered to specialized cardiological centre

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Background: Age and gender, diabetes mellitus (DM) and lipid disorders are considered to be independent risk factors and predispose to higher risk of cardiovascular complications and poor outcome, thus require more aggressive treatment strategies and follow-up.
Purpose: The main objective of this study was to describe trends in age, gender, prevalence of DM and lipids disorders in adult hypertensive patients referred to specialized cardiology clinic during the period of January 2010 - December 2014.

Methods: Data included 59268 (21153 males and 38115 females) records of patients, mean age 58.3±13,8 years, referred to specialized clinic due to uncontrolled hypertension. Descriptive statistics were used to estimate the means in gender and age [under 35 years (n=4079), 35–49 (n=8566), 50–65 (n=26381), older than 65 (n=20242) years] subgroups. Linear regression was employed to determine the yearly trends. Age and gender-specific results were adjusted to Saint-Petersburg general population data for 5-years period and every studied year.
Results: During the 5-years period mean age increased from 56,6±13,8 to 59,7±13,8 years (R^2=0,98, p=0,002), both in male (from 51,1±16,0 to 53,8±11,7; R^2=0,98, p=0,01) and female (from 59,9±11,0 to 63,0±11,7; R^2=0,99, p=0,0005) populations, mostly due to subgroup over 65 years (from 28% to 39%; R^2=0,90, p=0,01). The proportion of male hypertensive patients was 35,5% without significant 5-years trends. The average prevalence of known lipid disorders for the studied period was 3,7% (2160 patients) without any significant trends. Increased level of total cholesterol in combination with increased low density lipoprotein levels was the most frequent disorder (917 cases; 42,7%). There were no significant changes in prevalence and characteristics of lipids disorders in gender subgroups. Analysis of age groups demonstrated increase in lipid disorders frequency in patients over 65 years (R^2=0,80; p=0,04). The average prevalence of known diabetes was 14,5% (8592 patients) and impaired glucose tolerance 0,9% (518 cases) without any significant trends during studied period in overall population and in gender subgroups. While in subgroup of hypertensive patients over 65 years there was an increase in prevalence of diabetes and impaired glucose tolerance during the last 5 years (R^2=0,78, p=0,05 and R^2=0,95 p=0,005, respectively).
Conclusions: During the last five years referred hypertensive patients became older mostly due to increase of proportion of patients over 65 years, which is associated with excess prevalence of metabolic disorders in difficult to control hypertension. These trends may be important for the development of total risk reduction programs in the elderly and explain general poor blood pressure control.

PERCUTANEOUS STRUCTURAL HEART INTERVENTIONS

P567 | BEDSIDE
Comparison of outcomes between nonagenarian and younger patients undergoing transcatheter aortic valve replacement (TAVR) with the LOTUS valve

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Introduction: Nonagenarians have high periprocedural risk following transcatheter aortic valve replacement (TAVR). Outcomes in nonagenarians following Lotus valve implantation is currently not known.
Aim: Compare the outcomes of nonagenarians and younger patients undergoing TAVR with the Lotus valve.
Methods: 104 consecutive patients with Lotus valve implantation were divided into two groups (nonagenarian group ≥88 yrs and control cohort <88 yrs). Data was collected on peri-procedural complications and 30 day follow-up outcomes. Primary endpoint was 30 day mortality and disabling stroke. Secondary endpoints included procedure time, length of stay and complications.
Results: 104 patients (Nonagenerians n=23 mean age 90.6±2.6 yrs, control group n=81 patients mean age 81.1±4.6 yrs). Baseline characteristics were similar in both groups except for more hypertensives in the controls (p=0.013). Surgical risk was similar in both groups. There was one death and no myocardial infarcts in both groups (p=0.337) and one disabling stroke (2%) in the control group. Procedure time (120.4 vs 133.8 min, p=0.073), length of stay (mean 9.7 vs 9.5 days, p=0.888) and rates of complications were similar in nonagenarians and controls. There was a higher proportion of patients in the nonagenarian group requiring rehabilitation (43% vs 22% p=0.046).

Outcomes post Lotus valve implantation

Outcome	Nonagenerian (n=23)	Control (n=81)	p value
Age (SD), years	90.6 (2.6)	81.1 (4.6)	<0.001
Male (%)	12 (52)	36 (44)	0.512
Procedure time (min)	120.4 (26.2)	133.8 (44.1)	0.073
Death (%)	1 (4)	1 (1)	0.337
Myocardial infarction (%)	0 (0)	0 (0)	–
Disabling stroke	0 (0)	1 (1.2)	0.595
Mean length of stay (SD)	9.7 (7.4)	9.5 (8.6)	0.888
Rehab admission (%)	10 (43)	18 (22)	0.046
Major vascular complications (%)	3 (13)	10 (12)	0.929
Emergency surgery (%)	1 (5)	2 (2)	0.635
AKIN stage II/III AKI (%)	0 (0)	6 (7)	0.179

Conclusion: Nonagenarians may have similar outcomes and length of stay with increased rates of rehabilitation when compared to younger patients post Lotus valve implantation.
Acknowledgement/Funding: Boston Scientific and Medtronic and proctor fees from Boston Scientific.

P568 | BEDSIDE
Mitral balloon valvuloplasty long-term follow-up of single balloon versus inoue balloon techniques. Independent predictors of survival and event free survival

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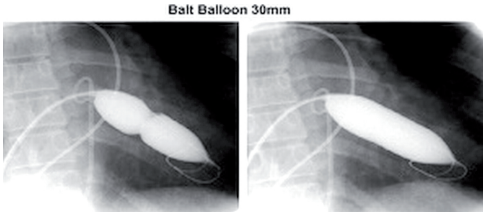
Background: The single balloon (SB) is the less expensive technique to perform mitral balloon valvuloplasty (MBV). This study aimed to demonstrate that MBV done with SB Balt has similar outcome and long-term follow-up (FU) than MBV done with the Inoue worldwide accepted technique.
Methods: From 1987 to 12/31/2013 a total of 526 procedures were performed, being 313 with a FU, 57 (18.8%) with Inoue balloon (IB), the IB group (IBG) and 256 (82.1%) SB Balt group (SBG). The mean FU in IBG was 33±27 (2 to 118) months and in SBG 55±33 (1 to 198) months (p<0.0001). Univariate analysis and multivariate Cox analysis were utilized to determine independent predict of survival variables and event free survival (EFS) in both technique groups being major events (ME): death, cardiac surgery and new MBV.
Results: In IBG and SBG there were: female 43 (75.4%) and 222 (86.7%) procedures, (p=0.0276), mean age 37.3±10.0 (19 to 63) and 38.0±12.6 (13 to 83) years (p=0.7138), sinus rhythm 51 (91.1%) and 215 (84.0%), (p=0.1754), echo score (ES) 7.6±1.3 (5 to 10) and 7.2±1.5 (4 to 14) points (p=0.0528), echo mitral valve area (MVA) pre-MBV 0.96±0.18 and 0.93±0.21 cm^2 (p=0.2265). Post-MBV mean MVA (Gorlin) were 2.00±0.52 and 2.02±0.37 cm^2 (p=0.9550) and at the end of the FU: echo MVA 1.71±0.41 and 1.54±0.51 cm^2 (p=0.0552), new severe mitral regurgitation in 5 (8.9%) and 17 (6.6%) patients (p=0.5633), new MBV in 1 (1.8%) and 13 (5,1%), (p=0.4779), mitral valve surgery in 3 (5.4%) and 27 (10.4%), (p=0.3456), deaths 2 (3.6%) and 11 (4.3%) deaths, (p=1.000), cardiac deaths 1 (1.8%) and 9 (3.5%), (p=1.0000), ME 5 (8.9%) and 46 (18.0%), (p=0.1449). In univariate analysis and in multivariate Cox analysis the SB or IB do not predict survival or event free survival and independent risk factors to survival in multivariate Cox analysis with 2 models with 5 and 6 variables were: age <50 years (p=0.016, HR=0.233, CI 95% 0.071–0,764), ES ≤8 (p<0.001, HR=0.105, CI 95% 0.34–0.327), MBV dilatation area (p<0.001, HR=16.838, CI 95% 3.353- 84.580) and no mitral valve surgery in the FU (p=0.001, HR=0.152, CI 95% 0.050–0.459) and to event free survival: no prior commissurotomy (p=0.012, HR=0.390, CI 95% 0.187–0.813) and post-MBV MVA ≥1.50 cm^2 (p<0.001, HR=7.969, CI 95% 3.413–18.608).



Conclusions: SB and IB MBV had similar survival and event free survival in the FU. Independent predictors of survival were: age, ES, MBV dilatation area and no mitral valve surgery in the FU and event free survival: no prior commissurotomy and post-MBV MVA

P569 | BEDSIDE
Effect of bivalirudin vs unfractionated heparin in transcatheter aortic valve implantation with balloon-expandable valves. The BRAVO-3 trial

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Background: Selection of valve type may impact bleeding and vascular complications in transcatheter aortic valve implantation (TAVI). Whether bivalirudin (BIV) reduces bleeding vs unfractionated heparin (UFH) with balloon expandable (BE) TAVI is not known.
Purpose: To explore the differences in outcomes with BIV vs UFH in patients undergoing TAVI solely with BE valves.
Methods: The BRAVO-3 trial included 500 patients undergoing transfemoral TAVI with BE valves and randomized to receive BIV vs UFH. Primary endpoint was Bleeding Academic Research Consortium (BARC) type ≥3b bleeding at 48 h. Major adverse cardiovascular events (MACE) were a composite of death, myocardial infarction or stroke. Net adverse cardiovascular events (NACE) were a composite of MACE or BARC ≥3b bleeding.

Results: Of the study cohort, 251 were treated with BIV and 249 with UFH. Mean patient age was 81.8±6.7 years; mean EuroScore I was 16.5±10.2; 51% were women. There were no significant baseline differences between groups. Clinical outcomes at 48 h and 30 days are presented in the Table.

Clinical outcomes in patients receiving balloon-expandable valves

		BIV n=251	UFH n=249	P-value
48 hours	BARC ≥3b bleeding	19 (7.6%)	20 (8.0%)	0.85
	Death	4 (1.6%)	4 (1.6%)	1.00
	Stroke	6 (2.4%)	4 (1.6%)	0.75
	MACE	10 (4.0%)	9 (3.6%)	0.83
	NACE	26 (10.4%)	28 (11.2%)	0.75
30 days	≥3b bleeding	24 (9.6)	21 (8.4)	0.65
	Death	8 (3.2)	9 (3.6)	0.79
	Stroke	8 (3.2%)	7 (2.8%)	0.81
	MACE	14 (5.6)	18 (7.2)	0.45
	NACE	34 (13.5)	35 (14.1)	0.86

Conclusions: Patients undergoing TAVI with BE valves had similar early outcomes with BIV or UFH.
Acknowledgement/Funding: The Medicines Company

P570 | BEDSIDE
Transradial versus the transfemoral approach in alcohol septal ablation

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Aims: The efficacy, feasibility and acute procedural outcomes of TR versus transfemoral (TF) approach for alcohol septal ablation (ASA) have not yet been determined.
Methods and results: We retrospectively analyzed 240 patients who underwent an ASA procedure at our institution from November 1999 to November 2015. The TR approach was performed in 172 cases and the remaining 68 cases through the TF approach. The use of TR progressively increased from 62% in 1999–2005 to 91% in 2012–2015 (p=0.0001). All procedures were performed under conscious sedation with echocardiography guidance. Procedural success was defined as more than 50% decrease in peak gradient without any in-hospital major cardiac event.
Mean age was 57.6±15.7 vs. 58.4±14.7 years in the TR and TF, respectively (p=0.70). Baseline NYHA class (III or IV: 67.5% vs. 62.1%, p=0.45) and mean resting or exercise left ventricular outflow tract (LVOT) peak gradient (93.3±41.92 vs. 94.3±42.34 mmHg, p=0.86) were similar between the TR and TF, respectively. Total contrast used (74.2 vs. 100 ml, p=0.43), total radiation Air kerma area product (43.7 vs. 72.9 Gy.cm-2, p=0.38) and acute resting LVOT peak gradient post-ASA (19.3±19.70 vs. 20.5±18.11 mmHg, p=0.77) were similar in both the TR and TF groups, respectively.
Procedural success was 91.9%and 91.2% in the TR and TF groups, respectively (p=0.97). New pacemaker implantation rates were similar in both groups (10.7% vs. 11.9%, p=0.82). There was only 1 intra-hospital death for the full cohort from the TF group and one coronary dissection in the TR group.
Conclusion: Alcohol septal ablation procedure can be performed safely, effectively and with high success rates from the radial approach.

P571 | BEDSIDE
Long term follow up after transcatheter tricuspid valve-in-valve replacement using Edwards Sapien XT valve

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Background: Percutaneous tricuspid valve-in-valve replacement can be a feasible treatment for high-risk patients with previous tricuspid bioprosthesis that undergo valve degeneration and develop refractory heart failure. No data on long-term follow after trans catheter tricuspid valve-in-valve replacement is currently available.
Purpose: The purpose of this analysis is to report data on clinical and echographic long term follow up of patients treated with tricuspid valve-in-valve replacement in our center.
Methods: Procedural and clinical in-hospital outcome data was collected from our institutional registry. Long-term follow up was assessed with transthoracic echocardiography and outpatient clinic visits as part of our standard care program.
Results: From January 2013 to June 2014 three patients underwent transfemoral tricuspid valve-in-valve replacement at our institution. One patient presented with severe TR whereas the other two had severe symptomatic steno-insufficiency of degenerated biological prosthesis. Edwards Sapient XT 29 mm valve were implanted in all cases. Mean age and weight were 60.3 (54.3–66.6) years and 70 (54–89) kg. Procedure succeeded in all patients, with no procedural complications observed. At hospital discharge, all patients had mild to trivial tricuspid with consistent and immidiate improvement of the functional class (from NYHA III-IV to NYHA I-II). All patients were alive at mean follow up of 27.2 (19.9–36.5) months and no cardiovascular event has been registered. At long-term echocardiographic assessment a mean TV gradient <4mmHg was found in all patients. TR was estimated as mild in two cases and moderate in one patient.
Conclusion: Trancatheter tricuspid valve-in-valve replacement is a valuable option to treat high-risk patients with symptomatic severe TR or steno-insufficiency that recurs after surgical valve degeneration. Sapient XT valves implanted on tricuspid degenerated biological prosthesis are performing well at long-term follow up.

P572 | BEDSIDE
5 years after percutaneous edge-to-edge mitral valve repair, what has happened?

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Background: Percutaneous edge-to-edge repair of the mitral valve has shown to be a good alternative to conservative therapy, for patients with symptomatic severe mitral valve regurgitation who are denied surgical treatment. Not much is known about the long term durability of this relatively new percutaneous treatment.
Aim: The main aim of this study is to evaluate morphologic and physiological changes of the heart, 5 years after treatment with percutaneous edge-to-edge mitral valve repair. Secondary aims are to evaluate clinical status and quality of life at long term follow-up, and to compare the primary patient cohort to a control cohort who have met a hard end point.
Methods and results: From 2009 and ongoing, our department has performed over 250 percutaneous mitral valve repair interventions using the MitraClip system. Medical history, transthoracic echocardiography, 6-minute-walk-test and laboratory blood testing have been registered prospectively. Most of our patients treated with the MitraClip are high-surgical-risk, with a mean European system for cardiac operative risk evaluation II of 9.6±7.7% and left ventricular ejection fraction of 36.4±15.3%.
After excluding for hard endpoints (death, "redo" percutaneous intervention, surgical mitral valve repair/replacement or heart transplantation), we have selected 32 patients with a median follow-up of 1802 days. For this group, we have planned clinical follow-up including transthoracic echocardiography, a 6-minute-walk-test and laboratory blood testing. The main goal of this study is to compare pre- and peri-procedural baseline characteristics with data at 5 years of follow-up.
We have also identified a cohort of 32 patients previously treated with the MitraClip who have met an endpoint, with a "theoretical" (if we ignore the fact that they have met an endpoint) median follow-up of 1739 days. We will compare this control group with the original cohort to identify predictors for mortality or re-intervention.
Conclusions: To our knowledge, this is currently the only study evaluating 5 years follow-up after MitraClip treatment for patients with mitral valve regurgitation in a "real world" setting. We expect to have acquired all data to perform final analysis by March-April 2016.
Acknowledgement/Funding: Experiment TopZorg, ZonMw

P573 | BEDSIDE
Is multiparametric FRANCE-2 score better than EuroSCORE II and STS PROM in predicting early mortality after transcatheter aortic valve implantation?

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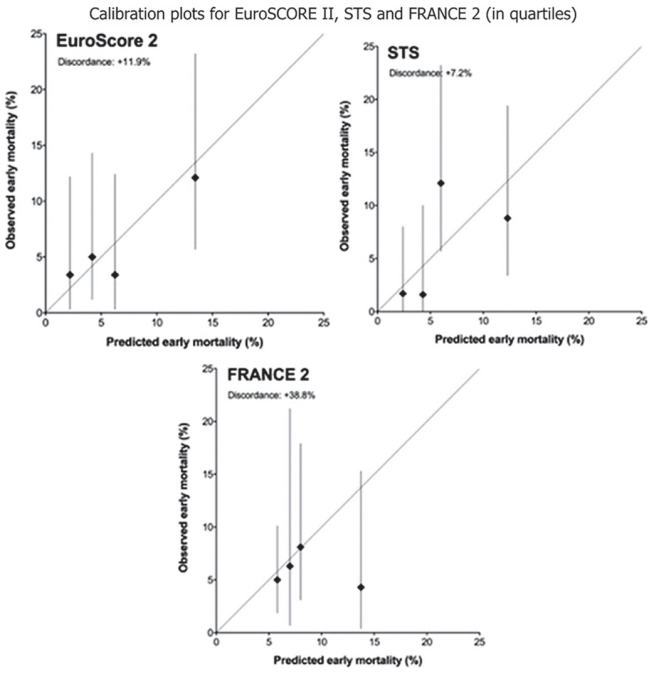
Background: The decision on the therapeutic technique in severe aortic stenosis must balance the risk of surgery and transcatheter aortic valve implantation (TAVI). Surgical risk scores have been widely used to identify patients at high surgical risk who may benefit from TAVI. Recently it was presented a multiparametric TAVI mortality risk score based on French registry – FRANCE 2.
Purpose: To evaluate the FRANCE 2 score performance in early mortality when compared with the EuroSCORE II (ES II) and STS Prom (STS) in our population.
Methods: Longitudinal prospective single-center registry including 240 patients submitted to TAVI. The discriminative power was evaluated by using the area under the receiver operating characteristic curve (AUC) and net reclassification index (NRI), and plots assessed calibration.
Results: The population had a mean age of 81±7 years and 57% were female. Transfemoral approach was used in two thirds of patients. There were 14 deaths in the first 30 days (5.8%). The ES II and STS were better discriminative than FRANCE 2 by receiver operating characteristic curves (AUC for ES II 0.67, confidence interval CI 95% 0.51–0.84, p=0.029; AUC for STS=0.67, 0.55–0.80, p=0.029, AUC for FRANCE 2 0.53 0.39–0.66, p=0.724). The NRI of ES II versus FRANCE 2 was 0.57 (p=0.019) and the NRI of STS versus FRANCE 2 was 0.21 (p=0.220). ES II, STS and FRANCE 2 overestimated early mortality by 11.2%, 7.2% and 38.8%, respectively.
Conclusions: The ES II was the most discriminative and calibrated score at predicting early mortality in our population.



Abstract P584 – Figure 1

P574 | BEDSIDE
Application of echocardiographic three-dimensional printed left atrial appendage model to guide transcatheter left atrial appendage occlusion

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Background: In recent years, the novel three dimensional printing technology has been introduced for cardiovascular disease clinical application. Percutaneous left atrial appendage (LAA) closure is applied to prevent cerebrovascular embolism due to atrial fibrillation. Previous studies suggested that significant variations in LAA morphology could increase the risks of injury of the LAA and the chances of thrombosis and cardiac tamponade.
Objectives: This study aimed to determine the feasibility of three dimensional (3D) printed left atrial appendage (LAA) models based on 3D transesophageal echocardiography (3D TEE) data and its application value in the interventional LAA closure.
Methods: Eighteen patients who had interventional LAA occlusion underwent pre-procedure TEE and cardiac CT. TEE 3D full volume raw data of the LAA were acquired and post-processed to create a 3D model file. Two modes of the LAA model (cardiac chamber model, cardiac wall model) were printed out by 3D printer. The LAA morphologic classification was assessed by 3D printed chamber model and the LAA dimension measurement was performed on 3D printed wall model. Additionally, preoperative rehearsal was performed on the 3D printed cardiac wall models in the cases with complex LAA structure.
Results: In all the patients, 3D TEE full volume data of the LAA were successfully reprocessed and printed out as 3D LAA chamber models and 3D LAA wall models. The consistency of LAA morphologic classification judgment based on 3D printed models and cardiac CT was 0.918 ($P<0.01$).The LAA ostium dimension measured on 3D printed model was greater than 2D TEE ($P<0.01$) and smaller than X-ray (P=0.02), and the LAA depth was greater than 2D TEE ($P<0.01$) whereas was not significantly different with X-ray (P=0.54).Based on 3D model morphology, there were 3 complex LAA which were recommended a particular occlusion plan after pre-procedure rehearsal on 3D model. The occlusion success rate was 100%.
Conclusions: Echocardiographic 3D printing technique is feasible and have promising value in supporting planning the transcatheter LAA occlusion.

P575 | BEDSIDE
Unilateral carotid artery occlusion is associated with higher stroke rate after TAVI

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Aim: This study aimed to assess the prevalence and effect of carotid artery disease on clinical outcomes after transcatheter aortic valve implantation (TAVI) for severe aortic stenosis.
Methods and results: This single centre retrospective analysis assessed 676 consecutive patients undergoing elective transfemoral TAVI using routinely available balloon-expandable or self-expanding valves between November 2011 and June 2015. Pre-TAVI carotid duplex data, baseline characteristics, and 30-day outcomes according to Valve Academic Research Consortium 2 (VARC-2) were collected. In total 8% (56/676) of cases were excluded due to unavailable carotid or 30-day follow up data, resulting in 620 patients for analysis. A balloon-expandable valve was used in 87% (534/616) of patients and post-dilatation was employed in 32% (199/616). Overall, the rate of 30-day stroke was 3%; the combined VARC-2 safety endpoint criterion was reached in 16.4%. The prevalence of carotid artery disease (CAD) – defined as internal carotid artery stenosis ≥50%, or prior carotid intervention – was 17% (108/620) overall and further subdivided into – unilateral 50–99% stenosis, 12% (76/620); unilateral 70–99% stenosis, 3% (18/620); bilateral ≥50%, 3% (18/620); and unilateral occlusion, 2% (15/620). Overall, there was no significant difference in 30-day stroke rate between patients with and without CAD (4% versus 3%; p=0.773). No strokes occurred in patients with unilateral 50–99%, 70–99%, or bilateral ≥50% stenosis (p=>0.999). However, the group with unilateral occlusion had a significantly higher rate of stroke compared to those without unilateral occlusion (20% (3/15) versus 3% (18/605); p=0.012). Unilateral occlusion remained the only significant variable in multivariate analysis assessing the effect of age, gender, creatinine clearance, EuroSCORE, post-dilatation, diabetes, atrial fibrillation and impaired left ventricular function on 30-day stroke rate (OR 8.1, 95% C.I. 2–31).
Conclusion: Carotid artery disease was common in this real-world TAVI population. Overall, CAD was not associated with worse 30-day stroke rate. However, the stroke rate was significantly higher in the unilateral carotid occlusion subgroup.

P576 | BEDSIDE
Effect of transcatheter aortic valve replacement on pulmonary artery systolic pressure

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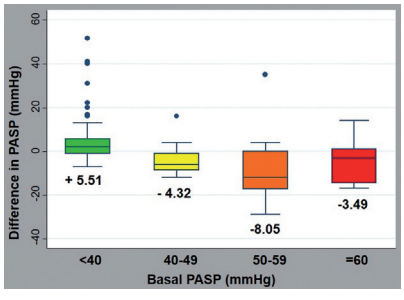
Introduction: Pulmonary arterial hypertension (PAH) is a common comorbidity in patients with aortic stenosis that has been proved to dampen long-term survival after transcatheter aortic valve replacement (TAVR). Nevertheless, the procedure itself may positively impact on right heart haemodynamics, leading to a decrease in pulmonary artery systolic pressure (PASP). The extent of this change in patients with or without PAH has not been well established to date.
Purpose: The aim of our study was to determine the effect of TAVR on PASP, with special attention on patients with a previous finding of PAH.
Methods: An observational study including prospectively collected data from 124 consecutive patients undergoing TAVR in a single tertiary centre was conducted. PASP was estimated by adding the tricuspid regurgitation gradient and estimated right atrial pressure obtained by transthoracic echocardiography before and 48 hours after the procedure. PAH was defined as a PASP ≥40 mmHg prior to the procedure, and classified as mild for PASP between 40 and 49 mmHg, moderate between 50 and 59 mmHg and severe over 60 mmHg.
Results: PASP before and 48 hours after the procedure could not be determined in 29 patients (23.4%) because of lack of acceptable echocardiographic window, absence of tricuspid regurgitation or delayed echocardiographic control. Of the remaining 95 cases, 42 patients (44.2%) had elevated PASP qualifying as PAH prior to the procedure. At 48 hours, PASP decreased in the group with PAH (–5.45 mmHg) while it increased in the group without PAH (5.51 mmHg) in a statistically significant manner ($p<0.0001$).
Considering the different degrees of PAH, the most important decline was observed in the group with moderate PAH (-8.05 mmHg), compared to those with mild (-4.32 mmHg) or severe (-3.49 mmHg), although in a pairwise comparison applying Bonferroni correction, both mild and moderate groups experienced a statistically significant fall compared to the group without PAH (-9.83 mmHg for mild PAH vs no-PAH (p=0.021); -13.54 mmHg for moderate PAH vs no-PAH (p=0.001); and -9.00 mmHg for severe PAH vs no-PAH (p=0.176)).
The decline in PASP was related to diastolic function prior to the procedure, so that the better the function, measured as the ratio of transmitral Doppler early filling velocity to tissue Doppler early diastolic mitral annular velocity, both in the lateral and medial mitral annulus, the greater probability of achieving at least a 5 mmHg drop in PASP (OR =1.25 with p=0.008, 95% CI 1.06–1.48, for the lat-



eral annulus and OR=1.07 with p=0.018, 95% CI 1.01–1.14, for the medial annulus).
Conclusions: In patients with aortic stenosis undergoing TAVR, the procedure can provide a fast and significant decrease in PASP, particularly in patients with PAH of mild and moderate severity and in those with more preserved diastolic function. The clinical impact of this findings should be assessed in further studies.

P577 | BEDSIDE
Percutaneous left atrial appendage closure: clinical results in the medium and long term

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Introduction: Left atrial appendage (LAA) closure is a valid solution for the prevention of thromboembolism in patients with non-valvular atrial fibrillation (AF) and contraindication/high risk for oral anticoagulation (OAC).
In this study we will describe the clinical follow-up results in the medium and long term of patients who underwent percutaneous LAA closure in our center.
Methods: Retrospective analysis of medical records of all patients undergoing percutaneous LAA closure, between May 2010 (first procedure) and November 2015. All patients underwent pre-planning imaging, typically with transoesophageal echocardiography (TEE). The procedure was performed under TEE guidance. It was recommended 1 month of dual antiplatelet therapy (DAPT) and at least 6 months of single antiplatelet therapy (SAPT). On November 2015 we made clinical follow up (100% of patients, median 31 months, IQR 16–47), with MACCE (cardiovascular death, myocardial infarction, stroke or re-intervention) and overall mortality analysis.
Results: Fifty patients (success rate of 92.6%) placed the device, average age 74.9±8 years, mean CHA2DS2-VASc 4.3±1.4, mean HAS-BLED 3.64±1,0. Contraindications for ACO were: severe bleeding or anemia (74%), high risk of bleeding (10%), INR labile or difficult to control (10%) and recurrent embolic events despite INR at therapeutic levels (6%).
Thirty-three patients put the Amplatzer Cardiac Plug and 17 Amplatzer Amulet. The average size of the device was 23.7±3.4 mm and the landing zone, measured by three-dimensional TEE, 20.9±3.1. There was one peri-procedural complication - pericardial tamponade after transseptal puncture, solved with pericardiocentesis. After 1 year 10 patients made no antiplatelet therapy, 27 SAPT, 1 DAPT and 3 patients resumed ACO (1 for ischemic stroke, 1 deep vein thrombosis and 1 by adhering thrombus to the device). Five patients died during follow-up (10%), 2 of them from cardiovascular causes. MACCE incidence was 8%.
On imaging follow up (40 patients), performed by TEE or cardiac computed tomography (CT), there were 2 thrombi adherent to the device, 16 leaks (40%), 2 pericardial effusion: 1 of moderate volume and 1 minimum. One of the patients with thrombus in the LAA died of toxic megacolon, single event in the population with imaging follow-up alterations.
Conclusion: In this group of high risk patients and with contraindications to OAC, percutaneous LAA closure was shown to be a safe procedure with low incidence of peri-procedural complications and long-term events. The prevalence of leaks is higher than the data published, probably by the use of CT in the follow-up imaging. The occurrence of leaks did not correlate with clinical events.

P578 | BEDSIDE
A single-center comparison of the SAPIEN S3 versus the SAPIEN XT transcatheter heart valves

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Aims: The balloon-expandable Sapien 3 transcatheter heart valve (S3) has a lower profile delivery system and an external sealing cuff in order to reduce vascular complications and paravalvular leak (PVL), respectively. The objective of this retrospective analysis was to compare the procedural, 30-day clinical outcomes and one-year mortality of TAVI with the S3 versus the Sapien XT valve (XT) in patients with symptomatic severe AS.
Methods and results: Between March 2010 and October 2015, 507 patients underwent TAVI with the Sapien XT valve and 284 patients received the Sapien S3 valve at our institution through the transfemoral, transaortic or transapical approach. Dedicated clinical research assistants collected clinical outcome data as part of local and national registries.
Mean age was 82.8±7.1 vs. 83.5±7.0 years in the S3 and XT groups, respectively (p=0.14). Mean STS score was significantly lower in the S3 group compared to the XT group (5.3±3.5 vs. 6.4±4.0%, respectively [p<0.0001]). Mean EuroScore 2 was also lower in the S3 group (5.1±4.2 vs. 6.6±4.7%, respectively [p<0.0001]). Pre-dilatation was performed routinely in the XT group (86.8%), which was not the case in the S3 group (17.7%, p<0001). Post-dilation was performed similarly in both groups (S3: 15.9%; XT: 12% [p=0.13]). Percentage of valve oversizing decreased from 22.9% in the XT group to 11.5% in the S3 group (p<0.0001).
The rates of both major vascular complication and greater than mild PVL were almost 4 times lower in the S3 group compared to the XT group (major vascular complication: 2.8 vs. 9.9%, p<0.0001; PVL > mild: 2.4 vs. 9.7%, p<0.0001). However, the rate of new pacemaker implantation was almost twice as high in the S3 group (17.3 vs. 9.8%, p=0.03).
Mortality at 30 days was similar between the S3 and the XT group (3.5% vs. 8.7%, respectively [p=0.21]). Mortality at one year was also similar between groups (S3: 25.7 vs. XT: 20.1% [p=0.24]).
Conclusions: The Sapien S3 valve is associated with lower rates of major vascular complications and PVL compared to the Sapien XT, but higher rates of pacemaker implantation.

P579 | BEDSIDE
Efficacy of percutaneous transluminal pulmonary angioplasty for mid-term outcome in inoperable chronic thromboembolic pulmonary hypertension

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Background: Percutaneous transuluminal pulmonary angioplasty (PTPA) has been demonstrated to improve hemodynamic parameters in patients with inoperable chronic thromboembolic pulmonary hypertension (CTEPH). However, midterm persistent efficacy of PTPA has not already clarified yet.
Purpose: The purpose of this study was to investigate the 3-year outcome and efficacy for pulmonary hemodynamics after PTPA.
Methods: This study retrospectively included 68 patients with inoperable CTEPH patients who underwent PTPA until January 2013. Firstly, we investigated the 3-year survival and revascularization rate in overall. Secondary, hemodynamics parameters such as mean pulmonary arterial pressure (PAP), pulmonary vascular resistance (PVR) and cardiac index (CI) at baseline, after 1 year, 2 and 3 years in 39 of 68 patients were compared.
Results: A median of age, PTPA session performed per a person and dilated vessels per a person was 61 [56 - 69] years old, 4 [3–5] and 15 [11–18] respectively. The 3-year survival and revascularization rate were 97% and 3%. Hemodynamic parameters significantly improved as compared with baseline after PTPA and were maintained effectively (baseline vs After 1 year, 2 and 3 years; PAP: 42 [34–46] vs. 21 [19–25], 20 [16–25] and 21 [19–24] mmHg, P value <0.0001 vs. at baseline for all time points, PVR: 8.3 [6.0–14.5] vs. 2.6 [2.2–3.3], 2.3 [1.6–3.2] and 3.0 [2.1–4.1] wood unit, P value <0.0001 vs. at baseline for all time points, CI: 2.5 [2.1–2.9] vs. 3.1 [2.5–3.6], 3.1 [2.5–3.5] and 2.7 [2.4–3.2] L/min/m^2, P value <0.01 vs. at baseline for all time points).
Conclusion: PTPA could expect not only to improve pulmonary circulation continuously about 3 years at least, and but also to become a favorable outcome.

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Morphological assessment of the left atrial appendage by gray-scale inverted imaging of three-dimensional transesophageal echocardiography: a comparative study with computed tomography

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Objective: To acquire volume-rendered images of the left atrial appendage (LAA) chambers by three-dimensional transesophageal echocardiography (3DTEE) using a novel image mode called Gray Values Inverted Imaging (GVI). This mode of imaging can achieve similar effects to cardiac computed tomography angiography (CCTA) and can accurately assess the morphology of the LAA.
Background: Accurate assessment of LAA morphology is crucial in determining an LAA occlusion strategy. This study aims to create a novel echo volume-rendered imaging technique to visualize LAA morphology.
Methods: Three-dimensional transesophageal echocardiography (3DTEE) and CCTA were performed on 40 patients with atrial fibrillation prior to catheter ablation. Full-volume 3D data were acquired and displayed in gray values inverted (GVI) mode. Threshold segmentation and Interactive segmentation were used to create 3D digital replicas of LAA chambers. The LAA morphology classification, number of lobes and LAA dimensions were analyzed and compared with the data obtained by CCTA.
Results: LAA morphology and measurements were successfully acquired by CCTA and 3DTEE-GVI in all 40 cases. In terms of the LAA morphology classification, 19 cases of chicken wing, 8 of windsock, 9 of cauliflower and 4 of cactus were determined by 3DTEE-GVI, and 20 cases of chicken wing, 8 of windsock, 8 of cauliflower and 4 of cactus were determined by CT-VR. The consistency between these two methods was 97.5%. The measurements of long axis, short axis, ostial area, and depth of the LAA by CT were larger using 3DTEE-GVI than CT-VR (p<0.01); however, agreements existed between them. Formed thrombosis was well displayed by both CT-VR and 3DTEE-GVI as well.
Conclusion: 3DTEE-GVI can acquire LAA morphologic volume-rendered images that are similar to CT volume-rendered images, and it shows promise as a feasible and valuable modality for individual LAA occlusion planning.

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Influence of baseline ejection fraction on the clinical outcome after transcatheter aortic valve implantation in patients with aortic stenosis

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Patients with severe aortic stenosis and reduced left ventricular ejection fraction (LVEF) have a poor prognosis with conservative therapy but a high operative mortality when treated surgically. Recently, transcatheter aortic valve implantation (TAVI) has emerged as an alternative to surgical aortic valve replacement for patients considered at high or prohibitive operative risk. The objective of this study was to analyze the impact the TAVI in patients with severe aortic stenosis with reduced left ventricular ejection fraction.

Methods and results: Between April 2008 and December 2015, 500 patients with symptomatic aortic valve stenosis who were considered high risk or non surgical candidates underwent implantation with the CoreValve prothesis. Echocardiographic data were collected before and after the procedure. Impaired LV function was defined by a left ventricular ejection fraction (LVEF <40%). In 85 patients (17%) had reduced left ventricular ejection function (LVEF <40%).

Results: The patients with reduced LVEF had more comorbidities compared with normal function: Charlson index 4±1.8 vs. 3.2±1.7, P=0.001; Karnosfky index 49±18 vs. 63.8±17.6, P=0.001), Frailty 29.4% vs. 15.4%, P=0.002, worse Logistic EuroSCORE 26.9±16 vs. 15.4±9.7, P<0.001, were more often males (58.8% vs. 37.2%, P=0.01, more symptomatic (NYHA class IV 58.8% vs. 24.3%, p<0.001, were younger (75.7±7.4 vs. 79.8±5, P=0.001) and had a higher prevalence of prior coronary artery disease (62.4% vs. 39%, p=0.001). Patients with reduced LVEF showed a good evolution of left ventricular ejection fraction over time (pre, post-procedure and 1 years): 33.9±5 vs. 44.2±11 vs. 51.7±12%, respectively p=0.001

No difference was observed between the 2 groups in mortality at 30-days (4.7% vs. 3.4%, P=0.548). At a mean follow-up of 53.6±39 months, there was a less mortality in patients with reduced LVEF (12.2% vs. 21.4%, p=0.057).

Conclusions: In patients with severe aortic stenosis and depressed LV systolic function, TAVI is associated with better LVEF recovery and the immediate and long-term outcome after TAVI not seem to differ between patients with an impaired and preserved LVEF.

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Patient selection for a percutaneous ventricular partitioning device implantation after antero-apical myocardial infarction with left ventricular systolic dysfunction: a single center experience

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Background: Parachute is a novel percutaneous ventricular partitioning device proposed to treat patients with ischemic heart failure (IHF) due to an antero-apical myocardial infarction (MI) associated with regional wall motion abnormalities (WMA). However selection of patients who may benefit from this procedure remains a major challenge.

Purpose: In our study we sought to describe the selection protocol adopted by our Center to identify potential candidates to Parachute implantation.

Material and methods: From December 203 to January 2015, 45 consecutive patients with IHF due to an anterior MI occurred at least three months before clinical evaluation, were referred for Parachute implantation screening. Each patient underwent a three-phases selection process including initial clinical evaluation (NYHA class ≥ II) and a secondary screening step based on echocardiographic functional (Left Ventricular Ejection Fraction ≤40 ≥15%, apical/anterior akinesia) and anatomical parameters (Left Ventricular End-Diastolic Diameter LVEDD ≥42 mm and ≤67 mm measured respectively at 3,5 cm and 4,5 cm from LV apex). Finally patients encountering the echocardiographic criteria, were selected for 3D cardiac computed tomography (CT). Patients with cardiac masses, apical thrombus, ventricular septal defect, apical pseudoaneurysm, more than mild valvular heart diseases (VHD), apical trabeculation and calcification in anchor or apical region were deemed not suitable for Parachute implantation, whereas patients fulfilling clinical and instrumental criteria were scheduled for the procedure.

Results: From a total of 45 patients (mean age 69±10 years) with previous anterior MI referred to our Center, 20 patients with NYAH ≥ II were screened according to echocardiographic criteria. Seventeen patients met the echo inclusion criteria and considered eligible to cardiac CT scan, 3 patients were excluded: 1 patient for more than mild VHD, 2 patients for WMA not limited to apical region; however, only 13 patients underwent cardiac CT imaging (3 patients refused further examination, 1 patient recovered with medical therapy). According to CT criteria, 6 patients were considered suitable for Parachute implantation. Causes for exclusion were apical chordae in 2 patients, LV thrombus in 2 patients; excessive apical trabeculations in 1 patient and too large LV in 2 patients. The device was successfully implanted only in 3 patients, since the other suitable 3 patients refused to undergo the procedure. Clinical follow-up of treated patients showed a significant improvement of quality of life and NYHA class.

Conclusion: Although, feasibility and efficacy of Parachute have already been demonstrated in clinical trials, the use of this device in real world is still hampered by the complex selection of suitable patients. Moreover from our experience, it emerges that beside a good selection protocol, motivation and compliance of patients is crucial for a successful implantation program.

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Transeptal and transapical transcatheter mitral valve replacement with a novel self expandable prosthesis: procedural results and follow up

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Background: Mitral regurgitation (MR) is a frequent valvulopathy and often patients do not receive surgical therapy because considered at high risk. Transcatheter mitral valve replacement (TMVR) with dedicated bioprosthesis has been used in small series of patients, the experience is limited with few data on medium-term follow up. We report the institutional experience with the CardiAQ™ Edwards (Edwards Inc., Irvine, CA, USA), a trileaflet bovine pericardial tissue sewed in a nitinol based self-expanding frame, using both transapical (TA) and transseptal (TS) access.

Purpose: Test the feasibility, safety and efficacy of a novel percutaneous transcatheter mitral valve bioprosthesis in human on compassionate base.

Methods: From March to November 2015 were treated four consecutive patients with severe secondary MR, not eligible for mitral valve surgery. All cases were screened by an heart team and evaluated with a trans-esophagel echocardiogram (TEE) and multislice computed tomography. Ethical Committe approval for compassionate use and patient's informed consent were obtained. The procedures were performed under general anesthesia, fluoroscopic and TEE guidance. The TA was used in the first two patients while in the last two the TS access was used, via right femoral vein with a double transseptal puncture: one for the DCS and one for a snare system which facilitated the navigation of DCS from the right atrium to the left ventricle.

Results: Procedural success was obtained in all patients without the use of extracorporeal circulation support. Mean procedural time was 128 min (range 90–180); mean hospitalization was 12 days (range 4–24). All patients were discharged on antiaggregation therapy. Mean follow up was 4,5 months (range 1–9); one patient died on day 35 for non cardiac causes; in the other patients the mean left ventricular ejection fraction improved from 30% (range 20–35%) to 45% (range 40–45%) and the NYHA class from III to I with normal quality of life.

Conclusion: The procedure with CardiAQ Edwards was safe and reproducible using both TA and the TS access. Intraprocedural hemodynamic was stable, the device implantation steps were well visualized with TEE. The mitral bioprosthesis performance has been excellent in all patients, with a marked improvement of functional class in survivors. The TS group had a significantly shorter in hospital stay with faster recover when compared to the TS group. TMVR is a novel and promising therapy for MR in a selected patient population.

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Modifications on mitral regurgitation in patients with severe aortic stenosis undergoing transcatheter aortic valve implantation

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Introduction: Mitral regurgitation (MR) can be found in 74% of patients with severe aortic stenosis (AS) and represents a negative prognostic factor when it is moderate or severe. However, the evolution of MR after transcatheter aortic valve implantation (TAVI) is not well established.

Purpose: This study aims to assess modifications on MR in patients undergoing TAVI, and to identify factors associated with these modifications.

Methods: We conducted an observational study with all patients with symptomatic severe AS who underwent TAVI between January 2009 to April 2015, in two centers of expertise. In addition to severity of MR, we evaluated clinical and echocardiographic data before and one year after intervention, in order to identify whether the regurgitation regressed or worsened, and factors related to these modifications. Patients were divided into two groups according to the severity of the MR before the procedure: Group I consisted of patients with trace or mild MR and group II corresponded to patients with moderate or severe MR. Patients who did not complete one year of follow-up or who had died in the first 30 days of procedure were excluded.

Results: From a total of 270 patients who underwent TAVI, 91 patients met the

inclusion criteria. Considering the whole group of patients, there was a significant change in the degree of MR after TAVI (p=0.013). In Group I (67 patients, 82.7%), 92.5% of patients remained with the same MR grade, while 7.5% showed a worsening after TAVI (p<0.001). In group II (24 patients, 17.3%), there was a regression in the degree of MR in 66.7% of patients, while in the other 33.3% regurgitation remained moderate or severe (p=0.076). Comparisons among patients in group II have shown no differences regarding age (85.12±5.84 vs. 84 25±7.94, p=0.559), presence of coronary artery disease (50% vs. 37.5%, p=0.673), left ventricular function (56.68±13.06 vs. 48.87±16.63, p=0.358) and severity of pulmonary arterial hypertension (57.62±12.10 vs. 52.37±15.28, p=0.391) in patients with regression or maintenance of MR degree respectively. Patients whose MR regressed had less illnesses according to EuroEscore II (5.68±3.32 vs. 11.03±5.30, p=0.023) and STS morbidity (25,87±7,91 vs. 34,88±11,93, p=0,027).
Conclusions: There was significant change in the degree of MR after TAVI, with maintenance in those with mild MR and a trend towards improvement in those with moderate or severe MR. In patients with moderate or severe MR, improvement was correlated with lower preoperative risk scores.

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Increased survival of females with severe aortic stenosis after transcatheter aortic valve implantation compared to surgical aortic valve replacement; a meta-analysis of randomised controlled studies

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Background: Despite signals in several studies suggesting prolonged survival of females versus males undergoing transcatheter aortic valve implantation (TAVI) for severe aortic stenosis, to date no study has examined whether TAVI offers improved survival compared to surgical aortic valve replacement in females with aortic stenosis.
Purpose: The aim of the current meta-analysis was to evaluate the mid-term (up to 2-year) survival in females with aortic stenosis undergoing TAVI versus surgical aortic valve replacement.
Methods: Randomised controlled trials reporting mid-term survival of female patients with severe aortic stenosis treated with TAVI versus surgical aortic valve replacement were searched through MEDLINE, EMBASE and COCHRANE databases and proceedings of international meetings. The results of all studies were combined using a random-effects model to minimize heterogeneity between groups. A 2-tailed alpha of 5% was used for hypothesis testing.
Results: Four randomised controlled trials (reported by different authors at different time points) including a total of N=1844 patients were analysed (PARTNER 1, NOTION, CoreValve US Pivotal Trial, STACCATO). In these studies a total of 831 females were treated with either TAVI (N=422) or surgical aortic valve replacement (N=409). An increased survival was demonstrated in female patients treated with TAVI versus surgical aortic valve replacement, both at 1-year (hazard ratio 0.60, 95% confidence interval: 0.37 to 0.97) and 2-years (hazard ratio 0.65, 95% confidence interval: 0.47 to 0.91) (Figure 1). A similar trend was not observed in the male subgroup., neither in 1 (hazard ratio 1.09, 95% confidence interval 0.78 to 1.51)], nor in the 2-year (hazard ratio 1.02, 95% confidence interval 0.74 to 1.41) follow-up. This beneficial effect could be attributed to the reduced peri-procedural mortality and bleeding complications in the TAVI group alongside the increased post-procedural aortic valve area, which could expedite favourable left ventricular remodelling.

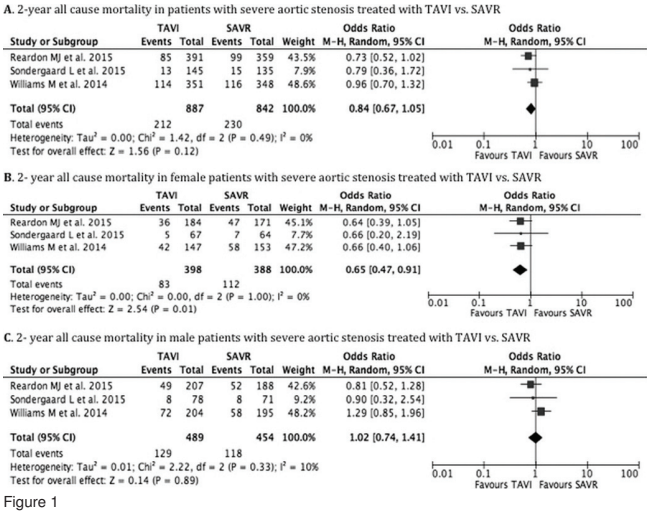

Figure 1

Conclusions: The current meta-analysis suggests an increased mid-term survival in female patients undergoing TAVI versus surgical aortic valve implantation for severe AS.

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Percutaneous left atrial appendage occlusion in high-risk patients: a prospective study of long-term follow up

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Aims: Percutaneous left atrial appendage occlusion may be considered for stroke prophylaxis in patients with non-valvular atrial fibrillation believed to be at high thromboembolic risk and with relative or absolute contraindications to oral anticoagulant therapy. Data on safety of device implantation and long term follow up are presented.
Methods and results: Percutaneous left atrial appendage occlusion was performed using mainly Amplatzer Cardiac Plug and Amulet device in 149 consecutive patients, with mean CHADS2-VASC2 score of 4,1±1,43 and HAS-BLED score of 2,92±1,37. Follow up data were collected over a mean follow up period of 712±142 days, comprising a total implant experience of 267 patient-years. Device implantation was successful in 96,6% of the procedures. The rate of major peri-procedural complications was 4.7%, with no reported mortality. All patients received life long therapy with aspirin 100 mg/die and clopidogrel 75 mg for the first three months. During the follow up we observed one ischemic stroke, two minor bleedings and two major bleedings. The reduction of observed ischemic stroke related to expected events was 79.7%, and the reduction in major and minor bleedings was 41.1%.

Primary end points

	Number of patients (%)	95% CI
Death from any cause	5 (4%)	2,26–11,11%
Cardiovascular	3 (2,4%)	9,90–81,59%
Non cardiovascular	2 (1,6%)	9,90–81,59%
Stroke	1 (0,6%)	2,45–13,67%
Myocardial infarction	2 (1,6%)	0,19–5,62%

Primary end-point: absolute and percent frequencies and 95% confidence intervals of individual components of the primary end point at 12 months. Percentages are calculated on number of patients with at least one follow-up up to 455 days after procedure.

Conclusions: Left atrial appendage occlusion is safe and effective in preventing ischemic stroke in a high-risk of non-valvular atrial fibrillation cohort of patients, both at implantation and during a long follow up period. Both risk of stroke and of bleeding are markedly reduced when compared to anti-platelet therapy alone.

PERIPHERAL INTERVENTIONS

P587 | BEDSIDE
The difference of clinical factors on patency after endovascular therapy for femoropopliteal lesions between stent implantation and balloon angioplasty

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Background: It has not well assessed the difference of clinical factors on patency after endovascular therapy (EVT) for femoropopliteal (FP) lesions between stent implantation and balloon angioplasty (BA).
Methods: This study was an observational study examining consecutive patients performing EVT for de novo FP lesion from July 2004 to March 2015. Study population included 1371 patients 1799 limbs with stent implantation (n=984) or BA (n=815) at index procedure. Kaplan-Meier analysis about restenosis was performed at 3 year to compare the efficacy of stent implantation to BA. Cox proportional hazard model was also performed to investigate clinical factors on patency after EVT.
Results: The incidence of restenosis at 3 year was significantly lower in stent implantation group than BA group (42.1% versus 46.3%, p=.049). On the other hand, there were no significant differences in the incidence of TLR and MALE between two groups (31.8% versus 32.2%, p=.70, 35.2% versus 37.2%, p=.197). Cox proportional hazard analyses were performed to assess the risk factors on restenosis in stent implantation and BA group. In stent implantation group, Diabetes Mellitus (hazard ratio [HR], 1.36; 95% confidential interval [CI], 1.07–1.73; p=.012), hemodialysis (HR, 1.40; 95% CI, 1.04–1.86; p=.029), cilostazol (HR, 0.69; 95% CI, 0.52–0.89; p=.005), and small vessel (HR, 1.52; 95% CI, 1.12–2.02; p=.008). And in BA, hemodialysis (HR, 1.58; 95% CI, 1.20–2.09; p=.001), cilostazol (HR, 0.69; 95% CI, 0.51–0.91; p=.009), and lesion length >100mm (HR, 1.95; 95% CI, 1.33–2.81; p=.0009).
Conclusions: Our study suggests that clinical factors on patency after stent implantation or BA are almost similar. However, restenosis after stent implantation was associated with vessel diameter. On the other hand, restenosis after BA was associated with lesion length.

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Clinical outcomes of endovascular therapy for patients with critical hand ischemia

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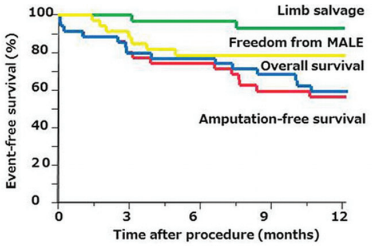
Purpose: Little is known about real-world clinical outcomes of endovascular therapy (EVT) for critical hand ischemia (CHI). The purpose of this study was to investigate the clinical outcomes of EVT for CHI.
Methods: This was a multicenter retrospective study. From January 2003 to December 2013, 36 consecutive patients (40 limbs; mean age 65.7±10.3 years; 52.8% male) who underwent EVT for de novo upper limb artery disease with CHI were retrospectively analyzed. Initial success with balloon angioplasty alone was defined as ≤50%, and stent implantation was ≤30% of residual stenosis without complications. The primary end point was amputation-free survival (AFS) at 12 months. The secondary end points were overall survival (OS), limb salvage (LS), and freedom from major adverse limb events (MALE; any repeat revascularization for a limb and major amputation [i.e., above-the-wrist amputation]) at 12 months.
Results: The mean follow-up duration was 26.8±27.8 months. Fifty percent of patients had diabetes, and 67% of patients were on hemodialysis. Initial success was achieved in 87.5% (35/40) of patients, whereas perioperative complications (POCs) occurred in four patients. The 12-month AFS rate, OS rate, LS rate, and MALE free-rate was 56.4%, 59.4%, 93.1%, and 78.5%, respectively. The predictors of AFS were diabetes (p=0.03), hemodialysis (p<0.001), peripheral artery disease (p=0.003), and the presence of a wound (p<0.001). During the follow-up period, 20 (56%) patients died. Among these patients, a cardiovascular cause accounted for 40% of deaths. Hand symptoms were alleviated in 92.5%, whereas complete wound healing was achieved in only 7.7%.



	Months	0	3	6	9	12
Limb salvage	at risk	40	29	26	24	19
	%	100	96.8	96.8	93.1	93.1
Freedom from MALE	at risk	40	29	26	24	15
	%	100	88.0	78.5	78.5	78.5
Overall survival	at risk	36	29	26	24	21
	%	100	80.7	74.4	68.6	59.7
Amputation-free survival	at risk	36	29	26	21	18
	%	100	80.1	71.5	59.6	56.4

Event-free survival curves after endovascular therapy (EVT)
MALE, major adverse limb events.
The standard errors did not exceed 10% at 12 months.

Conclusion: Endovascular therapy for upper limb artery disease with CHI was feasible, but the prognosis of CHI was extremely poor in real-world clinical practice.

P589 | BEDSIDE
Revascularization by endovascular treatment restores peripheral sensory disturbance in patients with critical limb ischemia

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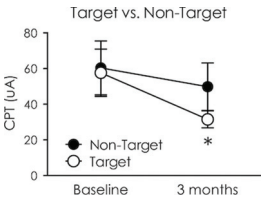
Background: Sensory disturbance (SD) is a common consequence of nerve damage associated with diabetes and acute ischemia. Progression of sensory disturbance with diminished sensation to touch, vibration and temperature is placing patients at high risk for lower extremity ulcers, amputations, and falls. SD has been thought to be progressive and irreversible, and possibly caused by microvascular dysfunction.
Purpose: The purpose of this study was to determine whether endovascular revascularization (EVR) demonstrates quantifiable changes in SD on chronic critical limb ischemia (CLI) patients with neuropathy.
Methods: Cumulative total number of 36 legs from 28 chronic CLI patients who were underwent elective EVR between Sep. 2012 and Apr. 2014 was prospectively enrolled. Ankle-brachial index (ABI) and current perception threshold (CPT) that is an established diagnostic parameter for SD were measured before and 3 months after EVR.
Results: The study population was typically elderly (average age: 68 year-old), and 71% male with a normal body mass index (22 kg/m^2) and diverse comorbidities, including 64% diabetes and 54% maintenance hemodialysis. Target lesions consisted of 11% aortoiliac, 47% femoropopliteal and 81% below-the-knee arteries, including 58% total occlusion. Overall CPT value on target foot was significantly improved at 3 months after EVR (58 to 32 uA, p<0.01). In contrast, EVR did not change CPT on non-target foot (60 to 50 uA, p=0.12). The higher baseline CPT achieved the larger decrease in CPT at 3 months (r=0.84, p<0.01). Additionally, baseline CPT did not correlate with baseline ABI (r=0.06, p=0.80); whereas baseline CPT had significantly positive association with baseline pulse wave velocity (PWV) (r=0.60, p<0.01). However, EVR did not affect ABI (0.91 to 0.98, p=0.27) nor PWV (2288 to 2517 cm.sec, p=0.59). Interestingly, baseline CPT values were not different between DM and Non-DM patients (64 vs. 44 uA, p=0.96), and patients with impaired CPT were similarly prevalent in both populations (68 vs. 55%, p=0.44).



Conclusions: EVR may be a promising option to improve sensory disturbance associated with peripheral ischemic neuropathy. This brand new concept suggests the advantage of EARIER intervention than ulcer formation on ischemic legs.

P590 | BEDSIDE
Optimal antithrombotic therapy for patient with an indication for long term oral anticoagulation undergoing femoropopliteal stenting

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Background: Although the combination of oral anticoagulation (OAC) and aspirin was the antithrombotic treatment initially adopted after coronary stenting, it is unclear that single antiplatelet therapy for patients with an indication for long term OAC are truly efficient and safe compared to standard dual antiplatelet therapy (DAPT) after femoropopleteal (FP) stenting.
Purpose: To evaluate the outcomes of single antiplatelet therapy with OAC after FP stenting.
Methods: This is a single center, retrospective study. Between January 2010 and June 2013, total of 246 patient underwent FP stenting in our hospital. 161 patients underwent standard DAPT after EVT (DAPT group). 12 patients received single antiplatelet and OAC (SAPT+OAC group) 19 patients received DAPT and OAC (DAPT+OAC group). 4 patients suffering acute limb ischemia, 9 patients who dropped out from follow-up and 41 patients receiving other antithrombotic regimens were excluded. Finally total of 192 patients with 249 limbs were enrolled in this study. Primary endpoint is incidence of early stent thrombosis (ST). Secondary endpoint is incidence of major bleeding complication. We also compared the clinical outcomes as primary patency, incidence of stent re-occlusion, major adverse limb events (MALE), and all-cause death.
Results: Mean follow-up period was 902±597 days. Backgrounds of 3 groups were almost similar. Incidence of ST in 90 days were 2.9% (6 patients) in DAPT group, 0% in SAPT+OAC group and 3.9% (1 patient) DAPT+OAC group (p=0.75) 2 year incidence of major bleeding complications was statistically significant higher in DAPT+OAC group. (2.5% vs 0% vs 26.3%; p<0.0001) Major bleeding complication occurred in 9 patients. Over half of them (5 patients; 56%) suffered intracranial bleeding. Among them, 3 patients died for cerebral bleeding. Clinical outcomes as primary patency, incidence of stent re-occlusion, MALE and all-cause death were not significant different between 3 groups.
Conclusions: SAPT+OAC is not inferior to DAPT and DAPT+OAC for avoidance of ST. DAPT+OAC significantly leads to higher incidence of bleeding complications. Single antiplatelet therapy with OAC has possibilities to be optimal thrombotic therapy for patient with an indication for long term OAC after femoropopliteal stenting.

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A comparison of combined balloon expandable and self-expandable nitinol stent vs double self-expandable nitinol stents for long aorto-iliac disease

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Background: The strategy of intervention for long aorto-iliac (AI) disease was not well known.
Purpose: The aim of this study was to compare the outcomes of balloon-expandable/self-expandable nitinol stent and double self-expandable nitinol stents for long AI disease.
Methods: From November 2005 to March 2015, 1160 patients (915 male,1555 limbs) underwent endvascular therapy for AI lesion. 191 consective patients (210

limbs, mean age 73, 77% male) implanted two stents for de-novo long AI lesion and were analyzed retrospectively.
We divided into combined stent group (balloon-expandable nitinol stenting for common iliac artery/self-expandable nitinol stent for external iliac artery and double self-expandable nitinol stent group).
Outcome measures were primary patency (PP), secondary patency (SP) and major adverse limb events (MALE; any repeat revascularization for limb and leg amputation).
Results: At 7 years, no significant difference was observed in PP, SP and freedom from MALE.
On multivariate analysis, female gender, dyslipidemia and age >75 were found to be independent predictors of primary patency for de-novo long AI lesion.there are no difference between two groups in PP (hazard ratio, 0.64, 95% confidential interval: 0.18–2.10; adjusted P=0.47),SP (hazard ratio, 3.48, 95% confidential interval: 0.32–37.8; adjusted P=0.28) and freedom from MALE (hazard ratio, 0.75, 95% confidential interval: 0.39–1.43; adjusted P=0.38)
Conclusions: PP, ASP, AP and freedom from MALE showed no significant difference between two groups. Dyslipidemia, age >75 and female gender were found to be independent predictors of primary patency for long AI disease.

P592 | BEDSIDE
Prevalence and importance of below the pedal artery disease for wound heal in the patients with critical limb ischemia

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Background: Tissue microcirculation is considered to be important for wound heal in the patient with critical limb ischemia (CLI). However, below the pedal artery (BTP) disease for example occlusive lesion in metatarsal artery or digital artery have not been evaluated. So, the aim of this study was to evaluate the risk factors of BTP disease and correlation between wound heal and BTP disease.
Methods: We retrospectively reviewed the data of consecutive patients with CLI. Sixty nine patients with CLI (Rutherford 5) and successfully treated at least one vessel to the foot were enrolled. We judged whether there was BTP disease or not from final digital subtraction angiograms of endovascular therapy (EVT).
Results: In the 69 limbs, 21 limbs had BTP (30.4%). Patients with chronic kidney disease (CKD) and daily dialysis was significant risk factor of BTP disease. Wound heal within 3 months were obtained in 45 patients (65%). Wound heal <3M rate in the patients without BTP disease was significantly higher than patients with BTP disease (94% vs. 24%, P<0.001).
Conclusion: Presence of BTP disease was associated with CKD and delayed wound healing. It is hard to treat, but it is thought that it is extremely important to evaluate BTP disease to decide a treatment strategy after EVT.

P593 | BEDSIDE
Perioperative and long term outcomes of endovascular treatment for renal artery stenosis

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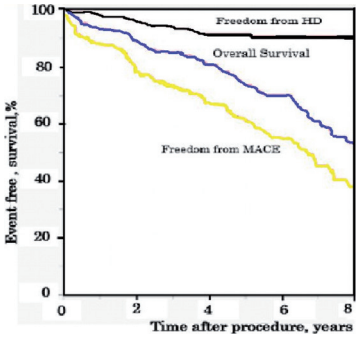
Purpose: To investigate the perioperative and long term of endovascular therapy (EVT) for renal artery stenosis Major Adverse Cardiac Events (RAS).
Methods: This study analyzed the outcomes of 296 patients (351 lesions) who underwent EVT for RAS from 1999 to June 2015 in an hospital in Japan. Primary endpoint is all cause death. Secondary endpoints are the introduction of hemodialysis (HD) and (MACE).
Result: The mean follow-up was 57±39 months. Procedure success was 100%. The perioperative complication rate was 5.69%. The overall survival rates were 93.3±1.5%, 85.3±2.2%, 76.9±2.8% at 1, 3, and 5 years, respectively. The freedom from the introduction of HD rates were 97.8±0.9%, 93.8±1.5%, and 90.4±2.1%. The freedom from MACE rates were 88.4±1.9%, 75.9±2.6%, 64.7±3.2%.There were 55 deaths during follow-up. Half of them were due to cardiovascular disease. On multivariate analysis, single kidney (hazard ratio [HR] 2.4, 95% 1.48 to 3.78, P<0.01), CKD (HR 2.3, 95% 1.27 to 4.06, P<0.01), Smoker (HR 1.72, 95% 1.07 to 2.74, P=0.03) were negative independent predictors of death.
CKD (HR 8.4, 95% 1.12 to 63.1, P=0.04), eGFR 20% down after EVT (HR 7.59, 95% 2.74 to 21.04, P<0.01) were negative independent predictors of the introduction of HD.
eGFR 20% down after EVT (HR1.8, 95% 1.04 to 2.28, P<0.01), CKD (HR 1.8, 95% 1.14 to 2.99, P=0.01), Smoker (HR 1.29, 95% 0.87 to 1.91, P=0.03) were negative independent predictors of MACE.
Conclusion: In terms of perioperative complications, survival rates, the introduction of HD rates, and MACE rates, EVT for RAS afforded acceptable outcomes.



		Time after procedure					
		0	1 y	2 y	3 y	4 y	5 y
Over all survival	No. at risk	297	255	230	195	162	133
	%	100	93.3	90.2	85.3	82.4	76.9
Freedom from HD	No. at risk	297	252	223	186	153	124
	%	100	97.8	96.2	93.8	92.3	90.4
Freedom from MACE	No. at risk	297	241	209	174	141	113
	%	100	88.4	82.2	75.9	70.3	64.7

P594 | BEDSIDE
Clinical efficacy of fractional flow reserve for assessing the functional optimality of stenting and for predicting restenosis in femoropopliteal disease

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Background: Fractional flow reserve (FFR) is useful tool to evaluate functional optimality after stenting for coronary artery disease. However, the clinical efficacy of post-stenting FFR for femoropopliteal disease remains unclear. We evaluated clinical impact of post-stenting FFR on future restenosis in femoropopliteal disease, and also evaluated IVUS findings that associated with low FFR value.
Methods and results: Between July 2013 and June 2014, we prospectively measured post-stenting FFR in 51 femoropopliteal lesions. We calculated post-stenting FFR, and investigated the relationship between FFR value and restenosis at 12 months. Post-stenting FFR was significantly lower in the restenosis group (0.85±0.07 vs. 0.93±0.05, P=0.001). Receiver operator characteristics curve (ROC) analysis showed that post-stenting FFR had good ability to predict future restenosis (area under the curve: AUC 0.84, 95% CI 0.71–0.96, P=0.001). The best post-stenting FFR cut-off value for predicting restenosis was 0.92. The restenosis rate at 12 months was significantly lower in the high post-stenting FFR group (>0.92) than in the low post-stenting FFR group (≤0.92) (4.5% vs. 35.7%, P=0.008). In IVUS findings, minimum stent area (MSA) was significantly smaller (14.5±4.9 vs. 21.3±6.8, P=0.001), stent expansion defined as MSA divided by reference cross sectional area was significantly poorer (0.64±0.26 vs. 0.83±0.22, P=0.009), and stent eccentricity defined as minimum stent diameter divided by maximum stent diameter was also significantly poorer (0.73±0.12 vs. 0.84±0.11, P=0.002) in the low post-stenting FFR group (≤0.92). In addition, MSA, stent expansion, and stent eccentricity were significantly correlated with FFR value (MSA: r = 0.458, P=0.002, stent expansion: r = 0.344, P=0.022, stent symmetry: r = 0.472, P=0.001). ROC analysis showed MSA had the highest AUC (0.798, P=0.001) and best cut-off value to predict low post-stenting FFR (≤0.92) was 14.7mm^2 (sensitivity 0.950, specificity 0.542).
Conclusions: Post-stenting FFR is useful for evaluating functional optimality and predicting restenosis in femoropopliteal disease. Small MSA assessed by IVUS was associated with low post-stenting FFR.

P595 | BEDSIDE
Clinical impact of infection severity in critical limb ischemia with tissue loss after endovascular treatment

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Purpose: Critical limb ischemia (CLI) with infectious wound has been recognized to have a poor prognosis. In addition, evaluation of the infection severity is recommended as shown by WIFI risk score (Wound, Ischemia, Foot Infection). However, little is known how infection severity influence clinical outcome of CLI patients with tissue loss.
We investigated the impact of infection severity on clinical outcomes in CLI with tissue loss after endovascular treatment (EVT).
Method: Between April 2007 and August 2014, we enrolled 263 patients (328 limbs) who received EVT for CLI with tissue loss. In the limb examined, 369 individual wound existed. We evaluated wound infection using the Infectious Disease Society of America classification (class 0: uninfected wound, n=104; class 1: local infection involving only the skin and the subcutaneous tissue, n=116; and class 2: local infection with erythema >2 cm, or involving structures deeper than skin and subcutaneous tissues, n=135; class 3: Local infection with the signs of SIRS, n=14). We also investigated the wound healing rates at 12 months and limb salvage and major amputation-free survival rates 2 years after EVT.
Results: The wound healing rate at 12 months 0, 1, 2 and 3 were 84%, 68%, 32% and 7%, respectively (log-rank P<0.0001). The limb salvage and major

amputation-free survival rates at 2 year were lower in mild infectious wounds than severe infectious wounds (limb salvage rate: 97%, 92%, 71%, and 15%, respectively; P<.0001; major amputation-free survival: 70%, 67%, 45% and 10% respectively; P<0.0001). In only Rutherford 5, the wound healing rates at 12 months and limb salvage and major amputation free survival rates at 2 year were stratified according to wound infection (wound healing rates: 79% in class 0, 1 and 42% class 2. 3; P<0.001; limb salvage rates: 95% in class 0, 1 and 75% in class 0, 2; P<0.001; major amputation-free survival rates: 69% in class 0, 1 and 52% in class 2, 3 P=0.048).
Conclusion: Wound infection affects the clinical outcomes of CLI with tissue loss.

P596 | BEDSIDE
Acceptable long term clinical outcomes after stent implantation with full-jailed deep femoral artery - a retrospective multicenter registry

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Purpose: To clarify the difference in clinical outcomes of patients after ostial superficial femoral artery (SFA) stenting in accordance to jailing or not jailing entry of deep femoral artery (DFA) entry.
Methods: This retrospective study included 125 successful endovascular procedures performed at 7 institutes in Japan which implanted stents in ostial SFA lesions between January and December 2013. All procedures were allocated to 2 groups according to the condition of DFA after stenting: not jailed or partially jailed (NPJ, n=71) and fully jailed (FJ, n=54). Style of stent deployment was dependent on operator's choice. Overall incidence of target lesion revascularization (TLR, consistent of repeat endovascular treatment for the target lesion, and bypass surgery for the target limb), and major adverse limb events (MALE, consistent of major amputation and TLR) at 12 and 24 months were evaluated.
Results: Baseline clinical and procedural characteristics were similar in both groups. There were 24 (33.8%) and 17 (31.5%) CLI patients in the NPJ and FJ group, respectively (p=0.85). Three patients in the FJ group (5.6%) with diseased DFA ostia developed DFA occlusion after stenting. There were no significant differences between the NPJ and FJ group in incidence of TLR (16.0% vs 33.3%, p=0.08, 37.1% vs 53.6%, p=0.21) and MALE (20.0% vs. 33.3%, p=0.22, 41.7% vs. 53.6%, p=0.45) at 12 and 24 months respectively. However, among patients who received stents smaller than 7 mm in diameter, there was a significantly higher incidence of TLR in the FJ group compared to the NPJ group at 12 months (75.0% vs. 23.5%, p=0.028).
Conclusions: Stent implantation fully jailing the DFA entry does not worsen clinical outcome. However, fully jailing might be avoided for diseased DFA orifices or when smaller stents are implanted.

P597 | BEDSIDE
Comparison of clinical outcomes of aggressive stent implantation versus balloon angioplasty for chronic total occluded superficial femoral artery

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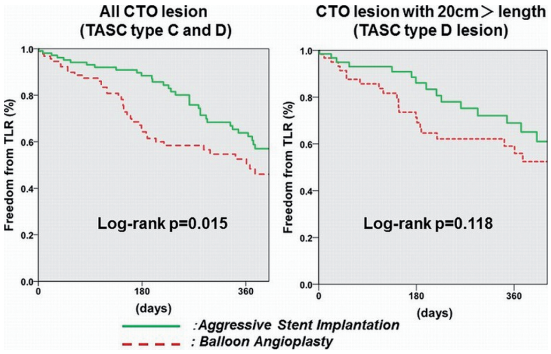
Background: Although endovascular treatment (EVT) to superficial femoral artery (SFA) has become the first line therapy in clinical practice, it's thought that vessel's patency after EVT is dependent on the lesion characteristics. Despite advances in revascularization techniques and devices, the trans-atlantic inter-society consensus (TASC) type C and D still remains a challenging issue in the field of EVT, in especially longer chronic total occlusion (CTO).
Purpose: We investigated the direct comparison of the effect on target lesion revascularization (TLR) of aggressive stent implantation versus balloon angioplasty for SFA lesion with long CTO from three well-experienced hospitals.
Methods: From January 2011 to December 2015, 247 lesions in 183 patients were received EVT for long CTO lesion of SFA in 3 hospitals. In Ohashi hospital, 103 lesions with long CTO were treated by balloon angioplasty (n=103), whereas 136 patients were treated by aggressive stent implantation in other 2 hospitals. SFA lesions with CTO were also analyzed according to the TASC type C (15cm ≤ CTO length ≤20cm) and D (20cm < CTO length). Primary endpoint was clinically driven TLR at 12 months after EVT.
Results: The mean age of patients was 72 years, 76% of them were males, 42% had on hemodialysis. Clinical presentation were 140 claudication and 107 critical limb ischemia.
The TASC type C and D were 75 and 172 lesions, respectively. TLR rate at 12 months was significantly higher in balloon angioplasty group compared with aggressive stent implantation group (40.8% vs. 27.2%, p=0.001). Regarding patients with the TASC type D, there was no different in TLR rate between balloon angioplasty and aggressive stent implantation (39.4% vs. 29.8%, p=0.118). However, aggressive stent implantation showed the superiority with respect to TLR rate in non-hemodialysis patients of TASC type D (46.3% vs. 27.7%, p=0.047).



Conclusion: The strategy with aggressive stent implantation was effective in SFA lesion with relatively short CTO. However, in longer CTO lesion that is TASC type D, the therapeutic efficacy of aggressive stent implantation diminished. It might be influenced by not only lesion characteristics, but also patient characteristic.

P598 | BEDSIDE
Predictors of the blood pressure improvement in patients with renal artery stenosis referred to renal artery stenting

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In the light of randomized trials, renal artery stenting (PTA) seems to have questionable effect on clinical outcome. However, smaller observational studies indicated that still there might be a field for intervention in the selected subset of subjects.
Therefore, the present study aimed to investigate what features distinguish subjects who improved in terms of the systolic blood pressure (SBP) reduction after PTA from those who did not benefit.
Methods: Study enrolled 118 (57M, 63.9±8.8y.) consecutive patients referred to PTA for ill-controlled hypertension. Blood pressure control was obtained using 24-hour ABPM, with assessment of the mean SBP and DBP, the loads of SBP and DBP in patients on antihypertensive drugs, before PTA and 12 months after PTA. Study group was divided retrospectively with regard to achieved SBP control. Subjects in whom SBP decreased by at least 20 mmHg during 12 month FU after PTA were comprised in Group I: 25 (21%) patients. Group II comprised 93 (79%) subjects in whom SBP reduction was lower than 20mmHg or deteriorated.
Results: Analysis showed that Group I vs Group II patients had higher renal artery stenosis (RAS) degree (75.2±14.7% vs. 66.7±10.5%, p=0.001). The initial SBP, DBP, SBP load and DBP load were significantly higher in Group I vs Group II subjects (154.8±16.7 vs 130.6±16.4 mmHg, p<0.001; 86.1±11.7 vs. 72.7±8.8mmHg, p<0.001; 77.9±18.7 vs. 40±28.2 mmHg, p<0.001, and 50±26.4 vs. 21±18.5, p<0.001, respectively). The mean number of blood pressure lowering agents was similar in Group I and Group II subjects, both before (3.44±1.3 vs. 3.26±1.1, p=0.479) and 12 months following PTA (3.12±1.4 vs. 2.95±1.2, p=0.541). This may indicate that the effect of BP values decrease was associated rather with PTA, than drug regiments. On backward logistic multivariable analysis, independent predictors of significant blood pressure reduction after the PTA were: higher RAS degree (OR=1.24; 95% CI 1.07–1.44; p=0.006), higher initial SBP (OR=1.27, 95% CI 1.03–1.56; p=0.026), higher initial DBP load (OR=1.33, 95% CI 1.09–1.64; p=0.007) and bilateral RAS or RAS of single functioning kidney (OR=1.16, 95% CI 1.00–1.36; p=0.053).
Conclusions: Among patients after PTA, about 20% are high responders with regard to blood pressure control. Positive effect following PTA of RAS can be expected in patients with higher initial SBP and DBP parameters, with high-grade RAS and subjects with bilateral RAS or RAS of single functioning kidney. Our results indicate that PTA of RAS is justified in carefully selected patients.

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Resolution of ischemic symptoms following percutaneous angioplasty for a symptomatic subclavian artery stenosis

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Background: One third of the patients with subclavian or innominate artery occlusive disease (SAS) experiences symptoms of posterior fossa ischemia (PFI), upper limb claudication (ULC) or cardiac ischemia due to subclavian-coronary steal (SCS) in some instances.
Purpose: The study aimed to assess the impact of percutaneous angioplasty (PTA) of SAS on long-term symptom resolution and to determine factors related with SAS recurrence.
Methods: 232 consecutive subjects after successful PTA of SAS (61.9±8.4y.o., 53.4% men) were evaluated for long term symptom resolution as well as incidence of restenosis (RS) during a mean follow-up time of 101±40 (range 5–188) months.
Results: PTA resulted in resolution of ULC, dizziness, imbalance, visual disturbances, syncope and SCS in 98.7%, 85.4%, 94.4%, 97.1%, 97.8%, and 100% subjects respectively, in short-term observation. RS was found in 37 (15.9%) patients in long term observation. The ULC, dizziness, imbalance and SCS were significantly more frequent in patients with SAS recurrence, as compared to patients with patent artery (65.9 vs. 3.1%, P<.001; 63.4 vs. 19.4%, P<.001; 26.8 vs. 9.4%, P=.005 and 100% vs. 15.4%, P=.018, respectively). Smaller stent diameter (OR=0.87,CI: 0.79–0.96,P=.004), implantation of ≥2 stents to cover the lesion (OR=1.15,CI: 1.05–1.26,P=.003), concomitant stenosis in the carotid or vertebral artery (OR=1.10,CI: 1.01–1.21,P=.036), hsCRP level (OR=1.20,CI: 1.09–1.31,P<.001), and HDL level (OR=0.91,CI: 0.82–0.98,P=.021) were independently associated with RS risk, while recurrence of ULC (RR=1.71, CI: 1.55–1.90, P<.001), dizziness (OR=1.26, CI: 1.14–1.39, P<.001), limb paresthesia (OR=1.14, CI: 1.04–1.25, P=.005), and angina in subjects after CABG (OR=1.11, CI: 1.01–1.21, P=.024) were associated with RS/SAS progression following PTA.
Conclusions: Angioplasty of SAS leads to symptom resolution in most patients. ULC, dizziness and angina recurrence are predictors of RS or SAS progression, while hsCRP, smaller stent diameter, number of implanted stents predict RS.

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Drug-eluting stent versus balloon angioplasty for treatment of femoropopliteal in-stent restenosis

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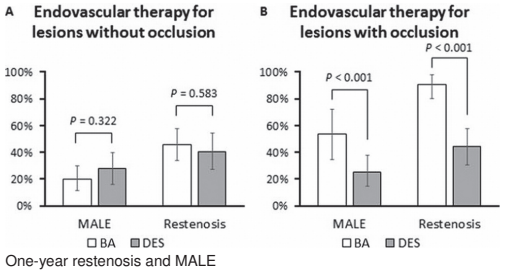
Purpose: To compare drug-eluting stent (DES) implantation with balloon angioplasty (BA) in the treatment of femoropopliteal in-stent restenosis (ISR).
Methods: We retrospectively compared data of 112 patients originally enrolled in the ZilvEr PTX for tHe Femoral ArterY and Proximal Popliteal ArteRy (ZEPHYR) registry with 119 femoropopliteal ISR lesions treated with a drug-eluting stent (Zilver PTX®) with data of 116 patients with 133 lesions treated with BA after stratifying by lesions with and without occlusion. The primary outcome measure was the 1-year incidence of restenosis.
Results: A total of 101 lesions (40%) were occlusive. In the subgroup without occlusion, there was no significant difference in the 1-year incidence of restenosis or major adverse limb events (MALE) between DES and BA (40.5% vs. 45.7%; p=0.583, and 27.8% vs. 20.7%; p=0.322, respectively). In the subgroup with occlusion, DES implantation was associated with a significantly lower incidence of restenosis and MALE (44.1% vs. 90.3%; p<0.001, and 25.5% vs. 53.6%; p<0.001, respectively) than BA. Multivariate analysis confirmed that DES implantation had a significant independent negative association with the risk of restenosis in the subgroup with occlusion (p=0.006), but not in the subgroup without occlusion (p=0.617).



One-year restenosis and MALE

Conclusion: DES implantation may be more effective than BA in the management of femoropopliteal ISR with occlusion, but equally effective to BA in ISR without occlusion. These results require confirmation in prospective randomized studies.
Acknowledgement/Funding: General Incorporated Association Japan Endovascular Treatment Conference

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Zilver PTX post-market surveillance study of paclitaxel-eluting stents for treating femoropopliteal artery disease in Japan: 24-month results

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Objective: The paclitaxel-coated Zilver PTX stent is the first drug-eluting stent (DES) approved for the superficial femoral artery. Previously, the results from a large randomized study and a complementary, large single-arm study supported the safety and effectiveness of the DES. This multicenter, prospective, post-market surveillance study in Japan evaluates the paclitaxel-coated Zilver PTX stent in real-world patients with complex lesions.
Methods: The first approximately 900 patients in Japan treated with the DES were enrolled in the study. Clinically-driven target lesion revascularization (TLR) was defined as re-intervention performed for ≥50% diameter stenosis after recurrent clinical symptoms of peripheral artery disease. Clinical benefit was defined as freedom from persistent or worsening symptoms of ischemia. Patency was evaluated by duplex ultrasound where physicians considered this standard of care.
Results: In total, 907 patients with 1,075 lesions were treated with 1,861 DES at 95 institutions in Japan. The current study enrolled patients with more complex disease compared to previous trials of this DES, including significantly more chronic kidney disease (p<0.01, 44%) and higher Rutherford classification (p<0.01, 22% critical limb ischemia). The lesions were also significantly longer (p<0.01, mean ~15cm) and more challenging (p<0.01, 19% in-stent restenosis, 7% with no runoff vessels). Follow-up through 24 months was obtained for >85% of eligible patients. The rate of site-reported total occlusion of suspected thrombotic origin through 24 months remains low. Freedom from TLR was 85.0%, and clinical benefit was 79.3% through 24 months. The 24-month patency rate was 72.3%.
Conclusions: This study continues to show positive, long-term outcomes for the Zilver PTX stent in complex lesions providing further evidence for the benefit of the Zilver PTX stent.

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Incidence, Predictors, and Clinical Outcomes of Slow Flow Phenomenon after Infrapopliteal Balloon Angioplasty

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Background: Slow flow after infrapopliteal balloon angioplasty sometimes occurs, but the impacts are less known. So, the aim of this study is to investigate incidence, predictors, and its clinical relevance to slow flow phenomenon after infrapopliteal balloon angioplasty.
Methods and results: This study is a retrospective, single center study with CLI consecutive 176 patients (107 men; mean age 72±11 years) in 263 limbs and 596 lesions who underwent EVT for infrapopliteal lesions from January 2012 to May 2015. The overall technical success rate was 87%. Of these lesions, 96 lesions which were presented with slow flow or no-flow immediately after angioplasty were detected. We analyzed predictors and compared clinical outcomes of slow flow after angioplasty.
CTO and severe calcification were more common and lesion length was longer in slow flow group. (63% vs 86%; p<0.0001, 12% vs 59%; p<0.0001,131±81mm vs 193±84mm; p<0.0001) After multivariate analysis, severe calcification (OR: 6.5 95% CI:3.0–14.7, p<0.0001), and CTO (OR: 8.4 95% CI:1.6–15.4, p=0.008) were demonstrated as the predictors of slow flow phenomenon. Kaplan-Meier curve showed freedom from major amputation and wound healing at 1 year was significantly lower in slow flow group (92% vs 67%; log rank p<0.0001, 79% vs 52%; log rank p=0.001). Cox proportional hazard analysis revealed age (HR: 1.06 95% CI:1.01–1.12, p=0.01), BMI<18.5 (OR: 3.6 95% CI:1.04–10.8, p=0.04), Rutherford 6 (HR: 4.7 95% CI:1.5–14.3, p=0.001), HD (HR: 3.0 95% CI:1.01–10.5, p=0.05), and slow flow phenomenon (HR: 4.1 95% CI:1.5–10.5, p=0.006) were independent predictors of major amputation.
Conclusions: Slow flow phenomenon after infrapopliteal balloon angioplasty occurred in 16% and its independent predictors were severe calcification and CTO. Slow flow phenomenon might cause poor outcomes.

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Clinical outcome, long-term survival and prognostic factors of cardiovascular events in patients treated with percutaneous angioplasty for renal artery stenosis

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Studies indicate that patients with renal artery stenosis (RAS) are at high risk of cardiovascular events (CVE), e.g. myocardial infarction (MI), stroke (IS), and cardiovascular death (CVD). However, the impact of renal artery stenting (PTA) in subjects with RAS on the long-term prognosis and factors associated with this unfavorable prognosis are still debated.

The present study aimed to evaluate impact of PTA on renal function, blood pressure and survival in patients treated with PTA for RAS, as well as to identify independent risk factors of CVE in long-term follow-up.

Methods: Two-hundred-and-forty renal artery angioplasty procedures were performed in 208 consecutive subjects (113M, mean age 64.5±11.9y.) for the mean RAS degree of 70.3±13.4% between June 1997 and December 2015. The immediate and long term outcome of PTA was assessed with regard to renal function, blood pressure values and incidence of restenosis.

Prevalence of CVE, including CVD, MI, and IS were recorded prospectively. The potential prognostic risk factors of CVD/MI/IS were analyzed.

Results: The procedural success was 239/240 procedures. Mean creatinine level decreased from pre-PTA: 133±62 to 116±55.9 at 6 month, and to 117±58.6 μmol/L at 12 months after PTA (p=0.003). Systolic blood pressure changed from 142±21.8 before PTA to 130±15.9, at 6 month, and to 130±15mmHg at 12 month ($p<0.001$), while diastolic blood pressure from 78±12.3 to 74±9.2, and to 73.7±9.5 ($p<0.001$) respectively. The mean number of blood lowering agents was reduced from 3.33±1.2 before PTA to 3.06±1.3 at 12 month following PTA (p=0.003).

Restenosis occurred in 24/207 (11.6%) patients and it was treated with repeated PTA. Factors associated with restenosis were: hyperlipidemia (OR=1.23, 95% CI: 1.06–1.42, p=0.005) and diabetes (OR=1.15, 95% CI: 1.0–1.33, p=0.055).

During the mean follow-up period of 62.1±37 (range 1–213) months, CVE occurred in 54 (26%) patients (24 CVDs, 17 non-fatal MIs, 13 non-fatal ISs). Initial serum creatinine (OR=1.25; 95% CI:1.04–1.51, p=0.02) and creatinine at 12 month (OR=1.18; 95% CI:1.03–1.35, p=0.015), concomitant coronary artery disease (OR=1.19; 95% CI:1.04–1.36, p=0.011), and SBP at 12 months after PTA (OR=1.16; 95% CI:1.02–1.33, p=0.025) were independently associated with CVD/MI/IS risk.

Conclusions: PTA of RAS resulted in significant reduction of creatinine level, blood pressure values and the number of blood lowering agents. During mean 5-year period following PTA of RAS, the CVE rate was 26%. Factors independently associated with CVE risk were pre procedural and 12 month levels of serum creatinine, SBP at 12 months following PTA and concomitant coronary artery disease. Restenosis occurred in 11.6% and it was associated with hyperlipidemia and diabetes.

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Long term clinical impact of subintimal angioplasty for infrapopliteal arterial occlusions in patients with critical limb ischemia

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Objective: The relationship between subintimal angioplasty (SA) for infrapopliteal arterial occlusions and clinical outcomes in patients with critical limb ischemia (CLI) has received little research attention. We sought to compare the efficacy and long-term outcomes of SA with transluminal angioplasty (TA) for infrapopliteal arterial occlusions in patients with CLI.

Methods: We reviewed 308 CLI patients treated with endovascular therapy from 2006 through 2013. We classified patients into two groups according to angioplasty technique: TA (n=190), and SA (n=118) group. The primary endpoint was major adverse limb events (MALE), a composite of re-intervention, limb salvage, and unplanned amputation.

Results: Significant angiographic differences between TA and SA group included complete vessel occlusion (59.5% vs. 79.7%; $P<.001$), target lesion length (205.6±130.1mm vs. 249.3±118.0mm; P=.003), severe calcification (31.4% vs. 14.4%, P=.001), and diameter stenosis (93.0±10.6% vs. 97.2±6.8; $P<.001$). Procedural success rate was 90.7% in SA group, whereas TA was successful in 160 patients (84.2%, P=.104). There were no significant differences in procedural complication including major vascular ruptures. The overall median follow-up duration for all patients after procedure was 24.5 months. MALE (34.1% vs. 39.7%; P=.500), re-intervention (24.6% vs. 29.3%; P=.383), limb salvage (4.3% vs. 5.6%; P=.280), and unplanned amputation (19.1% vs. 19.7%%; P=.944) occurred similarly in both groups at 2-year follow-up.

Clinical adverse events at 2 years

	TA (n=190)	SA (n=118)	P-value
Composite of MALE	44 (34.1)	29 (39.7)	0.500
Re-intervention	34 (24.6)	24 (29.3)	0.383
Limb salvage	4 (4.3)	3 (5.6)	0.280
Unplanned any amputation	22 (19.1)	13 (19.7)	0.944
All-cause mortality	15 (12.1)	8 (11.8)	0.722
Cardiac death	9 (7.3)	2 (3.2)	0.346

Conclusions: SA was an effective revascularization technique performed safely for long, totally occlusive, and non-calcified infrapopliteal lesions. Compared with TA, clinical outcome of SA showed non-inferiority with respect to MALE. Therefore, SA can be considered an option for infrapopliteal artery revascularization in patients with CLI.

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Subclavian CTO stenting using bilateral retrograde radial approach

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Background: Transradial approach (TRA) is the preferred access site for PCI (percutaneous coronary intervention) in experienced radial centers. Recently TRA is gaining recognition in the peripheral interventions. There are still insufficient randomized studies and published data regarding TRA interventions of subclavian artery occlusions.

Purpose: To assess the procedural safety and results of subclavian artery stenting using bilateral retrograde radial approach.

Methods: We report 27 consecutive patients that underwent retrograde opening and stenting of subclavian artery occlusions using TRA with contralateral control from the opposite TRA. Primary outcome was procedural success rate. Secondary outcomes were: presence of procedural complications, restenosis, MI, stroke or death and presence of any type of access site bleeding events. The same technique was used in all patients: 6F guiding catheter Judkins right 4.0 was most frequently used (n=20) for coronary hydrophilic wire retrograde crossing of the occlusion and ballon predilatation. Exchange of wire was made with 0,035 guide wire. Balloon expandable stents were implanted solely through the short hydrophilic sheath, with contralateral contrast check. We used contralateral injection strategy to confirm proper wire advancement within the lesion and optimal stent positioning. Most frequently used guide wire for CTO oppening was CROSS IT 400. The average stent diameter was 7 mm (range 5.0–9.0 mm), and the average stent length was 29, 1 mm (range 15–80 mm). One year clinical follow up and duplex ultrasonography was done in all patients.

Results: 25 procedures were successfully done using bilateral retrograde radial approach. Only two patients required transfer to transfemoral approach to open the subclavian chronic total occlusion. Minor access site bleeding complications were recorded in 4 patients. There were no other complications. Seven patients were discharged the same day, the others one day after admission. At follow up only one patient had symptomatic in stent restenosis and a balloon angioplasty was done inside the stent 3 years after the primary intervention, the patient was a smoker. One other patient had asymptomatic in stent restenosis documented 6 months after the intervention with duplex follow up.

Conclusions: Our results suggest that bilateral radial access can be a successful and safe strategy in opening of subclavian artery occlusions with a low rate of complications.

P606 | BEDSIDE

Pseudoanuerysm related to transpedal arterial access for treatment and evaluation of peripheral arterial disease

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Background: Similar to the rise in the transradial access for coronary catheterization, there has been an increasing trend towards the use of a feasible transpedal arterial access for evaluation and treatment of peripheral arterial disease (PAD) over a transfemoral approach as it is expected to be associated with better patient comfort, less recovery time and possibly less access site complications.

Purpose: There is no data available on any access site complications mainly pseudoaneurysm (PSA) related to the transpedal approach. Here we report a first ever series of PSA related to access site complicating peripheral catheterization via the transpedal approach.

Methods: We prospectively studied 1460 patients with symptomatic PAD who underwent 2236 peripheral diagnostic and/or interventional procedures between 06/2014 and 01/2016 via the transpedal approach (access via dorsalis pedis/anterior tibial artery, posterior tibial artery (PTA) or peroneal artery). Access sheath after full dose of heparinization was removed. Patent hemostasis technique by a radial artery compression device for 2 hours was used. PSA related to the access site were identified clinically (pain and pulsatile mass 1 week post intervention) and confirmed with an ultrasound; the morphological features, treatment method, success and complications were evaluated.

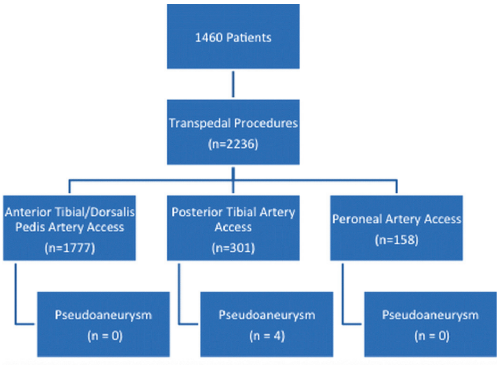
Results: The incidence of PSA related to any access site was 0.002%. However, It occurred only in PTA, after an interventional procedure (Figure). Patient demographics, PSA characteristics and treatment is depicted in Table. All patients were treated successfully with no residual complications.

Conclusion: PSA associated with the transpedal access is extremely rare. This was only seen in the PTA likely related to the vessel anatomy giving unfavourable circumstances for adequate hemostasis. Patent hemostasis or compression de-

Abstract P606 – Table 1. Clinical characteristics

No.	Age, sex	Clinical characteristics	Rutherford class	Access site/Sheath size	Hemostasis method	PSA morphology	Treatment
1	80, Male	HTN, smoker	3	L. PTA/4Fr	RACD	1.0×1.3 cm, neck 1.9 mm	UGTI
2	77, Female	HTN, HLD, CAD	3	L. PTA/4Fr	RACD	1.4×1.6 cm, neck 1.5 mm	UGTI
3	77, Male	HTN, HLD, DM, smoker, CAD, A. Fib	3	R. PTA/4Fr	RACD	1.0×1.5 cm, neck 1.2 mm	UGTI
4	87, Male	HTN, A. Fib, CAD, DM, smoker	4	R. PTA/4Fr	RACD	1.6×1.1 cm, neck 1.6 mm	UGTI

HTN: hypertension, HLD: hyperlipidemia, CAD: coronary artery disease, DM: diabetes mellitus, A. Fib: atrial fibrillation, L: left, R: right, PTA: posterial tibial artery, Fr: French, RACD: radial artery compression device, UGTI: ultrasound guided thrombin injection.



Incidence of Pseudoaneurysm

vice might be adequate, however it can be easily treated with ultrasound guided thrombin injection with no residual complications and preserving the patency of the artery.

RENAL DENERVATION, AORTIC AND CAROTID DISEASE

P607 | BENCH
Pulmonary vein isolation with concomitant renal artery denervation is associated with reduction of both arterial blood pressure and atrial fibrillation burden: data from implantable cardiac monitor

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Background: Renal artery denervation (RDN) has provided incremental atrial fibrillation (AF) suppression after pulmonary vein isolation (PVI) in patients with AF in the setting of drug-resistant hypertension.
Objectives: To assess the relationship between mean blood pressure (BP) changes and AF recurrences/AF burden after PVI combined with RDN.
Methods: All patients from two randomized studies (NCT01117025 and NCT01897545) with a history of symptomatic paroxysmal AF and/or persistent AF and resistant hypertension (≥3 antihypertensive drugs) who underwent PVI only (n=37) or PVI with RDN (n=39), and implantable cardiac monitor (ICM) implantation, were eligible for this study. Kaplan-Meier method was used to assess freedom from AF recurrences during the 12-month follow-up. Mixed effects linear models were used to investigate the effect of RDN on mean BP and AF burden and associations between the two.
Results: At the 12-month follow-up examination, freedom from AF recurrence was 0.61 (95% CI 0.51 to 0.81) in PVI with RDN group and 0.41 (95% CI 0.27 to 0.59) in PVI group (p=0.013, log-rank test), with associated hazard ratio of 0.44 (95% CI 0.22 to 0.86, p=0.017). Every 5 mm Hg reduction of mean BP was associated with reduced hazards of AF recurrence (HR 0.90, 95% CI: 0.84 to 0.96, p=0.001). RDN was associated with a significant reduction of both mean systolic BP (-13±8 mm Hg vs -2±6 mm Hg, p<0.001) and mean AF burden (9.7±5.6% vs 20.2, p<0.001) Reduction of mean BP, adjusted for mode of treatment and time, was negatively related with AF burden (p=0.034).
Conclusions: RDN when added to PVI significantly decreases AF recurrences, AF burden and mean BP. Mean BP is significantly associated with both AF burden and recurrences. Further studies are needed to uncover mechanistic pathways of BP reduction by RDN.

P608 | BEDSIDE
Distal renal denervation performed mainly in segmental branches of renal artery versus conventional mode of the intervention: a randomized controlled trial in patients with resistant hypertension

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A failure of renal denervation (RDN) done as 4–6 point treatments equally distributed within main trunk of renal artery (RA) was absolutely predictable. It may only be effective if renal nerves are closely attached to the artery during its whole course. However, surgical studies show that proximally majority of renal nerves go at a distance from RA and converge mainly to its distal part.
Objective: To evaluate whether denervation treatment in distal part of RA is more effective than conventional RDN.
Methods: We developed a distal mode of RDN performed mainly in segmental branches of RA and compared its efficacy and safety to those of conventional RDN in a single-center double-blind 1:1 randomized controlled parallel group study in patients with resistant hypertension. Inclusion criteria: men and women 18–80 years, office systolic BP≥160 or diastolic BP≥100 mmHg despite ≥3 antihypertensive drugs including a diuretic, written informed consent. Exclusion criteria: secondary hypertension, 24h-mean systolic BP<135 mmHg, eGFR<30 mL/min/m^2, extended RA disease, comorbidities causing high risk of the intervention (investigator's assessment). Computer-based random assignment of the treatment mode was consecutively performed in Cath lab and remained unknown to patients and investigators. Primary study outcome was the between-group difference in the change of 24h-mean systolic BP from baseline to 6 month.
Results: Of 45 patients enrolled in the study (24 in distal RDN and 21 – in conventional RDN group) 41 (89%) completed 6 months follow-up and were included in per-protocol analysis. The 24h-mean systolic BP decreased significantly in the distal treatment group (n=23): -22.4 (SD 20.5) mmHg, p=0.00004 and only slightly - in conventional RDN group (n=18): -8.7 (SD 18.8), p=0.06. The difference in the decrease of 24h-mean systolic BP between 2 groups was statistically significant, p=0.036.
Conclusion: Superiority of distal RDN over conventional mode of the intervention confirms better availability of renal nerves from segmental branches of RA. RDN technology development needs to be urgently re-directed to producing devices for use in segmental branches of RA.

P609 | BENCH
Effects of sympathoadrenergic modulation on expression of Receptor for Advanced Glycation End products (RAGE) and its ligands in obese spontaneously hypertensive rats

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Background: The Receptor for Advanced Glycation End products (RAGE) activates inflammatory programs responsible for oxidative stress and tissue remodeling when engaged by its ligands Advanced Glycation End products (AGEs) and High Mobility Group Box-1 protein (HMGB1). Secretory circulating isoforms referred to as soluble RAGE (sRAGE) comprise only the extracellular ligand binding domain and serve as decoy receptors neutralizing RAGE-ligands. sRAGE has been shown to prevent f.e. late diabetic complications. The metabolic syndrome however is associated with increased RAGE and RAGE-ligand expression and decreased sRAGE plasma levels.
Renal sympathetic denervation (RDN) decreases sympathetic renal nerve activity and has been shown to provide beneficial effects in obese and hypertensive rats with mild cardiac dysfunction and disturbed glucose tolerance. The effects of sympathetic modulation on RAGE-ligands and RAGE/sRAGE balance have not been investigated yet.
Purpose: To investigate the effect of sympathetic modulation on blood and cardiac RAGE-ligand levels of AGEs (Carboxymethyllysine (CML)) and HMGB1 and on RAGE/sRAGE balance in a rat model of metabolic syndrome, the Spontaneously Hypertensive Obese Rat (SHROB).
Methods: Spontaneously hypertensive obese rats with RDN at the age of 34 weeks (SHROB- RDN; n=5) were compared to sham operated SHROB (SHROB; n=5) and their hypertensive lean controls (SHR; n=6). Heart function was determined by magnetic resonance imaging (MRI) and invasive pressure measurements. Animals were sacrificed at the age of 48 weeks and renal norepinephrine was used as indicator of successful RDN. Cardiac remodeling was assessed by immunohistochemical analysis. sRAGE, CML and HMGB1 serum content and cardiac RAGE/sRAGE, CML and HMGB1 protein expression were assessed by Western blot.
Results: Myocardial RAGE was significantly increased (42% increase) and sRAGE was decreased (46% decrease) in SHROB compared to their lean littermates. While myocardial and serum CML were similar between SHROB and SHR, HMGB1 was significantly increased in SHROB (56%increase in myocardium and 29% increase in serum HMGB1 versus lean SHR).
RDN reduced myocardial tissue RAGE expression (-20%) and significantly increased sRAGE levels in heart (+46%) and blood (+65%) as compared to SHROB without RDN. Furthermore, RDN lead to a significant decrease in myocardial RAGE-ligand levels in SHROB (25% decrease in CML and 39% decrease in

HMGB1 as compared to sham-operated SHROB) and to significant reductions of serum RAGE-ligand levels (45% decrease in CML and 45% decrease in HMGB1). Myocardial sRAGE showed a negative correlation with myocardial fibrosis in SHROB and SHROB-RDN (n=10; r= -0.79; p=0.004) indicating sRAGE-mediated anti-remodeling effects.
Conclusion: Suppression of sympathetic nerve activity might provide a new mechanism to prevent RAGE-induced pro-inflammatory effects and progression of cardiac and vascular damage in metabolic syndrome.
Acknowledgement/Funding: Supported by Deutsche Stiftung für Herzforschung (The German Heart Foundation) and HOMFOR

P610 | BENCH
Renal Denervation reduces monocyte activation: an anti-inflammatory effect relevant for cardiovascular risk

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Background: Over-activation of renal sympathetic nervous system and low-grade systemic inflammation due to elevated inflammatory monocytes are common features of hypertension. Renal Denervation reduces sympathetic activity in patients with resistant hypertension. However, its effect on systemic inflammation has not been investigated.
Purpose: To determine the effect of Renal Denervation induced sympathetic inhibition on monocyte activation and systemic inflammation in patients with hypertension.
Methods: Peripheral blood was obtained from 42 patients who underwent renal denervation for uncontrolled blood pressure at baseline and at 3 and 6 months post-procedure. Ambulatory blood pressure, overall monocyte as well as monocyte subset activation and inflammatory markers were assessed at each time point.
Results: Renal Denervation significantly lowered 24-hour ambulatory blood pressure at 3 months (150.5±11.2/81.0±11.2 mmHg to 144.7±11.8/77.9±11.0 mmHg), which was sustained at 6 months (144.7±13.8/78.6±11.0 mmHg). Activation status of overall monocytes significantly decreased at 3 months ($p<0.01$) and 6 months ($p<0.01$) post-Renal Denervation. In particular, activation of the classical monocyte subset was reduced at 6 months ($p<0.05$). In line with this, we observed a reduction of several inflammatory markers including Monocyte-Platelet Aggregate formation (3 months $p<0.01$; 6 months $p=0.1387$), plasma MCP-1 levels (3 months $p<0.0001$; 6 months $p<0.05$) and plasma IL-1β levels (3 months $p<0.05$; 6 months $p<0.05$). A positive correlation was observed between baseline muscle sympathetic nerve activity and monocyte activation and changes observed at both time points post-procedure.
Conclusions: Inhibition of sympathetic activity via Renal Denervation is associated with a reduction of monocyte activation and other inflammatory markers in hypertensive patients. These findings point to a direct interaction between the sympathetic nervous and inflammatory system, which is of central relevance for the understanding of beneficial cardiovascular effects of Renal Denervation.

P611 | BEDSIDE
Renal denervation in resistant hypertension: are there differences in blood pressure reduction between unifocal and multifocal radiofrequency ablation catheters up to 24 months follow-up?

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Aims: To compare the effect of renal denervation (RDN) with single focus (unifocal) and many sites (multifocal) radiofrequency ablation catheters on reduction of 24-h ambulatory blood pressure (ABP) in a sample with resistant hypertension (rHTN) up to 24 months follow-up (FU).
Methods: One hundred and three patients (pts) with mean systolic ABP ≥140 mmHg despite treatment with ≥3 antihypertensive drugs including a diuretic, were included in our prospective study. In addition, antihypertensive medication had to be stable for ≥4 weeks. After exclusion of renal artery (RA) stenosis by angiography, we performed the RDN procedure either by introducing a 4 mm tip 7 French unifocal radiofrequency catheter (Marinr®; Medtronic Inc., USA) on 75 pts, or a multifocal ablation catheter (EnligHTN™, SJM Inc., USA) on 28 pts in both renal arteries (RA). To achieve circumferential lesions in the unifocal group, we applied 6 low-power RF up to 1 minute each, with titrated energy delivery of 8–12 watts (dependent on the pain level tolerated). In the multifocal group the ablation time was 60 seconds per basket set (performed twice). The FU at 1/3/6/12/24 months (M) comprised clinical and biochemical evaluations, and ABP measurement. Additionally, at 6/12 M duplex sonography of the RA was performed.
Results: Sample characteristics were: mean age 63 years; 65 male; mean number of antihypertensive drugs 6; mean baseline ABP 162/88 mmHg. Comorbidities included coronary artery disease (n=21), diabetes mellitus (n=48), chronic renal insufficiency (n=31), and treated obstructive sleep apnoea syndrome (n=23). At 1/3/6/12/24 M we observed reduction in mean systolic ABP of -11/-17/-13/-17/-18 mmHg (n=80/79/80/68/39; all $p<0.001$) and mean diastolic ABP of -5/-7/-6/-8/-9 mmHg (all $p<0.001$). We observed no significant differences between the uni- and multifocal RDN treatment groups. Logistic regression analysis with systolic ABP reduction ≥10 mmHg as criterion revealed that the mean systolic ABP (OR 1.1; $p<0.001$) as well as treatment with centrally acting antihypertensive agents (OR 5.3; $p<0.05$) were significant. Four of the pts (3.8%) developed RA stenosis (>70%). Subsequent stenting of the RA stenosis was performed without complications. In all other pts duplex sonography could exclude significant RA stenosis. Three not procedure-related deaths occurred during the 24-month FU.
Conclusion: RDN can be used with an acceptable risk to reduce substantially mean ABP in rHTN as shown in long-term FU. There were no differences in ABP reduction between uni- and multifocal RDN catheter systems.

P612 | BEDSIDE
Predictive value of carotid artery intima-media thickness and plaque characteristics for mortality in patients on haemodialysis

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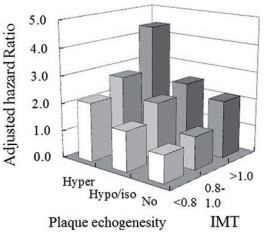
Background: Carotid atherosclerosis such as greater intima-media thickness (IMT) and plaques progression is associated with poor cardiovascular outcome. However, such relationship remains unclear in patients on haemodialysis (HD) even though they are consistently referred to be at highest cardiovascular risk. We investigated the association of IMT, plaque characteristics and their joint role with prediction of mortality in chronic HD patients.
Methods: Carotid ultra-sound was performed in a total of 821 CKD patients (male 63%, Age 65±12years, diabetes 41%) stably undergoing HD therapy. Patients were divided into tertiles according to IMT levels in common carotid artery; tertile 1 (T1): <0.8mm, T2: 0.8–1.0mm and T3: >1.0mm, and were also classified by echogenesity such as no plaque (n=266), with hypo- or iso-echoic plaque (n=333) and with hyperechoic plaque (n=225), respectively. They were followed up for 7 years.
Results: During follow-up period (median 67 months), 195 patients (23.7%) died. Kaplan-Meier analysis shows that survival rates at 7-year were 85.1%, 74.1% and 66.7% in T1, T2 and T3 of IMT ($p<0.0001$), and were 84.0%, 75.8% and 65.6% in no plaque, hypo- or iso-echoic plaque, and hyperechoic plaque group ($p<0.0001$), respectively. After adjustment for other confounders, greater IMT [hazard ratio (HR) 2.20, 95% confidence interval (IC) 1.38–3.60, p=0.0010 for T3 vs. T1] and plaque progression (HR 1.80, 95% CI 1.19–2.77, p=0.0054 for hyperechoic plaque group vs. no plaque group) were identified as independent predictors for mortality. In the joint setting of IMT and plaque echogenesity, the risk of mortality was 4.40-fold higher (95% CI 2.23–9.15, p=0.0008) in T3 of IMT with hyperechoic plaque compared to T1 of IMT without plaque (Figure).



Conclusions: Carotid IMT and plaque characteristics strongly predicted mortality in chronic HD patients, furthermore, the combination of these variables could stratify the risk of mortality. The presence of hyperechoic plaque might possibly be a manifestation of CKD-specific mineral and bone disorder.

P613 | BEDSIDE
Learning curve of the transradial approach of percutaneous carotid intervention

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Purpose: Recently transradial (TR) approach became a safe and effective alternative of percutaneous carotid intervention. We report the learning curve over 6 years in two high-volume interventional centers during the transition from transfemoral (TF) to transradial approach.
Patients and methods: Between 2010 and 2015, 1773 patients underwent carotid intervention in our centers. Clinical characteristics, radiation doses, volume of contrast material, screening and procedure times of consecutive patients were recorded prospectively in a register and restrospectively analysed.
Results: Transradial approach was applied in 494 patients, mean age was 68±8 years, 67% of them was male. The ratio of TR has grown from 3 to 7, 25, 43, 48 and 60% of the carotid interventions, during the years respectively. While the duration of the procedure (26, 30, 25, 25, 22.5, 25 min), the fluoroscopy time (11, 11, 10, 8, 8, 9 min), and the applied contrast material (128, 142, 95, 69, 90, 75 ml) has significantly decreased in the first 4 years, then an elevation is observed, as more complicated cases were enrolled. Significant improvement was observed

after the first 50 cases, in each parameter. Conversion to TF was needed in 7.5% and did not change significantly. No difference was observed in the incidence of minor or major vascular events and hospitalization days, over the years.
Conclusion: An initial learning curve was observed in the intervention parameters of transradial carotid stenting. The transition from TF to TR approach is achievable in 50 cases in experienced centers.

P614 | BEDSIDE
Real-world carotid stenting in patients with high risk versus standard risk for open carotid endarterectomy (REAL trial)

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Introduction: Until the irruption of the Carotid Revascularization Endarterectomy versus Stenting Trial (CREST), carotid stenting (CAS) has been mainly offered to those patients considered at "high risk" for open carotid endarterectomy (CEA) based on the available data from large randomized clinical trials. "High risk" has been defined as (1) patients with severe comorbidity (class III/IV congestive heart failure, class III/IV angina, coronary disease involving ≥2 major vessels, left ventricular ejection fraction ≤30%, myocardial infarction, severe pulmonary disease, severe renal failure) and (2) Technical/challenging anatomical criteria (previous neck surgery, cervical irradiation, contralateral carotid occlusion, post-endarterectomy restenosis, inaccessible lesions or tracheotomy). Several recent studies have called medical "high-risk" into question for CAS indication.
Objectives: This study evaluated the safety and perioperative and long-term effectiveness in patients with significant carotid artery stenosis with "high-risk" criteria (for CEA) treated with carotid stenting and proximal protection device compared to patients with standard-surgical-risk features.
Methods: This non-randomized double arm study included 125 patients (39.2% symptomatic), 71 (56.8%) with standard risk and 54 (43.2%) with high-risk criteria for CEA. The primary endpoint of the study was the cumulative incidence of any major adverse event (MAE), a composite of stroke, myocardial infarction and death, within 30 days after the intervention or ipsilateral stroke, after 30 days and up to 4 years.
Results: Technical success was achieved in 98.4% of procedures. There was no significant difference in the rates of the primary endpoint at 30 days between patients at "high-risk" and those with "standard-risk" (1.9% vs. 1.4%) but there were differences in the components, "high-risk" versus "standard-risk" (stroke 0% vs 1.4%, p=0.023; and death 1.9% vs. 0%, p=0.018). Acute myocardial infarction did not occur. No long-term ipsilateral stroke was reported in any of the 2 groups.
Conclusion: Results through four years post-procedure demonstrated that carotid stenting with proximal protection device is safe and effective with similar short and long-term for patients with and without high risk for CEA.

P615 | BEDSIDE
The role of the expression of nitric oxide (NO), hydrogen sulfide (H2S) and carbon monoxide (CO) generating enzymes in carotid plaque stability

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Background: Gasotrasmitters (NO, H2S, CO) gain increasing interest as signaling molecules that bestow protective effects on the cardiovascular system. However, although intraplaquely regulated NO improves plaque stability, the roles of H2S and CO on plaque stability are unidentified.
Purpose: We sought to elucidate the expression of NO, H2S and CO generating enzymes on the stability of carotid plaques attained from patients undergone endarterectomy. Furthermore, in order to access the role of nitroxidative stress in plaque stability and its correlation with the expression of the above mentioned enzymes, we determined nitrotyrosine levels and the expression of NADPH oxidase-4 (NOX4).
Methods: Carotid atherosclerotic plaque specimens were collected from 60 patients having undergone endarterectomy for internal carotid artery stenosis. Samples were divided into two groups according to the clinical presentation and the histopathological evaluation of the plaque morphology; symptomatic patients presenting unstable plaques (Unstable group, n=31) and asymptomatic patients with stable plaques (Stable group, n=29). Endothelial nitric oxide synthase (eNOS), peNOS (S1177), inducible nitric oxide synthase (iNOS), cystathionine beta synthase (CBS), cystathionine gamma lyase (CSE), heme oxygenase-1 (HO-1), soluble guanyl cyclase sGCα, sGCβ, nitrotyrosine and NOX4 expression levels were determined by immunoblotting.
Results: Western Blot analysis revealed that iNOS expression was downregulated in Stable group (p=0.02 vs Unstable), in favor of peNOS phosphorylation (p=0.003 vs Unstable) and eNOS expression (p=0.001 vs Unstable). Moreover, sGC subunits were upregulated in Stable group (p=0.005 and p=0.0001 respectively vs Unstable). CBS and CSE expression were both downregulated in Stable group (p=0.01 and p=0.04 respectively vs Unstable). Of note, HO-1 expression was also decreased in the Stable group (p=0.03 vs Unstable). Nitrotyrosine levels and the expression of NOX4 was decreased significantly in stable plaques ($p<0.05$).
Conclusions: We conclude that in stable plaques proportionally more NO comes from eNOS vs iNOS. Moreover, enhanced eNOS expression/phosphorylation is accompanied by decreased expression of the enzymes that generate H2S and CO and up regulation of sGC. Our findings confirm the existence of a dynamic interplay between gasotransmitters in the cardiovascular system. Further studies are required to determine whether these changes are causally associated with plaque stabilization and whether they are associated with better prognosis in patients with atherosclerosis.

P616 | BEDSIDE
Increased arterial inflammation assessed by positron emission tomography is associated with higher thermal heterogeneity and macrophage infiltration in carotid plaques

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Background: 18F-fluorodeoxyglycose Positron Emission Tomography (FDG-PET) is the leading molecular imaging technique for detection of local inflammatory activation in carotid disease. Recently, evidence emerged on the role of microwave radiometry (MWR) for the evaluation of arterial inflammation in atherosclerotic plaques by measuring temperatures.
Purpose: To investigate the relationship between FDG and MWR measurements in patients with high-grade carotid artery stenosis and their association with immunohistochemistry results.
Methods: Consecutive patients scheduled for carotid endarterectomy underwent FDG-PET and MWR measurements of both carotid arteries. FDG uptake within the carotid wall was quantified as maximum standardized uptake value (SUVmax) and ΔSUV (maximum difference of SUVmax values across each carotid respectively) on consecutive transaxial slices 2cm below to 2cm above the carotid bifurcation. Thermal heterogeneity of atherosclerotic plaques was estimated by ΔT (maximum minus minimum measured temperature across the carotid)above the respective carotid segments.CD 68 expression was quantified semi quantitatively in all the operated carotid plaques (sample score >2 high, ≤2 low).
Results: Forty-two carotids from 21 patients were assessed. There was a statistically significant positive correlation between ΔT and SUVmax (R=0.44, p=0.004) for all (n=42) carotid arteries. There was a similar correlation between ΔSUV and ΔT values (R=0.43, p=0.004). Correlations were stronger for the surgically operated carotid arteries (R=0.51, p=0.02 for SUVmax, and R=0.54, p=0.01 for ΔSUV). Furthermore, specimens with intense CD68 expression exhibited higher SUVmax and ΔSUV values compared to specimens with low CD68 count (2.33±0.53 vs 2.16±0.35 and 1.3±1.13 vs 0.66±0.29, p=0.04 and p=0.05, respectively). Similarly, carotid endarterectomy specimens with high CD68 expression had higher ΔT values compared to specimens with low CD68 expression (0.59±0.12 vs 0.52±0.19, p=0.04).
Conclusions: The degree of carotid inflammation assessed by FDG uptake is associated with temperature differences of the atherosclerotic plaque. Both measurements reflect macrophage infiltration during local inflammatory process.

P617 | BEDSIDE
Outcome in patients with chronic kidney disease after carotid artery stenting: data from a large single center with single operator experience

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Background: The presence of chronic kidney disease (CKD) is known to be associated with worse outcome in patients undergoing cardiac or peripheral vascular interventions. However, data concerning carotid artery stenting (CAS) are limited due to small sample sizes or multicenter studies with often more than one operator with varying experience and partially incomplete neurological follow-up.
Methods: The present analysis is based on an all-comer registry with a prospectively designed follow-up protocol including a complete pre- and postprocedural neurological assessment and a standardised yearly conducted questionnaire for long-term follow-up. Between 1999 and 2015 a total of 1000 procedures were consecutively performed by a single operator or a second proctored by him. CKD was defined as a glomerular filtration rate <60ml/min for at least 3 months.
Results: 218/1000 (21,8%) procedures were done in patients with CKD. Patients with CKD vs. no CKD were older (74 vs. 70 years; p<0,05), more often male (69% vs. 61%; p<0,05) and smokers (24% vs. 20%; p=0,26). Additionally, they suffered from diabetes (39% vs. 31%; p<0,05), concomitant coronary artery disease (77% vs. 60%; p<0,001) and COPD (11% vs. 5%; p<0,05) more often. The rate of the composite of 30-day stroke, death and myocardial infarction (MACCE) including procedural and in-hospital complications was more than twice in patients with CKD (20/218 (9,2%) vs. 30/782 (3,8%); p=0,0026).

Conclusion: Data of our large CAS registry with long experience show a significantly worse outcome in patients with CKD undergoing CAS. Therefore, patients with a known CKD should be paid special attention.

P618 | BEDSIDE
Novel carotid revascularization PARADIGM evaluation in a prospective clinical study in all-comer symptomatic and increased-stroke-risk asymptomatic carotid artery stenosis

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Background: MicroNet-covered embolic prevention stent system (MN-EPS) is an important technological advancement that may impact the way carotid artery stenosis (CS) is managed.
Recent diffusion-weighted magnetic resonance-controlled study showed MN-EPS low incidence/minimal size of carotid artery stenting (CAS)-associated cerebral lesions (indicating >50%/>10-fold reduction against conventional stent) but was underpowered for clinical end-points.
Purpose: To evaluate periprocedural and 30d clinical outcome of routine MN-EPS use in 101 (target) unselected subjects with symptomatic or increased-stroke-risk asymptomatic CS indicated for revascularization (NeuroVascular Team).
Methods: Non-industry-funded, academic study in all-comer (all-referrals-tracked) CS patients. Consecutive MN-EPS CAS. Asymptomatic subjects/lesions revascularization if ≥1 literature-documented increased-risk-for-stroke criterion. Independent neurologist evaluation before CAS, at 48h and 30d.
External angiographic corelab, data verification, statistical analysis.
Events were Clinical Event Committee (CEC)-adjudicated.
Results: Of 139 CS referrals over 11 months, 108 patients were NeuroVascular Team-indicated for revascularization; 31 were rejected (increased stroke risk criteria unmet-24, index CS occlusion-4, severe circulatory failure-1, severe disability-1, malignancy/short life expectancy-1).
101 subjects (age 51–86y, male-70%, symptomatics-55% incl. stroke-in-evolution in 9, CAD-63%, diabetes-41%) underwent 106 CAS. MN-EPS was used in 100% CAS (no other stent use during study). Surgical (CEA) management was in 7 (severe renal failure, hostile access, floating large thrombus in CCA).
Proximal/distal embolic protection device use in CAS was 46/54%; prox-EPD more frequent in symptomatic CS (56% vs. 35%, p=0.03). PCI as bridge to CAS was in 18, incl. simultaneous PCI+CAS in 4.
Angiographic diameter stenosis was 82±9% before vs. 7±4% after CAS. MN-EPS stent system procedural and clinical success was 100%. Nominal 30mm-long stent was 29.66±0.30mm post-implantation and 40mm was 39.73±0.34mm. Velocities were 3.7±1.2/1.2±0.5m/s at baseline vs. 0.68±0.29/0.18±0.08m/s at 30d.
30-day clinical (incl. neurologist) and duplex follow-up was 100%.
Death/major stroke/MI by discharge was 0%. One event, without focal neurologic symptoms or NIH-SS change vs. admission but hypotonia and discharge CT suggesting minor extension of a prior ipsilateral lesion was CEC-adjudicated as minor stroke (0.9%). By 30 days there were no new events (0%).
Conclusions: MN-EPS use was safe and effective in achieving full endovascular reconstruction across all-comer CS lesion subsets. 30d results in the high-risk CS population are consistent with MN-EPS protection extending throughout stent healing period.
Data from this externally-controlled, largest to-date MN-EPS study, with no exclusion criteria and MN-EPS use in 100% CAS, may be relevant to carotid revascularization evolution.

P619 | BEDSIDE
Prognostic value of acute kidney injury after transcatheter aortic valve implantation in patients with aortic stenosis

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Acute Kidney Injury (AKI) after cardiac surgery is associated with increased mortality, but very few data exist on the occurrence of AKI associated with Transcatheter Aortic Valve Implantation (TAVI). The aim of this study was to determine the incidence and prognosis of AKI after percutaneous treatment in patients with aortic stenosis.
Methods: Between April-2008 and December 2015, 492 patients with severe aortic stenosis were treated with the CoreValve prosthesis. The AKI was defined according to the Valve Academic Research Consortium criteria, as the absolute increase in serum creatinine ≥0.3 mg/dl at 72 hours after percutaneous procedure. We excluded patients died during procedure.
Results: The incidence of AKI was 16.5% and none required renal replacement therapy. After implantation there was a slight improvement in renal function, baseline serum creatinine decreased from 1.27±0.4 mg/dl to 1.17±0.4 mg/dl, p=0.001. In patients with AKI, the mortality at 30 days was 69.2% compared to 15.1% of patients without AKI, OR=12.7 (95% CI 3.85–42.4), p=0.001 and late mortality after a mean of 34.3±23 months was 20% in those patients with AKI compared to 14% without AKI, p=0.098. In the multivariable analysis AKI was an independent predictor of cumulative total mortality HR 1.93 (95% CI 1.23–3.01), p=0.006.
Conclusions: The incidence of AKI was associated with increase early mortality and also was a predictor of worse outcomes in the long-term follow-up.

P620 | BEDSIDE
Effect of previous growth hormone treatment on ascending aorta dimensions in Turner patients

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Purpose: Growth hormone treatment (GHT) in Turner patients is nowadays often used to achieve a higher body height. However, GHT might also have an effect on aortic dimension, which is less well known. We investigated the effect of previous GHT on aortic diameters in a large cohort of Turner patients.
Methods: In this retrospective single center study of Turner patients we investigated the association between GHT and ascending aorta diameters (measured by MRI or CT). In addition, the impact of other parameters such as: presence of a bicuspid aortic valve (BAV), history of aortic coarctation, karyotype, weight and length, and the presence of classic cardiovascular risk factors were taken into account. Descriptive statistical analysis and uni- and multivariate analysis were performed.
Results: Of the 239 Turner patients, 142 patients previously used GHT, while 97 did not. The mean age of the 2 groups were 25.7 (+7.8) and 39.3 (+10.2) (p<0.0001) years respectively. Karyotype 45X0 was present more often in the GHT group (p=0.001). There was significant less hypertension, dyslipidaemia and diabetes in the GHT group (p=0.006, p<0.0001 and p=0.032 respectively). Univariate analysis showed a significant association between ascending aorta diameter and GHT, age, BAV, karyotype 45X/0, body mass index, and blood pressure. Table 1 shows the multivariate analysis. Besides GHT, age, weight, hypertension, karyotype 45XO, and presence of BAV were associated with an increase in ascending aortic diameter.

Table 1

	b	Beta	p-value
Age (years)	0.27	0.58	>0.0001
Karyotype 45X0 presence	1.55	0.15	0.007
BAV presence	3.01	0,24	>0.0001
GHT	1.775	0.17	0.014
Hypertension	2.21	0.16	0.004
Weight (kg)	0.08	0.29	>0.0001
R 0.622	R square 0.387		R^2adjusted 0.370

BAV = bicuspid aortic valve; GHT = growth hormone treatment; age in years; weight in kg; b = unstandardized coefficient; beta = standardized coefficient.

Conclusion: GHT during childhood was found to be associated with ascending aorta dilatation, independent of classic predictors of aorta dilatation.
Acknowledgement/Funding: This study was funded by a grant of the Dutch Heart Foundation (grant number: 2013T093)

P621 | BEDSIDE
Hybrid repair of aortic arch pathology: long-term clinical outcomes and patency of extra-anatomic bypass grafts

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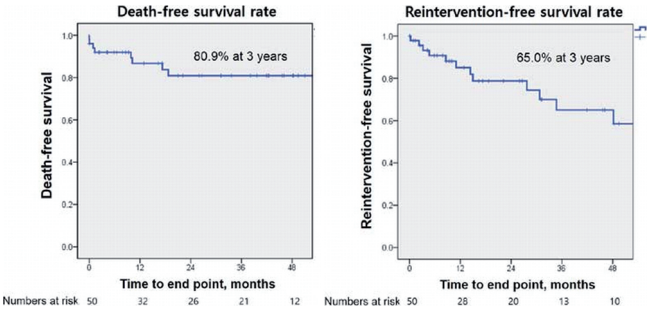
Purpose: Hybrid repair offers comparable short-term outcome with open surgery. However, longer-term studies are required to assess clinical outcomes and patency of the extra-anatomic bypass grafts.
Methods: A total of 50 consecutive patients (38 men, mean age 65.3±16.1 years) who underwent hybrid repair for aortic arch pathologies were analyzed.
Results: The indications for treatment included increased aneurysm size in 40 cases (80.0%), pseudoaneurysm in 5 cases (10.0%), and rapid growth of aortic dissection (≥10 mm/y) in 5 case (10.0%). Supra-aortic vessel transposition (n=15 for Zone 0, n=12 for Zone 1, n=23 for Zone 2) and stent graft implantation (n=19 with Seal thoracic stent graft, n=19 with Valiant stent graft, n=12 with Zenith TX2 proform stent graft) were achieved in all cases. Perioperative complications affected 15 patients (30.0%), as follows: bleeding (n=3, 6.0%); stroke (n=4, 8.0%); renal failure (n=4, 8.0%); vascular injury (n=4, 8.0%), pneumonia (n=1, 1.0%) and retrograde dissection (n=3, 6.0%). Three patients died within 30 days (6.0%) due to stroke and aortic rupture. Endoleaks were noted in 13 patients (26.0%). Two patients (2.0%) required emergency intervention for retrograde dissection

and aortic rupture. Reintervention was performed for type 1 endoleak in 6 patients and endotension in 2 patients, stent migration in 1 patient, distal stent edge dissection in 1 patient. One occlusion and one stenosis were noted in bypass graft, but which was not related clinical symptom. The death-free survival and reintervention-free survival rates at 3 years after index procedure were 80.9% and 65.0%, respectively.



Event-free survival rate

Conclusions: Hybrid repair may be a good alternative option in high risk patients and the patency of bypass graft was good. However, given the high reintervention rate, careful selection of patients and consideration of anatomic features are required to achieve satisfactory results.

P622 | BEDSIDE
Long-term outcome of patients presenting with type A acute aortic syndrome

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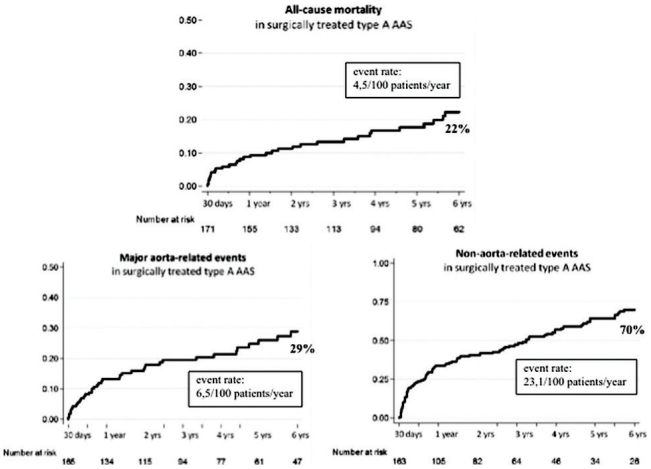
Background: Acute Aortic Syndromes (AAS) represent an emergency condition involving the aorta, with a common pathway and similar clinical manifestations. In type A AAS surgical treatment is the therapeutic cornerstone of treatment and results to be life saving. Although early phase clinical data and outcome have been well described, little is known about long-term outcome.
Purpose: The aim of this study was to evaluate mortality, aorta-related events and non-aorta-related events as well as predictors of mortality and aortic complications at long-term follow up in type A AAS.
Methods: Our registry contains all consecutive patients referred to our institution from 2000 to 2013 who received a final diagnosis of spontaneous AAS. The global population of the study was composed by 398 patients, 257 presenting with Type A AAS. The study was focused on 170 type A patients discharged after surgery. Long-term outcome was evaluated analysing the events occurred after the index hospitalization with Kaplan-Meier method, for a median follow up period of 3.24 years. Univariable and multivariable analysis of risk factors for global mortality and aorta-related events at 6-year follow up were performed in the patients who were events-free before discharge. We considered as major aorta-related events: aorta-specific mortality and re-hospitalization/re-intervention for aortic complications. On the other hand, non-aorta-related events included non-aorta-specific mortality and re-hospitalization for several causes (cardiovascular-related or non cardiovascular-related).
Results: Mean age was 64±12 years, the majority of patients were men (68.8%). Hypertension was the most represented risk factor (71.8%). Moderate to severe aortic regurgitation was present in 37.6% while cardiac tamponade in 12.9%. The 30 day-6 year mortality rate was 22% (event rate 4.5/100 patients/year). After discharge, major aorta-related events occurred in 29% of patients (event rate 6.5/100 patients/year), while non-aorta-related events in 70% (event rate 23.1/100 patients/year). Older age (HR 1.04, 95% CI 1.01–1.09, p=0.017) and lower GFR (HR 0.95 for each mL/min increase, 95% CI 0.94–0.98, p<0.001) were found to be risk factors for mortality at 6-year follow up. Increased diameter of the aortic bulb at presentation (HR 1.09, 95% CI 1.01–1.17, p=0.023) was associated with higher risk of major aorta-related events.
Conclusions: Among surgically treated type A AAS, the risk of death and adverse outcome was not limited to the acute phase but progressively increased during time. The rate of both aorta-related and non-aorta-related events was high at 6 years.



P623 | BEDSIDE
Cause of death in patients with Marfan syndrome

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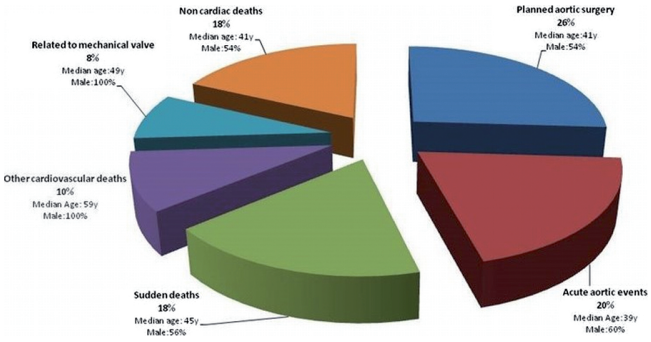
Background: The last 30 years have been associated with increased survival of 30 years in patients with Marfan syndrome (MFS). With familial screening, regular follow up, betablocker therapy and prophylactic aortic surgery, MFS patients have almost a normal life expectancy. We thought to assess cause of death in MFS patients nowadays.
Methods: Patients who came at least once in our clinic, had a diagnosis of MFS with a FBN1 gene mutation and who died were selected.
Results: 53 deaths were reported among the 1324 patients with MFS carrying a FBN1 gene mutation. Median age at death was 41 years (range:2–90 years) and 35% were women. 3 deaths occurred in children affected by a neonatal form of MFS at 2, 4 and 6 years old: 1) acute respiratory failure with severe MR and severe restrictive respiratory failure, 2) after planned surgery for MR and aortic aneurysm and 3) sudden death in a 6 years old boy with aortic root diameter at 42mm. Most of the deaths in adults were cardiovascular: -14 deaths occurred after planned aortic surgery performed for: isolated aortic root dilatation in 6, associated with mitral valve repair in 1; redo surgery in 2 (aortic root dilatation after supra coronary tube implantation and false aneurysm 8 years after a Bentall procedure); dilatation of dissected thoracic descending aorta in 4 patients; mitral valve repair in 1. -10 deaths were related to acute aortic events: Dissection of ascending aorta in 6, descending aorta in 1, abdominal aorta in 1 and rupture of a chronically dissected descending aorta in 2. -Nine sudden cardiac deaths without autopsy performed were reported. -Another specific cause was recognized in 5 men: myocardial infarction:2, Stroke:1, heart failure:1, ruptured mitral chordae tendinae:1. -4 related to the presence of a mechanical aortic valve: endocarditis in 2, valve thrombosis and hemorrhagic shock complicating anticoagulant therapy. -Lastly, 9 deaths were non cardiac.



Cause of death in adults with MFS

Conclusion: Despite a tremendously increase in life expectancy in MFS patients, cardiovascular death remains the leading cause of deaths (83%). Notably, 26% of the deaths occurred after planned aortic surgery and despite regular follow up, acute aortic events and sudden deaths still occur in young patients.

P624 | BEDSIDE
Twelve-months quality of life improvement and all-cause mortality in elderly patients undergoing transcatheter aortic valve replacement

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Background: Restoration of QoL and improvement of clinical outcomes are important issues in elderly patients undergoing TAVI.
Aim: We sought to evaluate changes in quality of life (QoL) and all-cause mortality after transcatheter aortic valve implantation (TAVI).
Methods: A total of 101 patients who underwent TAVI were included in this QoL study and assessed using EQ-5D-3L with a visual analog scale (VAS). Clinical outcomes after 12 months were assessed. In addition, QoL scores were compared between patients with transfemoral and non-transfemoral access.
Results: Patients who reported problems with mobility at baseline, showed bet-

ter mobility rates after 12 months (p=0.001), but those who reported issues with self-care, usual activity or pain did not show significant improvement (p=0.41; p=0.12; p=0.27, respectively). Patients reporting anxiety at baseline improved 12 months later (p=0.003). VAS score showed an incremental increase during follow-up (p<0.001). Transfemoral access was associated with higher VAS score values after 1 month (median (IQR): 65.0 (50.0–75.0) vs 54.0 (50.0–60.0); p=0.019) but not after 12 months (70.0 (62.5–80.0) vs 67.5 (55.0–70.0); p=0.07) as compared to non-transfemoral access. In multivariate linear regression analysis, only age and the presence of chronic total occlusion were independently associated with VAS score at 12 months. In-hospital, 1-, 6- and 12-month mortality rate was 6.9%, 10.9%, 15.8 and 17.8%, respectively.
Conclusions: TAVI provides improved QoL with good clinical outcomes, however not all health aspects are positively affected. Patients treated with TF access seems to have better quality of life than those who had non-TF access in the early postoperative period. Selecting proper candidates for TAVI is crucial for them to get most benefits after procedure.

P625 | BEDSIDE
Systemic vascular dysfunction in high-altitude dwellers with patent foramen ovale

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Introduction: Many millions of high altitude dwellers are exposed to chronic hypoxia. Recent data show that the presence of patent foramen ovale (PFO) in high altitude dwellers is associated with more severe hypoxemia and pulmonary hypertension. Chronic hypoxemia per se induces systemic and pulmonary vascular dysfunction. Aim of our study was to investigate if the presence of PFO in high altitude dwellers was associated with more severe hypoxemia and consequent systemic vascular dysfunction.
Methods: We included 46 Bolivian high altitude dwellers (mean age 42±16 y) without classical cardiovascular risk factors. The presence or absence of PFO was assessed by trans-esophageal echocardiography. To assess systemic vascular function we measured flow-mediated vasodilation (FMD) of the brachial artery, carotid-femoral pulse-wave velocity (PWV) and carotid intima-media thickness (IMT).
Results: PFO was present in 17/46 subjects (37%). The presence of PFO was associated with more severe hypoxemia (SaO2 86±6 vs. 89.5±3%, P=0.04) and systemic vascular dysfunction (FMD: 6.6±2.9 vs. 5.0±1.6%, P=0.03; PWV: 10.0±2.2 vs. 8.5±1.1 m/s, P=0.03; IMT: 578±158 vs. 595±140 μm, P=0.71). There was a significant positive correlation between SaO2 and FMD (r=0.52, P<0.001) and an inverse relationship between SaO2 and PWV (r=-0.66, P<0.001) and IMT (r=-0.47, P=0.001).
Conclusion: In high altitude dwellers without classical cardiovascular risk factors, the presence of PFO is associated with more severe hypoxemia and consequent systemic vascular dysfunction. We speculate that the presence of PFO in conditions associated with chronic hypoxemia accelerate the development of arteriosclerosis.

P626 | BENCH
Are two internal thoracic grafts better than one? Analysis of 1528 diabetic patients between 1996- 2010

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Background: Bilateral internal thoracic artery (BITA) grafting in diabetics is controversial due to a higher risk for sternal infection. The purpose of this study is to compare the outcome of BITA grafting to that of single ITA (SITA) in patients with diabetes.
Methods: Between 1996 and 2010, 964 diabetic patients with multi-vessel disease who underwent primary coronary artery bypass grafting (CABG) with BITAs were compared with 564 patients who underwent CABG with SITAs and saphenous vein grafts
Results: Patients undergoing SITAs were older, more often female, more likely to have chronic obstructive pulmonary disease, ejection fraction ≤30%, insulin-dependent diabetes, recent myocardial infarction, renal insufficiency, peripheral vascular disease and emergency operation. and less likely to have left main disease. BITA patients more often underwent CABG with ≥3 grafts.
Operative mortality (2.6% BITA vs. 3.0% SITA) and sternal infection (3.1% vs. 3.9%, respectively) of the two groups were similar. The mean follow-up was 12.2±4.3years.Unadjusted Kaplan Meier ten -year survival of the BITA group was better than that of the SITA group (65.3+3.1% vs. 55.5+4.5%, P=0.004), however after propensity score matching (501 well matched pairs)the 10-year survival (59.9+4.5% vs. 56.6+4.5%, P=0.565), as well as the Cox-adjusted survival (HR 0.928 95% CI 0.706–1.219, p=0.591) were not significantly different between the matched groups
Conclusions: This study does not support the routine use of BITA in all patients with diabetes. Similar long-term survival can be achieved with SITA. Selective use of BITA in lower risk diabetic patients might un-mask the benefits of BITA grafting.

SUDDEN CARDIAC DEATH

P627 | BEDSIDE
Supraventricular arrhythmias and implantable cardioverter defibrillator shocks in catecholaminergic polymorphic ventricular tachycardia

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Background: Patients (pts) with Catecholaminergic Polymorphic Ventricular Tachycardia (CPVT) may develop supraventricular arrhythmias (SVA), likely due to triggered activity as part of the spectrum of the disease. Data on the incidence of SVA, and on their role in favouring ICD shocks are lacking.
Goal: To analyse the occurrence of ICD shocks among CPVT pts enrolled in the International Left Cardiac Sympathetic Denervation (LCSD) registry. Specifically, we looked at the relationship between SVA and inappropriate shocks, electrical storms (ES, 3 or more separate appropriate ICD shocks in 24 hours) and "end of treatment" conditions (EOT, when consecutive appropriate ICD shocks lead to termination of therapies).
Results: The registry includes 64 high-risk CPVT pts who underwent LCSD. All pts were on optimized medical therapy (OMT, betablocker in 97% and/or flecainide in 16%) before LCSD and the median post-LCSD follow-up was 39 months. An ICD was implanted in 38 pts (59%) at a median age of 11 years: 33 at a median time of 41 months before LCSD, 2 simultaneously, and 3 after LCSD. A total of 78 inappropriate shocks occurred in 8/33 pts (24%) and the majority (n=68, 87%, median 7 shocks/pts) were due to SVA: atrial tachycardia/atrial fibrillation (AT/AF) in 5 pts (15% of ICD pts) and atrioventricular nodal reentrant tachycardia in one. Interestingly, 4/6 (67%) of pts with inappropriate ICD shocks due to SVA, also experienced electrical storms (ES, n=4, total 14 episodes) and/or end of treatment conditions (EOT, 2 pts, 7 episodes) before LCSD, compared to 8/27 (30%) among the pts with no inappropriate shocks. Considering the entire population of ICD patients before LCSD, 5/12 (42%) episodes of EOT condition were directly triggered by SVA. Denervation was associated with an 83% reduction (5/33 vs 1/38 pts) in the incidence of inappropriate shocks due to SVA: only 1/38 pts (3%) had recurrences, albeit in reduced number (26 pre vs 4 post LCSD). Notably, the incidence of inappropriate shocks due to SVA according to LCSD extension was 1/6 (17%) in pts with incomplete denervation (T1 or T4 spared) and 0/32 in pts with complete LCSD.
Conclusion: Supraventricular arrhythmia were a serious medical problem in this high-risk CPVT population. They caused inappropriate ICD shocks in 1 out of 5 patients and favoured the occurrence of ventricular tachycardias and end of treatment conditions 1 out of 10 patients. This analysis reports for the first time a reduction in the incidence of inappropriate shocks due to supraventricular arrhythmias after left cardiac sympathetic denervation.

P628 | BEDSIDE
Validation of a termination-of-resuscitation rule for out-of-hospital cardiac arrest in the emergency department

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Background: Implementation of the universally endorsed basic life support termination-of-resuscitation (BLS-TOR) rule for out-of-hospital cardiac arrest (OHCA) is not allowed in Japan. Therefore, we previously developed a new TOR rule to be used by emergency department (ED) physicians treating OHCA patients (ED-TOR rule); this was done using data from the nationwide Japanese registry from 2005 to 2009, when cardiopulmonary resuscitation (CPR) was performed according to the 2000 and 2005 guidelines. The ED-TOR rule recommends termination of CPR after arrival at the hospital when there is no prehospital return of spontaneous circulation (ROSC), the initial rhythm is not shockable, and bystanders do not witness the arrest. As recent improvements in the survival rate after an OHCA have been reported in Japan, we are obligated to validate the ED-TOR rule using more recent data where CPR was performed according to the 2010 guidelines.
Purpose: We aimed to validate the ED-TOR rule for ED physicians and com-

pare the relevance of the ED-TOR rule with the BLS-TOR rule that consists of the following 3 criteria: no prehospital ROSC, unwitnessed arrest by emergency medical services (EMS) providers, and no shock received.
Methods: We analysed the records of 238,174 patients (age ≥18 years) who experienced OHCA treated by EMS providers. Data were obtained from a prospectively recorded Japanese nationwide Utstein-style database from 2011 to 2012. The primary endpoints were specificity and positive predictive value (PPV) for predicting the 1-month mortality after OHCA with the ED-TOR and BLS-TOR rules.
Results: The overall 1-month survival rate was 4.4% (10,519/238,174). The proportions of OHCA patients who fulfilled the ED-TOR and BLS-TOR criteria were 57.3% and 80.1%, respectively. The specificity of the ED-TOR rule for predicting 1-month mortality was significantly higher than that of the BLS-TOR rule (90.6% [95% confidence interval (CI), 90.0–91.1%] versus 79.5% [95% CI, 78.8–80.3%]; P<0.0001). The PPV of the ED-TOR rule for predicting 1-month mortality was also significantly higher than that of the BLS-TOR rule (99.3% [95% CI, 99.2–99.3%] versus 98.9% [95% CI, 98.8–98.9%]; P<0.0001).
Conclusions: The ED-TOR rule for physicians treating OHCA patients in the ED was successfully validated using more recent data from a Japanese registry where CPR was performed according to the 2010 guidelines. The ED-TOR rule is a greater than 99% predictor of 1-month mortality. The use of the ED-TOR rule may help clinicians decide whether to terminate resuscitation efforts for futile OHCA patients in areas or countries where a TOR rule in the field is not implemented.
Acknowledgement/Funding: The Japan Society for the Promotion of Science (KAKENHI Grant Number 15K08543)

P629 | BEDSIDE
Abdominal obesity is associated with risk of sudden cardiac arrest in general population: analyzed from korean national health insurance database cohort

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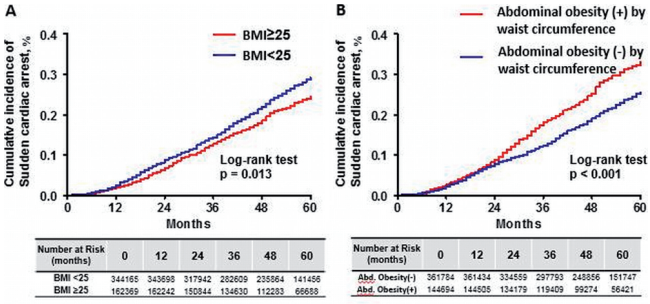
Introduction/Purpose: The increased risk of sudden cardiac arrest (SCA) in obese subjects is becoming a major clinical issue. We examined the association of body mass index (BMI), abdominal obesity using waist circumference (WC) and risk of SCA.
Methods: This study included 506,805 patients from Korean National Health Insurance Service-National Sample Cohort (NHIS-NSC) in 2009, and analyzed follow-up data until December 2013. Subjects were classified by overweight/obesity (BMI≥25 kg/m^2) and abdominal obesity (WC≥90 cm for men and ≥80 cm for women), and followed the risk of SCA.
Results: During a mean follow-up of 46±15 months, 1019 (0.2%) subjects with SCA were identified (mean baseline age 65±13 years, 65.1% male). Subjects with SCA had a lower baseline BMI (23.6±3.3 vs. 23.2±3.3 kg/m^2; p<0.001) and a higher baseline WC (80.0±9.3 vs. 82.5±8.9 cm; p<0.001) than those without SCA. SCA incidence according to overweight/obesity by BMI (0.18% vs. 0.21%, p=0.013 for BMI≥25 kg/m^2 vs. <25 kg/m^2) showed conflicting results as compared to those according to abdominal obesity by WC (0.24% vs. 0.18%, p<0.001 for subjects with abdominal obesity vs. without). In Cox proportional-hazards models, after adjusting relevant co-morbidity factors, there was continuous and positive associations between WC and risk of SCA, while there was an inverse relationship between BMI and risk of SCA. (HR=0.89, 95% CI: 0.859–0.917, p<0.001 for BMI; HR=1.02, 95% CI: 1.007–1.032, p=0.003 for WC).



Number at Risk (months)	0	12	24	36	48	60
BMI <25	344165	343698	317942	282609	235864	141456
BMI ≥25	162369	162242	150844	134630	112283	66688

Number at Risk (months)	0	12	24	36	48	60
Abd. Obesity(-)	361784	361434	334559	297793	243856	151747
Abd. Obesity(+)	144694	144505	134179	119409	99274	56421

Figure A, B. Kaplan-Meier curves for sudden cardiac arrest risk according to categories of BMI (A) and WC (B).
Kaplan-Meier curves

Conclusions: Obesity measured by BMI showed an "obesity paradox" in relationship with risk of SCA, and abdominal obesity using WC was independently associated with increased risk of SCA after adjustment of age, gender and comorbidity factors.

P630 | BENCH
Increased sudden death with chronic obstructive pulmonary disease in general population

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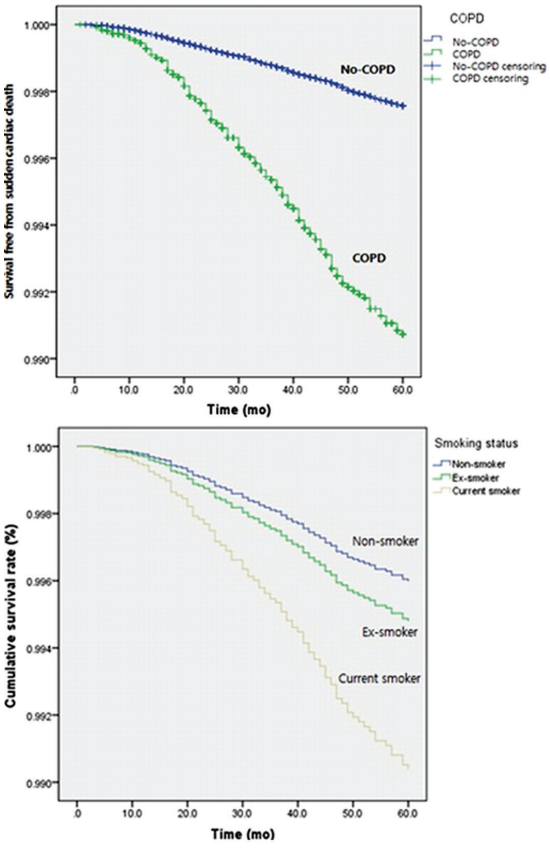
Introduction: Both sudden death and chronic obstructive pulmonary disease (COPD) are common conditions in the elderly. Previous studies have identified an association between COPD and cardiovascular disease, and with sudden death in specific patient groups. Our aim was to investigate whether there is an association between COPD and sudden death in the general population.
Methods: In Korean National Health insurance Service – National Sample Cohort (NHIS-NSC), 499,103 subjects who received national health check-up after 2009 were enrolled, and follow up until 2013.
Result: Of the 499,103 persons included in the analysis, 25,138 patients (4.96%) had a diagnosis of COPD and there were 154 cases of sudden death. During the mean follow-up period of 45.5±14.9 months, 0.61% of COPD patients died compared with 0.15% of no-COPD patients. Crude mortality risk of COPD was odds ratio 3.92 (95% confidence interval: 3.32 to 4.61, p<0.001). Chronic obstructive pulmonary disease was associated with an increased risk of sudden death (age- and sex-adjusted hazard ratio, HR, 1.27, 95% CI 1.07–1.51, p=0.006). The risk particularly increased in the current smoker with COPD compared with non-smoker. (age- and sex-adjusted HR 2.40, 95% CI 1.65–3.51, p<0.001). But there was no significant difference of the sudden death risk between ex-smoker and non-smoker (HR 1.30, 95% CI 0.42–2.00, p=0.24).



Sudden death by COPD and smoking status

Conclusion: Chronic obstructive pulmonary disease is associated with an increased risk for sudden death. The risk especially increases in persons with current smoker with the diagnosis of COPD.

P631 | BEDSIDE
Elevated testosterone serum levels contribute to adverse outcome in patients with arrhythmogenic right ventricular cardiomyopathy/dysplasia

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Background: Sex hormones have been reported to play a role in the pathophysiology of ventricular arrhythmias.

Purpose: Male patients with arrhythmogenic right ventricular cardiomyopathy/dysplasia (ARVC/D) develop life-threatening ventricular arrhythmias at an earlier age compared to females. Thus, we hypothesized that serum levels of sex hormones contribute to major adverse cardiovascular events in patients with ARVC/D.
Methods: Serum levels of testosterone, dehydroepiandrosterone, sex hormone binding globulin (SHBG), androstenedione, estradiol (E2), and progesterone as well as a routine panel of biochemical markers were measured in 50 patients fulfilling ARVC/D task force criteria. Sex hormone levels were correlated with major adverse cardiovascular events (MACE), defined as the occurrence of cardiac death, heart transplantation, survived sudden cardiac death, ventricular fibrillation, sustained ventricular tachycardia or arrhythmogenic syncope. The model was adjusted for known risk predictors such as male gender, competitive physical activity, right ventricular and left ventricular function.
Results: Twenty-six patients (52%) experienced MACE at the time of determination of sex hormone levels. In male patients with MACE, testosterone levels and SHBG levels were significantly increased, whereas dehydroepiandrosterone levels were decreased. In females, E2 levels were lower in patients with MACE. In males, increased testosterone levels remained significantly associated with MACE after adjusting for the prementioned established risk predictors. A cut-off value for total serum testosterone of >13.5 nmol/l was associated with MACE with a sensitivity of 84% and a specificity of 76% in males.
Conclusions: This study shows for the first time that elevated testosterone and/or decreased E2 serum levels are associated with clinical MACE in patients with ARVC/D. Thus, determining the levels of these two sex hormones might be useful for risk stratification of patients with this disease.

P632 | BEDSIDE
QUIDAM study assessment of hydroquinidine therapy in the management of Brugada syndrome patients at high arrhythmic risk and implanted with an ICD

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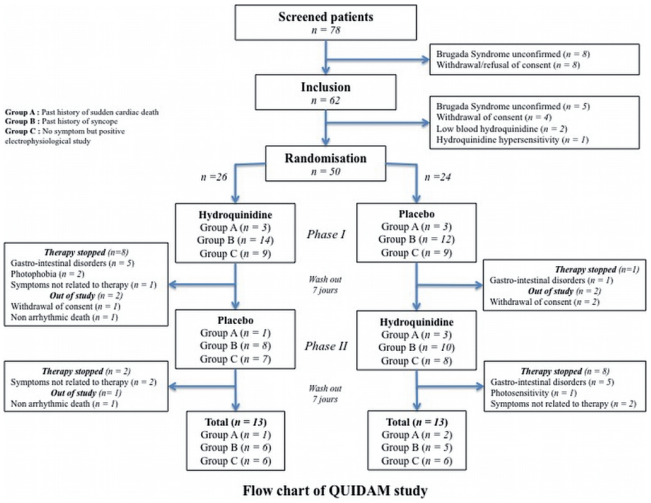
Background: During last decades, the knowledge in pathophysiological mechanisms of Brugada Syndrome (BrS) improved. Arrhythmic mortality was decreased using ICD implantation in high-risk patients. Based on experimental and clinical data hydroquinidine (HQ) seems a promising alternative for the management of ventricular arrhythmia but need to be evaluated.
Methods: Fifty patients were included in this multicentric, randomised (HQ vs placebo), double-blind study designed with two 18 months cross-over phases. Arrhythmic events, ECG parameters and clinical events were evaluated.
Results: Twenty-six (52%) patients completed the study. Thirty-four (68%) presented side effects, mainly gastrointestinal, related to HQ therapy, which was stopped in 13. One appropriate ICD shock, 1 VF with self-resolution and one inappropriate ICD shock occurred in absence of HQ but no statistical analysis has been done. No arrhythmic event occurred under therapy. HQ, at short or long-term, significantly lengthen QT interval, QTc (respectively 404 vs 417sm and 409 vs 433ms), Tpe and Tpe max (94,8 vs 106,6 ms and 89,4 vs 107,7ms) without any change on J-point elevation nor Tpe/QTc ratio. QTc interval was significantly longer during long than short-term treatment without any other effect on ECG parameters.
Conclusion: HQ side effects and rare arrhythmic events give difficulties to conduct large studies to prove its efficiency in BrS. HQ lengthens and increases the repolarisation dispersal, with electrocardiographic effects generally similar during short and long-term treatment. These considerations should not stop its use in daily clinical practice, especially for management of electrical storms.



QUIDAM Flow Chart

P633 | BEDSIDE
Ventricular tachyarrhythmias at presentation predicts sudden cardiac death after acute coronary syndrome

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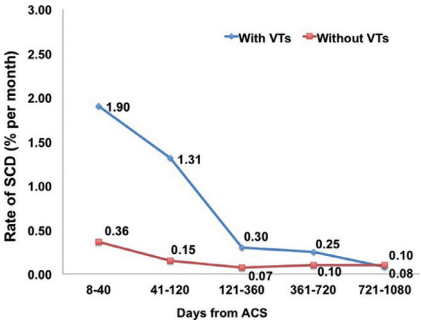
Introduction: Patients suffer from acute coronary syndrome (ACS) are at risk of sudden cardiac death (SCD), and the prognostic implication of the presence of ventricular tachyarrhythmias (VTs) at presentation remains unclear. Current guidelines do not support the use of implantable cardioverter defibrillator (ICD) for prevention of SCD in those patients who develop VTs within 48 hours of presentation.
Purpose: We sought to investigate the risk of SCD in patients with and without VTs within 48 hours of ACS.
Method: Consecutive patients admitted to our cardiac unit for ACS and received successful coronary intervention from 2010 to 2015 were retrospectively reviewed.
Results: A total of 905 patients (age: 65.8±13.4 years, 75.1% male) were included in the analysis. Documented VTs within the first 48 hours of ACS was observed in 106 (11.8%) patients, of which 59 (6.5%) required defibrillation and 47 (5.2%) terminated spontaneously. Compared to those without VTs, patients with VTs were more likely to be male (84.9% vs 73.8%, P=0.01), suffered from ST-elevated myocardial infarction (75.5% vs 63.7%, P=0.02) and lower left ventricular ejection fraction (LVEF; 39.3±11.8 vs 44.6±11.1, P<0.001), but less likely to have hypertension (40.6% vs 58.6%, P=0.001) or diabetes (22.6% vs 36.0%, P=0.006). However, there was no difference in the site of culprit lesion and peak troponin level between the two groups (P>0.05). After a mean follow-up of 32.4±22.3 months, 195 (21.5%) patients died. After exclusion of those who died within 7 days of ACS, or died of pulseless electrical activity or asystole, 10 (9.4%) patients with VTs and 28 (3.5%) without VTs developed SCD. In the multivariate cox regression analysis, VTs at presentation [Hazard Ratio (HR) 3.90 (95% confidence interval (CI) 1.86–8.20), P<0.001], prior coronary artery disease [HR 2.27 (95% CI 1.11–4.64), P=0.03], LVEF ≤35% [HR 2.32 (95% CI 1.21–4.45), P=0.01] and renal failure [defined by creatinine ≥200μmol/L; HR 3.08 (95% CI 1.39–6.79), P=0.005] remained independently predictive of SCD. Importantly, the incidences of SCD in ACS patients with VTs were much higher at 8–40 days, 41–120 days, 121- 360 days and 361–720 days of presentation compared to those without VTs. Nevertheless, the risk of SCD reduced and became same in both groups after 2 years (Figure).



Incidence of SCD after ACS

Conclusions: Despite successful coronary intervention, VTs at presentation independently increases the risk of SCD especially within the first 2 years after ACS. Consideration should be given to implant ICD for prevention of SCD in this group of patients regardless of LVEF. Subcutaneous ICD that can be safely removed in those without initial events may be preferred.

P634 | BEDSIDE
Age may not be most important factor in the decision to initiate cardiopulmonary resuscitation in the elderly

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Background: Japan is the first super-aging society in the world. Recent studies in Japan have demonstrated that the prognosis for elderly patients who experience out-of-hospital cardiac arrest (OHCA) is improving with time. However, an

upper age limit, above which initiating cardiopulmonary resuscitation (CPR) may be regarded as unethical, remains unclear.
Purpose: The aim of this study was to determine the relationship between age and outcomes in elderly patients with OHCA.
Methods: We analysed the records of 168,526 OHCA patients (age ≥70 years) treated by emergency medical service providers from a prospectively recorded Japanese national Utstein-style database from 2011 to 2012. Patients were divided into 3 groups according to their age: 70–79 years, 80–89 years, and ≥90 years. The endpoints were 1-month survival and 1-month survival with favourable neurological outcomes corresponding to a score of 1 or 2 on the Cerebral Performance Category scale (CPC 1–2).
Results: Of 168,526 OHCA patients, 5,320 (3.2%) survived for 1 month after OHCA, and 1,884 (1.1%) achieved a CPC 1–2 at 1 month. The crude and adjusted (using 11 prehospital variables) 1-month survival rates were 4.5% and 4.5% for patients aged 70–79 years, 2.8% and 3.3% for patients aged 80–89 years, and 1.7% and 2.1% for patients aged ≥90 years, respectively. The crude and adjusted 1-month CPC 1–2 rates were 1.9% and 1.9% for patients aged 70–79 years, 0.9% and 1.1% for patients aged 80–89 years, and 0.4% and 0.6% for patients aged ≥90 years, respectively. Recursive partitioning analyses revealed that the 3 prehospital variables most associated with improved 1-month survival were initial shockable rhythm, bystander-witnessed arrest, and younger age. In bystander-witnessed OHCA patients with initial shockable rhythm (n=5,302), the crude 1-month survival and 1-month CPC 1–2 rates were 27.7% and 17.6% for patients aged 70–79 years, 18.8% and 10.9% for patients aged 80–89 years, and 11.0% and 6.4% for patients aged ≥90 years, respectively. The adjusted 1-month survival and 1-month CPC 1–2 rates in those patients were 16.8% and 10.2% for patients aged 80–89 years, and 8.4% and 5.1% for patients aged ≥90 years, respectively. However, in bystander-unwitnessed OHCA patients with initial asystole (n=101,037), the crude 1-month survival and 1-month CPC 1–2 rates were extremely low: 1.23% and 0.23% for patients aged 70–79 years, 0.95% and 0.17% for patients aged 80–89 years, and 0.71% and 0.10% for patients aged ≥90 years, respectively. The adjusted 1-month survival and 1-month CPC 1–2 rates in those patients were 0.96% and 0.17% for patients aged 80–89 years, and 0.76% and 0.11% for patients aged ≥90 years, respectively.
Conclusions: In Japan, CPR for elderly patients with OHCA was not generally futile even in patients aged ≥90 years. Therefore, age itself may not be most important factor over other individual variables when deciding whether to start CPR for elderly patients with OHCA.
Acknowledgement/Funding: The Japan Society for the Promotion of Science (KAKENHI Grant Number 15K08543)

P635 | BEDSIDE
The usefulness of CHA2DS2-VASc score in predicting the risk of sudden cardiac death and ventricular arrhythmias in patients with atrial fibrillation

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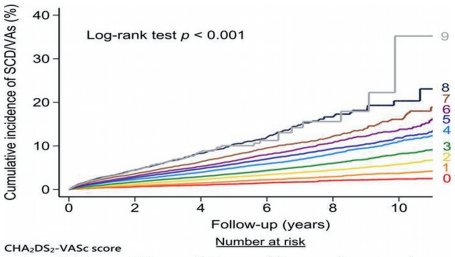
Background: Sudden cardiac death (SCD), the most devastating manifestation of ventricular arrhythmias (VAs), including ventricular tachycardia and ventricular fibrillation, was the leading cause of mortality among patients with atrial fibrillation (AF). CHA2DS2-VASc scheme is recommended by both American and European guidelines to guide anti-thrombotic therapies in AF patients. Since the risk components of the CHA2DS2-VASc scheme were also important risk factors of SCD/VAs, we hypothesized that the CHA2DS2-VASc score could be used to estimate the individual risk of SCD/VAs for each AF patient.
Methods: This study used the "National Health Insurance Research Database". From year 2000 to 2011, a total of 288,181 newly-diagnosed AF patients without antecedent SCD/VAs were identified as the study population. During the follow up, 11,166 patients experienced SCD/VAs.
Results: The annual risk of SCD/VAs for Chinese AF patients was 1.05%. Patients experiencing SCD/VAs had a higher CHA2DS2-VASc score compared to those without (median value = 5 versus 4, p<0.001). The annual risk of SCD/VAs continuously increased from 0.34% for patients with a CHA2DS2-VASc score of 0 to 2.63% for those with a score of 9. Cumulative incidence curve of SCD/VAs



Risk of SCD/VAs

in patients with different CHA2DS2-VASc scores were shown in Figure. The CHA2DS2-VASc score was a significant predictor of SCD/VAs with an adjusted hazard ratio (HR) of 1.21 (95% confidence interval = 1.20–1.22) per 1 increment of the CHA2DS2-VASc score after the adjustment for the potential confounders. The c-index for CHA2DS2-VASc in predicting SCD/VAs was 0.66 (95% confidence interval = 0.64–0.68, p<0.001).
Conclusions: CHA2DS2-VASc score was a convenient scoring system which could be used to predict the risk of SCD/VAs in AF patients in addition to its ability for stroke risk stratification.

P636 | BEDSIDE
NT-proBNP levels after 24 hours provide independent prognostic information in patients with ventricular arrhythmia-induced out-of-hospital cardiac arrest

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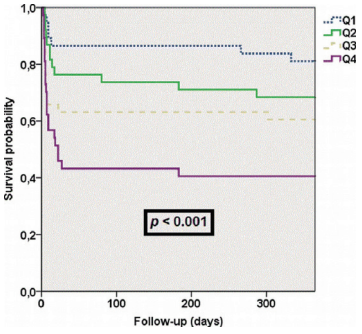
Background: Patients with out-of-hospital cardiac arrest due to ventricular tachycardia or fibrillation (OHCA-VT/VF) have a poor prognosis, but whether N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels improve risk prediction in in OHCA-VT/VF is not known.
Methods: We measured NT-proBNP levels in 155 patients with OHCA-VT/VF enrolled into a prospective multicenter observational study in 21 ICUs in Finland (FINNRESUSCI Study). Blood samples were drawn <6 h of OHCA-VT/VF and later after 24 h, 48 h, and 96 h. The co-primary end-points were mortality and neurological outcome classified according to Cerebral Performance Category (CPC) after one year. NT-proBNP levels were compared to high-sensitivity troponin T (hs-TnT) levels and established risk scores.
Results: NT-proBNP levels were higher in non-survivors compared to survivors on study inclusion (median 1003 [quartile 1–3 502–2457] vs. 527 [179–1284] ng/L, p=0.001) and after 24 h (1913 [1012–4573] vs. 1080 [519–2210] ng/L, p<0.001). NT-proBNP levels increased from baseline to 96 h after ICU admission (p<0.001) and NT-proBNP levels were significantly correlated to hs-TnT levels after 24 h (rho=0.27, p=0.001), but not to hs-TnT levels on study inclusion (rho=0.05, p=0.67). NT-proBNP levels at all time points were associated with clinical outcomes, including when stratifying patients according to quartiles of NT-proBNP (Figure; NT-proBNP quartiles after 24 h). Still, only NT-proBNP levels after 24 h predicted mortality and poor neurological outcome in models that also adjusted for SAPS II and SOFA scores. hs-TnT levels did not add prognostic information to the information obtained by measuring NT-proBNP alone.



NT-proBNP quartiles after 24h

Conclusion: NT-proBNP levels at 24 hours improved risk assessment for mortality and neurological outcome after one year on top of established risk models in OHCA-VT/VF, while hs-TnT measurements did not further add to risk prediction.
Acknowledgement/Funding: University of Oslo

P637 | BEDSIDE
QRS-complex fragmentation is associated with sudden cardiac death in adults with congenital heart disease

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Introduction: Sudden cardiac death (SCD) causes the majority of deaths in adult congenital heart disease (ACHD) patients. However, in part due to its low incidence, mainly in patients with mild congenital defects, identification of high-risk patients remains challenging. Fragmented QRS-complexes (fQRS) are a marker

for scarring, ventricular arrhythmia and SCD in patients with acquired heart disease, but data in ACHD patients is lacking.
Purpose: We evaluated the prognostic value of fQRS for SCD in ACHD patients.
Methods: This was a multicenter case-control study in a mixed cohort of 25,790 mild, moderate and severely affected ACHD patients. We included all SCD cases (n=165), and 310 controls, matched by age, gender, congenital defect and (surgical) intervention. We assessed 12-lead ECGs for fQRS, which was defined as ≥1 additional discontinuous deflection in narrow QRS-complexes, and ≥2 in wide QRS-complexes (>120ms), in ≥2 contiguous ECG-leads. We calculated odds ratios (OR) with corresponding P-values using uni- and multivariable conditional logistic regression models, adjusted for the established prognostic parameters for SCD (impaired systemic ventricular function (SVF), heart failure (HF) symptoms and QRS-duration).
Results: For 150 SCD cases (66% male, median age at death 34 years old) and 271 controls, the ECGs were of sufficient quality for fQRS analysis. fQRS was present in 49% of cases and 34% of controls (OR 1.8, P=0.007). The most common diagnoses among SCD cases were tetralogy of Fallot (ToF, 34 cases, 63 controls) and univentricular heart (UVH, both Fontan and uncorrected, 22 cases, 37 controls). In ToF, fQRS was present in 71% vs. 42%, respectively (OR 2.8, P=0.03). In UVH, fQRS was present in 55% vs. 30%, respectively (OR 2.9, P=0.13). fQRS in the anterior leads was more strongly associated with SCD (21% in cases vs. 11% in controls; OR 2.3, P=0.01), compared to lateral leads (12% vs. 7%; OR 1.4 P=0.39), inferior leads (28% vs 23%; OR 1.2, P=0.55) and other leads (14% vs. 15%; OR 0.8, P=0.61). In multivariable analysis, fQRS was independently associated with SCD (OR 1.7, P=0.04, figure 1).

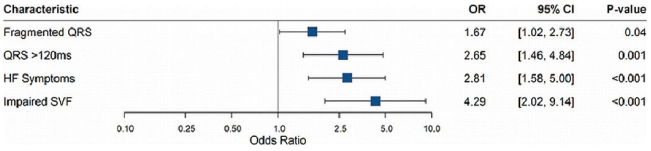

Figure 1

Conclusion(s): fQRS is independently associated with SCD in ACHD patients in this cohort of SCD patients and matched controls. fQRS in the anterior ECG-leads is most prognostic for SCD. Independently, fQRS may not be a robust enough prognostic factor to warrant primary prevention of SCD; however, it may contribute to the decision when evaluating ACHD patients for ICD implantation.
Acknowledgement/Funding: No specific funding was received for this study, other than from Academic Medical Center Medical Research BV.

P638 | BEDSIDE
The use of cardiac magnetic resonance imaging in the survivors of sudden cardiac death

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Background: Sudden cardiac death (SCD) is a severe condition that has multiple aetiologies. The SCD survivors require a detailed diagnostic work-up. Cardiac magnetic resonance imaging (CMRI) provides a complex non-invasive evaluation of myocardial function and structure.
Purpose: To evaluate the role of CMRI in the survivors of cardiac arrest in the diagnostic process and clinical decision-making.
Methods: Survivors of cardiac arrest, who were referred to our centre for detailed evaluation in the period 2010–2015, were screened for the purpose of this study. Enrolled were those who underwent CMRI as a part of complex diagnostic evaluation. The main aim of the study was to identify the number of patients where the CMRI contributed to the diagnosis of the SCD aetiology and influenced the choice of therapy.
Results: Forty-five patients (52±13 years, 12 women) were enrolled. CMRI showed abnormal findings in 35 (78%) patients: previous myocardial infarction in 12 (27%), acute myocardial infarction in 6 (13%), myocarditis in 6 (13%), dilated cardiomyopathy in 6 (13%), and hypertrophic cardiomyopathy in 1 (2%). Non-specific findings such as wall motion abnormalities or cardiac hypertrophy were noted in 4 (9%) cases.
Concerning the therapeutic implications, based on CMRI results, the indication of implantable cardioverter defibrillator (ICD) was confirmed in 12 patients with previous myocardial infarction who had no signs acute myocardial injury on CMRI. On the other hand, CMRI enabled the visualisation of acute myocardial necrosis and confirmed the diagnosis of acute myocardial infarction in 6 patients, who were not consequently referred for ICD implantation. In the remaining patients (n=27; 60%), the CMRI results did not directly influenced the therapeutic approach.
Conclusion: The CMRI may contribute to the diagnostic process in a substantial number of survivors of cardiac arrest. However, the therapeutic implications resulting from CMRI are limited mainly to patients with coronary artery disease.

P639 | BENCH
Incremental value of cardiac magnetic resonance imaging for diagnosis and prognosis in sudden cardiac arrest survivors without coronary artery disease

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Background: Determining the aetiology of sudden cardiac arrests (SCA) without coronary artery disease (CAD) is particularly challenging and is central for management and prognosis.
Cardiovascular magnetic resonance (CMR) can detect structural, functional and tissue abnormalities, potentially increasing our diagnostic ability. However, its value in assessing prognosis is still unclear.
Purpose: Our aim was to assess the diagnostic and prognostic value of CMR in survivors of SCA without CAD.
Methods: We enrolled consecutive SCA survivors without CAD admitted to our institutions between 2008–2014. All underwent CMR imaging and, when indicated, electrophysiology studies. CMR scans were analyzed blindly and final diagnosis made by consensus between 2 investigators.
The primary endpoint, major adverse cardiac events (MACE), was a composite of significant non-fatal arrhythmia [appropriate anti-tachycardia pacing or implantable cardiac defibrillator (ICD) shock, sustained ventricular tachycardia (VT) or ventricular fibrillation (VF)] and death.
SPSS® was used; p<0,05 for statistical significance.
Results: We included 164 patients, 65% male, mean of 48 (18–80) years.
In 80 patients (49%), CMR identified a likely cause for SCA.
A primarily arrhythmic cause was found in 24 cases (15%): a channelopathy in 13, accessory pathway in 5 and an acquired cause in 6.
In 36% (60) no underlying diagnosis was found.
In those with a CMR diagnosis, 8 conditions were detected, including dilated cardiomyopathy (34%), myocarditis or possible cardiac sarcoidosis (27.5%), missed myocardial infarction (16%) and hypertrophic cardiomyopathy (11%).
In the 84 without a CMR diagnosis, subtle non-diagnostic CMR abnormalities were seen in 35% and the scan was totally normal in 65%.
ICDs were implanted in 70% of all patients. During 32 months of median follow-up (IQR 17–52), MACE occurred in 31% of the entire cohort, including 9 deaths.
Patients with diagnostic CMR changes had significantly more MACE (41% vs 21%; p=0.007). However, time to MACE was not different and no association between different CMR diagnosis and prognosis was detected.
Regardless of diagnosis, the presence and extent of late gadolinium enhancement and left ventricular ejection fraction (LVEF) were significantly associated with MACE, but only LVEF was an independent predictor.
In those without a diagnosis, presence of non-specific CMR abnormalities did not affect outcome.
Conclusions: In survivors of SCA without CAD, CMR indicated a cause in nearly half of all patients. In more than one third, no aetiology was detected.
SCA survivors are at high risk of future events and CMR identification of a specific diagnosis was related with the worst prognosis.
Patients that did not receive a diagnosis were also at risk and subtle CMR abnormalities did not predict their outcome. Given the high recurrence and unpredictability of events, ICD implantation must be considered even when no diagnosis can be made.

P640 | BEDSIDE
Effect of continuous positive airway pressure on circadian patterns of cardiac repolarization in obstructive sleep apnoea: data from a randomized controlled trial

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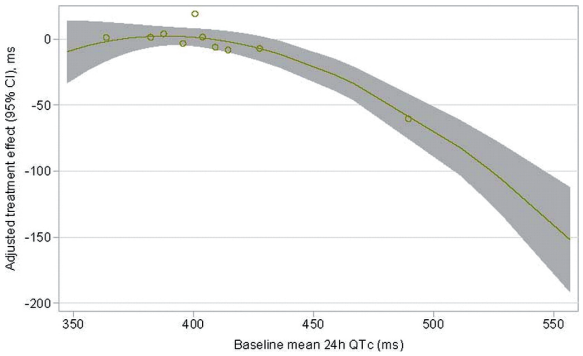
Background: Obstructive sleep apnoea (OSA) has been proposed as an independent risk factor for sudden cardiac death (SCD). This study takes advantage of a previous randomized trial, evaluating circadian patterns of the QTc-interval, a marker of cardiac repolarization and biomarker for SCD, in patients with OSA. We hypothesized that patients with OSA exhibit longest QTc during the nighttime and that continuous positive airway pressure (CPAP) therapy would reverse this.
Methods: 118 patients diagnosed with moderate-to-severe OSA were randomized to receive therapeutic or subtherapeutic CPAP for four weeks. Of these, 84 had full 24h-Holter monitoring data. Weighted means of all QTc-intervals were analysed over 24h, during four time-periods (12pm–6am, 6am–12am, 12am–6pm, 6pm–12pm) as well as during each hour.
Results: QTc-intervals at baseline were highest from 6pm–12pm (411.7ms) and shortest from 6am-12am (405.4ms). Overall-24h CPAP treatment effect on QTc was –11.3ms (p=0.039) and was estimated to be greater from 6pm-12pm than from 12pm–6am (p=0.068). The CPAP treatment effect on QTc was driven by those patients in the highest QTc decile at baseline (all >430ms). In these patients, CPAP allowed reclassification into lower risk associated values of QTc <430ms.



Conclusions: CPAP treatment led to an overall reduction in the QTc-interval. This reduction seems more pronounced during evening hours and in patients with a QTc>430ms.

P641 | BEDSIDE
Association of nighttime with decreased survival and resuscitation efforts for out-of-hospital cardiac arrests

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Background: Out-of-hospital cardiac arrest (OHCA) is a major public health problem worldwide. Despite the recent advances in the management of OHCA, the fatality rate remains unsatisfactory. Shift work disrupts circadian rhythms, causing health risks and deteriorating the shift worker's abilities and performance regarding attention, motivation, and decision-making. Thus, nighttime circumstances may alter resuscitation efforts of healthcare providers when OHCA occurs. Time differences and clinical outcomes of patients with OHCA did not yield consistent conclusions. Furthermore, the associations of time of day with altered resuscitation efforts remain insufficiently tested.
Purpose: We aimed to test that patients who had OHCA during the nighttime had poor clinical outcomes, then we tested for the association of nighttime OHCA with altered resuscitation efforts of bystanders and healthcare providers.
Methods: We used a large, multicenter cohort collected for the Survey of Survivors after Out-of-Hospital Cardiac Arrest in the Kanto Region (SOS-KANTO) by the 2012 Study Group in Japan, which includes both prehospital and in-hospital resuscitation data collected by emergency medical services and hospital staff. We studied 13,780 adult OHCA patients in the SOS-KANTO 2012 study from January 2012 to March 2013 in Japan. The primary variable was 1-month survival. The secondary outcome variables were prehospital and in-hospital resuscitation efforts by bystanders, emergency medical services personnel, and in-hospital healthcare providers. Daytime was defined as 7:01 to 15:00, evening was defined as 15:01 to 23:00, and night was defined as 23:01 to 7:00. We adjusted potential confounding factors using multivariate logistic regression analyses and possible clustering effects of institutions using a generalized estimating equation.
Results: The patients with night OHCA had significantly decreased 1-month survival compared to the patients with daytime OHCA (night vs. daytime, adjusted odds ratio [OR] 1.46; 95% confidence interval [CI], 1.16–1.82; P=0.0011). The nighttime OHCA patients had significantly decreased call-response intervals, bystander CPR, in-hospital intubation, and in-hospital blood gas analyses compared to the daytime and evening OHCA patients (call-response interval: OR, 0.95 and 95% CI, 0.93–0.96; bystander CPR: OR, 0.85 and 95% CI, 0.78–0.93; in-hospital intubation: OR, 0.85 and 95% CI, 0.74–0.97; in-hospital blood gas analysis: OR, 0.86 and 95% CI, 0.75–0.98).
Conclusions: The patients who experienced OHCA during the nighttime had significantly decreased 1-month survival rates compared to those who experienced OHCA during the daytime. Since the nighttime OHCA patients had decreased implementation rates of bystander CPR, in-hospital intubation, and blood gas analysis, increasing resuscitation efforts during the nighttime may improve patient survival after OHCA.
Acknowledgement/Funding: The Japanese Association for Acute Medicine of Kanto

P642 | BEDSIDE
Lower Spatial QRS-T angle rules out sustained ventricular arrhythmias in hypertrophic cardiomyopathy

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Introduction: The spatial peaks QRS-T (SPQRS-T) angle has been shown to differentiate hypertrophic cardiomyopathy (HCM) patients from controls. The SPQRS-T angle has also demonstrated ventricular arrhythmia risk stratification in those with ischemic heart disease. We hypothesize that the spatial QRS-T angle will differentiate HCM patients with ventricular arrhythmias (VA's) from those without VA's.
Methods: A retrospective study of 228 HCM patients was performed. Corrected QT interval (QTc), QRS duration (QRSd) and spatial peaks QRS-T angles (SPQRS-T angle) were assessed on patients with VA's (>30 seconds and those without VA's). Significance, positive/negative predictive values and odds ratios (OR) were calculated.
Results: Twenty seven HCM patients had VA's (23.6±14.4 years, 76.9% male). Two hundred and one HCM patients did not have VA's (20.0±13.8 years, 72.1% male). Twenty patients with VA's were identified. The QTc differentiated those with VA's from those without VA's with values of 473.4±46.9ms and 443.7±50.3ms, respectively (pvalue= 0.008). At an optimum value of 460ms, the QTc positive and negative predictive values (PPV and NPV) were 21.7% and 91.7%, respectively with an OR of 3.0 (95% CI 1.3 to 6.9). The SPQRS-T differentiated those with VA's from those without VA's, 145.8±24.2 versus 114.3±43.3 degrees (p value<0.001). At a cut-off value of 124.1 degrees, there was a PPV and NPV's of 21.9% and 98.3%, respectively with OR of 16.1 (95% CI 3.7 to 69.6). QRSd values did not significantly differ. Only the SPQRS-T angle remained an independent predictor of VA.
Conclusion: In our HCM cohort, the SPQRS-T angle and the QTc differentiate HCM with VA's from those without VA's. The SPQRS-T angle was the only independent predictor of VA.

P643 | BEDSIDE
Out of hospital cardiac arrest: a matter for cardiologists. First year results for the first long follow-up cardiac arrest registry by cardiologists

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Background: Out-of-hospital cardiac arrest (OHCA) kills about 1 person in 1000 every year and the mean survival in Europe is about 6–7%. The key interventions for an OHCA are summarized by the chain of survival whose diffusion, knowledge and improvement are on the base of the Utstein formula for survival.
Purpose: Our aim Is to create the first registry of OHCA with a long follow-up (5 years) proposed by cardiologists and created according to the 2014 Utstein style.
Methods: All the patients who suffered an OHCA of any aetiology in our Province (about 550000 inhabitants) from October 2014 onwards in whom CPR was attempted were enrolled in the registry. The main outcome was the survival at 1 month, and the secondary outcomes were the survival at 6 month and then every year until 5 year after OHCA.
Results: In the first 12 months (October 2014-September 2015) we enrolled 481 confirmed OHCA [male 60.9% (n=293); mean age of 74.2±15.2 years]. The mean EMS response time was 11:38±5:38 mins. 78.4% (n=377) of the OHCA occurred at home, 10.2% (n=49) in nursing facilities, 1.9% (n=9) during work, 0.4% (n=2) during sport and 9.1% (n=44) in public location. 53.8% (n=259) were witnessed by bystander, 15.8% (n=76) by EMS and the others were unwitnessed. The rate of bystander CPR were 29.7% (n=143), whilst an AED was used before the EMS arrival in 1.7% (n=8) of cases, with a shock delivered in 37.5% (n=3) of them. Concerning the aetiology 94.4% (n=454) were medical, 3.9% (n=19) traumatic, 0.2% (n=1) by overdose, 0.2% (n=1) by drowning and 1.2% (n=6) asphyxial. The first rhythm was shockable in 15.2% (n=73) (94.5% VF, 5.5% VT without pulse), and non-shockable in the remaining 84.8% (n=408) (69.8% asystole, 29.2% PEA and 1% AED non-shockable). According to the 2014 Utstein recommendations we calculated the survival of different groups of patients as presented in Table 1.
Conclusions: Our results, among the first to be presented according to the 2014 Utstein recommendations, appear aligned to literature. We believe that our

Abstract P643 – Table 1. Survival of different groups of patients calculated according to the 2014 Utstein recommendations

		Total	Any ROSC	Survived event	Survival 30 days	CPC ≤2
EMS witn. included	All EMS treated	n=481	n=104 (21.6%)	n=80 (16.6%)	n=35 (7.3%)	n=26 (5.4%)
EMS witn. Excluded (n=405)	Shockable bystander witnessed	n=50	n=34 (68%)	n=31 (62%)	n=17 (34%)	n=13 (26%)
	Shockable bystander CPR	n=35	n=21 (60%)	n=20 (57.1%)	n=14 (40%)	n=13 (34.3%)
	Non-shockable witnessed	n=207	n=31 (15%)	n=18 (8.7%)	n=3 (1.4%)	n=1 (0.5%)

registry, due to its long follow-up, will provide interesting elements to better understand the long-term issues to improve OHCA survival.

P644 | BEDSIDE
Sudden death in Wolf-Parkinson-White: report of 19 cases from a large pathology registry

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Aims: The prevalence of pre-excitation (Wolff-Parkinson-White (WPW) pattern) is estimated at 0.3%. The risk of malignant arrhythmias in asymptomatic individuals is low and ablation of the accessory pathway is considered to diminish the risk of sudden cardiac death (SCD). The aim of the study was to describe clinical characteristics and pathological features of SCD victims with a pre-morbid diagnosis of WPW.
Methods: Between 1994 and 2014, 3684 cases of SCD were referred to our cardiac pathology centre; 19 (0.5%) with known pre-excitation on their ECG. Clinical information were obtained from referring coroners. All subjects underwent detailed post-mortem evaluation including histological analysis by an expert cardiac pathologist.
Results: The majority of patients were males (n=16, 84%) of Caucasian descent (n=17; 89%). The mean age was 31±15 years (2 patients over the age of 50). Five cases (26%) were asymptomatic. Of the 14 symptomatic patients, 13 (68%) reported palpitations, 1 (5%) syncope. Five individuals (26%) had a previous ablation, 4 of which were judged to be successful with resolution of pre-excitation on the ECG. In the majority of cases (n=15; 79%) SCD occurred at rest. The mean heart weight was 408±105 g. In 10 patients (53%) the post-mortem exam revealed a normal heart, in 5 cases there was a definitive cardiac pathology (n=4 with hypertrophic cardiomyopathy, n=1 with cardiac sarcoid), and 4 cases demonstrated autopsy findings of uncertain significance (n=2 with idiopathic left ventricular hypertrophy, n=1 with idiopathic fibrosis, and n=1 with enlarged left ventricle). Out of the 5 asymptomatic patients, the post-mortem revealed HCM in 3 and a normal heart in 2 cases. The patients that underwent previous ablation were characterized by a normal heart in 3 cases and by idiopathic left ventricular hypertrophy at the post-mortem.
Conclusions: 25% of SCD victims was asymptomatic, raising concerns relating to the value of symptoms in risk stratification of individuals with pre-excitation. In addition, accessory pathway ablation did not eliminate the risk of SCD possibly due to multiple pathways. Finally, pre-excitation was associated with additional structural abnormalities in almost 50% of cases, underscoring the necessity of performing baseline echocardiography in all individuals and suggesting that the combination of pre-excitation with additional cardiac pathology may render individuals at higher risk of SCD.

P645 | BEDSIDE
Girona Vital: performance evaluation of defibrillators in a regional public access defibrillation program

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Background and aims: Public access defibrillation programs have exponentially increased the availability of automatic defibrillators (AEDs) in public spaces. Little information about its performance is available. We performed a descriptive analysis of the AEDs performance since the launching of a public defibrillation program in our region.
Methods: Retrospective analysis of ECG tracings and AEDs performance in a public defibrillation program in the province of Girona between june 2011 to june 2015, based on the presence of both fixed and mobile devices. The records were analyzed by 4 independent blinded cardiologists.
Results: Of 231 AEDs activations, full information on 189 activations was obtained, 71.4% corresponding to mobile devices. Asystole was the most prevalent first rhythm (42%), while we identified a shockable first rhythm in 24% of the tracings. The specificity of AEDs identifying shockable rhythms was 100% but there were 8 false negatives in cases of fine ventricular fibrillation (sensitivity 84%). When a sockable rhythm was detected, the effectiveness of the therapy restoring the sinus rhythm was 45.9%. Analyzing the cardiopulmonar resuscitation waves of the tracings, maneuvers were performed in 79% of the cases, but only in 45% fulfilled pre-specified quality criteria. Of shockable rhythm patients 42.5% recovered spontaneous circulation, whereas 14% of the non shockable rhythms. There were no accidents related to the use of the devices.
Conclusion: Only one in four first rhythms were shockable. The AED performance analysis showed an excellent safety and specificity, with suboptimal sensitivity. Half of the patients who had shockable rhythm were treated successfully by the DEA. The inability to detect some of the fine ventricular fibrillation brings into question whether the AED should always provide a discharge when detecting asystole, to ensure that fine ventricular fibrillation is not left untreated.

P646 | BEDSIDE
Anxiety, depression and quality of life in acute high risk cardiac disease patients eligible for wearable cardioverter defibrillator: results from the prospective multicenter CRED-registry

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Background: Psychological distress is common in patients with cardiovascular disease and might affect quality of life, outcome and response to therapy. The prevalence of psychological distress is unknown in acute high risk cardiac patients who are potential candidates for a wearable cardioverter defibrillator (WCD).
Methods: The prospective multicenter "Cologne Registry of External Defibrillator" (CRED; NCT02073942) registry recruits consecutive patients at increased risk of ventricular arrhythmias who are candidates for WCD use. Quality of life (Short Form-12), depressive symptoms (Beck-Depression Inventory [BDI]-II) and anxiety (State Trait Anxiety Inventory) were assessed in 73 patients (age 59 + 15 years, 74% male) at enrollment and association with baseline characteristics was analyzed.
Results: 37%, 10% and 5% of patients showed minimal, mild and moderate depressive symptoms, respectively, and 53% of patients showed anxiety (state-anxiety score >40), with a significant correlation between BDI-II score and state-anxiety score (Pearson coefficient $r=0.52$, $p<0.0001$). Patients with at least mild depressive symptoms (BDI-II>14) and anxious patients showed a significantly lower mental component score (indicating poorer quality of life; 40 [+11] and 49 [+11]) compared to those without mild depressive symptoms (54 [+10], $p<0.001$) and non-anxious patients (55 [+10], $p=0.01$). Patients with mild depressive symptoms and anxious patients did not differ significantly regarding age, gender, blood pressure, diabetes, stroke, BMI, ejection fraction, renal function and NT-pro-BNP levels from patients without psychological distress.
Conclusions: In these high risk patients depressive symptoms and anxiety is frequent and associated with poor mental quality of life. Depressive and anxious patients cannot be identified by clinical characteristics assessed in routine practice.
Acknowledgement/Funding: The study was supported by Zoll Medical Corporation

P647 | BEDSIDE
Antibodies levels anti sCha as diagnostic and prognosis marker of malignant arrhythmias in chronic Chagasic patients

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Malignant arrhythmias associated to sudden death are the principal cause of mortality in Chagas disease. The final episode is often asymptomatic, raising concern about patients under sudden death risk, especially in areas where arrhythmias diagnosis is not widely available. Thus, the aim of this work was to test the potential of the auto-antibodies anti-sCha as diagnosis and/or prognostic marker of malignant arrhythmias. Serum samples were taken from the 37 Venezuelan and 55 and Colombian Chagasic patients stratified by arrhythmias for ELISA determination of sCha antibodies and Th1 (IL-2, IL-6, IFN-γ and TNF), Th2 (IL-10 and IL-4) and Th17 (IL-17) multiplex array of cytokine. Linear Discriminant Analysis (LDA) compared the centroids for each group, identifying the most relevant variable for discrimination and evaluating the prognosis value of the variables studied. A cytokine signature for each group of patients of patients with values higher to median of each variable was determined. Anti- sCha levels were higher in Venezuelan patients with high risk of sudden death and in Colombian patients with ectopy regarding to low risk or non-arrhythmic ones. Semi-quantitative analysis identified IL-2, IL-17 and sCha as a signature of arrhythmic group for both countries. LDA was able to significantly differentiate arrhythmic and non-arrhythmic patients for Venezuelan and Colombian groups and predicted 88.89% of accuracy for individuals with high levels of IL-2 and sCha. To our knowledge, this is the first report of a serological marker for arrhythmia diagnosis/prediction in Chagasic patients and opens a field for studying arrhythmias pathophysiology.
Acknowledgement/Funding: IVIC 305, CEAL

P648 | BENCH
The validation of the parachute-app smartphone alerting system for exercise-associated cardiac arrest: accuracy tested against the HAL s1020 12-lead ECG patient simulator

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Background: Exercise is the most cost-efficient "drug" for cardiovascular disease. Although low, the incidence of sudden cardiac arrest is several-fold higher during exercise than during rest, both in sedentary subjects and athletes. The phase of active exercise is hence potentially at risk, and is worth more vigilance,

both in healthy subjects and in patients with previous cardiac disease, who also require regular exercise. A new app, called PARACHUTE-Phone App for Rapid ACtion in Human Unconsciousness Threat during Exercise- which is in beta testing phase, may be useful during exercise in lonely settings where a bystander is not available. The app uses a patent-pending algorithm and requires only low-cost, commercially-available Bluetooth chest strap and a smartphone. It is capable to detect exercise-related cardiac arrest with immediate automatic alerting of emergency contacts, using multiple SMS text messaging including GPS coordinates, for rapid navigation to the site.
Purpose: The accuracy of the parachute app and the chest strap heart rate sensor in the detection of simulated exercise-associated cardiac arrest and subsequent emergency alerting was assessed using an advanced 12-lead ECG simulator, which can simulate standard and customised arrhythmias.
Methods: Two different bluetooth chest straps were alternatively tested (Polar H7 and Wahoo ticks), on one end connected to the simulator and via bluetooth to the smartphone running the app. Tests were conducted with 50 different types of ventricular tachycardia or ventricular fibrillation rhythms, always starting from sinus tachycardia (the normal exercise rhythm). Several different ECG amplitudes and waveforms were tested both for ventricular tachycardia and fibrillation. The smartphone was continuously agitated to simulate exercise-related motion until 10 seconds after the arrhythmia start. Primary end points were: a) Time to detection of cardiac arrest (which is based not only on arrhythmia detection) by the parachute-app and b) time to SMS alert message delivery to the prespecified emergency contacts. $<$40 seconds for cardiac arrest detection endpoint and $<$60 seconds for SMS delivery were the prespecified optimal intervals.
Results: The parachute-app did detect all simulated cardiac arrests (100/100) and all events led to the delivery of SMS to the prespecified emergency contact. Time to detection and time to delivery of the SMS alert message were always within the prespecified intervals.
Conclusion: The combination of a Bluetooth chest strap with the parachute-app is potentially a tremendous tool to for safer exercise, due to alerting backup in the rare case of a life-threatening arrhythmia. The system starts the chain of survival by activating the first alerting step. Fast emergency response, possibly within 8–10 min from arrest to defibrillation, remains critical to make this game-changer app also practically effective in reducing mortality.

P649 | BEDSIDE
Prediction of sudden death in patients with chronic heart failure: a prospective comparative study of cardiac iodine-123 metaiodobenzylguanidine imaging and right ventricular ejection fraction

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Background: Cardiac iodine-123 metaiodobenzylguanidine (MIBG) imaging and right ventricular (RV) systolic dysfunction provide prognostic information in patients with chronic heart failure (CHF). However, the prognostic value of RV systolic dysfunction for sudden death (SD) has not been well studied.
Methods: We studied 63 CHF outpatients whose radionuclide left ventricular ejection fraction (EF) was less than 40%. At the entry, cardiac I-123 MIBG imaging was performed, and the cardiac MIBG washout rate (WR) was calculated from the chest anterior view images obtained at 20 and 200min after isotope injection. Furthermore, RVEF was measured by radionuclide angiography. Abnormal WR was defined as more than 27% (the mean control WR +2SD). Reduced RVEF was defined as $\leq$37% as reported previously. The study endpoint was SD.
Results: During a follow-up period of 8.9±4.3 years, 13 of 63 patients died suddenly. At univariate Cox analysis, out of the variables including clinical, echocardiographic, hemodynamic, biochemical, MIBG parameters and RVEF, WR (p=0.0115), Lown grade (p=0.0122), and plasma noradrenaline (p=0.0469) showed a significant association with SD, while there was no association between RVEF and SD, and there was no significant difference in SD-free rate between patients with and without reduced RVEF. Multivariate analysis revealed that WR (p=0.018) and Lown grade (p=0.0154) were independent predictors of SD. Kaplan-Meier analysis showed that the patients with abnormal WR had a significantly higher risk of SD than those with normal WR (p=0.0247).
Conclusion: Cardiac MIBG WR would predict the risk of SD in CHF patients, although RVEF might not.

P650 | BEDSIDE
Long-term effects of septal myectomy on sudden cardiac death in patients with hypertrophic cardiomyopathy

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Purpose: The aim of this study was to determine the long-term outcomes (all-cause mortality, sudden cardiac death (SCD), and incidence of appropriate and inappropriate implantable cardioverter defibrillator (ICD) therapy) after extensive left ventricular septal myectomy in patients with diffuse-generalized form of obstructive hypertrophic cardiomyopathy (HOCM).
Method: This study included 54 consecutive patients with diffuse-generalized form of HOCM treated with either the extensive left ventricular septal myectomy (group A) or medical therapy (group B). Group A consisted of 22 patients (50.1±11.8 y.o., 11 females, 1 LEOPARD syndrome) and group B consisted of 32 patients (43.9±15.1 y.o., 16 females, 1 Danon disease). All patients underwent ICD implantation. The risk of SCD was assessed for each patient in group A before and 1 year after surgery and in group B before ICD implantation using standard "HCM Risk-SCD" calculator.
Results: The mean follow-up period was 2.5±2.2 years. Risk of SCD before and after procedure amounted to 4.0±1.9 and 1.6±0.6 in group A and 4.4±2.8 in group B, respectively. At 1 year after surgery in group A thickness of interventricular septum and the left atrium decreased from 19±3 to 15±2 mm and 45±4 to 42±3 mm, respectively. The peak systolic pressure gradient in the outflow tract of the left ventricle decreased from 76±6 to 20±3 mm Hg. During the observation period 1 patient with LEOPARD syndrome died probably from electrical storm (group A) and 1 patient died from unknown cause (group B). The overall mortality was 4.5% in group A and 3.1% in group B (p=0.08). Appropriate ICD therapy was lower (4.5% vs 6.3%; p=0.04), but inappropriate ICD therapy was higher (9.1% vs 3.2%; p=0.03) in group A. All episodes of inappropriate ICD therapy were caused by very fast conducted atrial fibrillation.
Conclusions: Patients with diffuse-generalized form of HOCM who are treated with extensive left ventricular septal myectomy have good survival and low SCD risk, similar to that of patients with non-obstructive HCM. In addition patients in surgery group had an increased incidence of inappropriate ICD therapy.

P651 | BEDSIDE
High sensitivity C-reactive protein (CRP) as an early marker of outcomes in out of hospital cardiac arrest acute myocardial infarction survivors treated with endovascular mild therapeutic hypothermia

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Background: The prediction of outcome in comatose patients after out of hospital cardiac arrest (OHCA) has major ethical and socioeconomic implications. At present, there is a lack of data comparing the predictive value admission blood levels of C-reactive protein (CRP) in OHCA survivors treated with endovascular therapeutic hypothermia.
Methods: 86 patients (64±14 years, 69 men) were evaluated after OHCA due to ventricular fibrillation (VF) during an acute myocardial infarction (MI). All patients (non-ST elevation acute MI 28% - 24/86, ST elevation MI 72% - 62/86) were indicated for urgent coronary angiography (culprit MI lesion percutaneous coronary intervention was performed in 79% patients – 68/86, non-ST elevation acute MI 14/24 – 58%, ST elevation MI 55/62 – 89%), echocardiography for left ventricular ejection fraction (LVEF) estimation using Simpson biplane formula and treated with mild therapeutic hypothermia (MTH) using intravascular temperature management to maintain target temperature (33 ℃) for 24 hours. Baseline measurements of serum laboratory markers (CRP, NT-proBNP, urea, creatinine, S100B, high sensitivity cardiac troponin T) were performed within 2 hours after admission. The Cerebral Performance Categories scale (CPC) was used as outcome measure and was assessed 3 months post admission; a CPC of 3–5 was regarded as a poor outcome (n=45), and a CPC of 1–2 (n=41) as a good outcome.
Results: Baseline CRP levels were early after admission significantly higher ($p<0.004$) in patients with poor outcomes (CPC 3–5) after OHCA (median 9.6; 5–95th percentile 0.8–64.3 mg/L) compared with CPC 1–2 patients (4.6; 1.0–17.8 mg/L). No significant differences in LVEF (40; 22–50 vs. 40; 21–62%, p=0.208), peak cardiac troponin T (1.5; 0.08–10.00 vs. 0.64; 0.04–5.28 μg/L, p=0.078), NSE (29.2; 15.7–54.9 vs. 25.8; 13.6–52.3 μg/L, p=0.26) and S100-B (0.17; 0.09–1.69 vs. 0.19; 0.04–1.14 μg/L, p=0.734) were found in CPC 3–5 and CPC 1–2 groups comparison. Using an optimal cut-off value $\geq$6.4 mg/L calculated from the receiver operating characteristic curve (area under curve = 0.69; p=0.004), the sensitivity of predicting survival with poor neurological outcome was 64% and the specificity was 75%. Multivariate analysis model analysis revealed that baseline CRP $\geq$6.4 mg/L was an independent predictor of CPC 3–5 outcome, with an adjusted odds ratio of 6.6 (95% confidence interval 1.1–41.3; p=0.043).
Conclusions: In patients after out of hospital cardiac arrest for ventricular fibrillation during acute myocardial infarction, baseline C-reactive protein level at admission gives early, reliable and on myocardial infarction extent independent information concerning outcome and prognosis after cardiopulmonary resuscitation.
Acknowledgement/Funding: Grant support: IGA MH CR NT 11046-6/2010, NT14288-3/2013

NON-INVASIVE STUDIES IN ARRYTHMIAS

P652 | BEDSIDE
T-wave polarity inversion following sudden shortening of diastolic interval: a novel ECG marker associated with a history of Torsade de Pointes in patients with long QT syndrome

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Background: There is a threshold of diastolic interval (DI), below which sudden shortening of ventricular action potential duration (APD) occurs in the subsequent beat. If APD is disproportionally long in some myocardial layers, the transmural heterogeneity of APD may manifest as T-wave polarity inversion (TWPI) in beats following sudden shortening of DI in patients with long QT syndrome (LQTS).
Purposes: 1) To determine the prevalence of TWPI in both healthy subjects and LQTS patients, and 2) to assess the association of TWPI with Torsade de Pointes (TdP) history and with T-wave alternans (TWA).
Methods: 24-h continuous 12-lead electrocardiogram (ECG) was recorded in 15 healthy subjects (9 men; median age, 24) and 39 LQTS patients (17 men; median age, 13); LQTS types 1 (n=18), 2 (n=4), 3 (n=4), and unclassified (n=13). TWPI was defined as polarity inversion of the T wave in the premature beats with coupling interval <80% of preceding sinus cycle length and without aberrant ventricular conduction. Peak TWA values were determined by the Modified Moving Average method.
Results: The 39 LQTS patients were divided into 2 groups: 10 patients with a history of TdP (TdP group) and 29 without (non-TdP group). 38.5% (15/39) of the LQTS patients exhibited TWPI, while none of the healthy subjects showed TWPI. TdP group had a significantly higher incidence of TWPI than non-TdP group [80% (8/10)) vs 24.1% (7/29); P=0.003]. Thus, TWPI provided 80% (95% confidence interval, 44.4 to 97.5) sensitivity and 75.9% (95% confidence interval, 56.5 to 89.7) specificity for an association with TdP history. In all 15 patients with TWPI, only a median of 1 (interquartile range, 1–2.5; minimum-maximum, 1–7) ECG lead exhibited TWPI. TWPI was detectable in the precordial leads V1–6 in 93.3% (14/15) of the patients. Peak TWA values in LQTS patients with TWPI were significantly higher than in those without [76 (55–106.5) vs 38 (30–58) μV, median (interquartile range), p<0.001]. In some patients, TWPI was transformed into TWA triggered by a run of extrasystoles or sudden increase in heart rate.

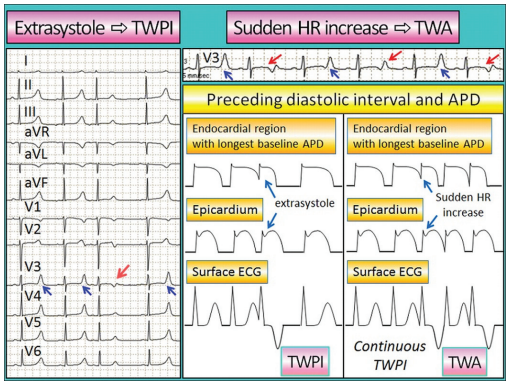

Figure 1

Conclusions: TWPI in the beat following sudden shortening of DI is strongly associated with TdP history in LQTS patients. Use of a limited set of ECG leads may lead to underestimation of TWPI, which is narrowly distributed in the precordial leads. TWPI and TWA may be essentially similar electrophysiological phenomena.

P653 | BEDSIDE
Value of the sodium channel blockers test in Brugada syndrome

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Introduction: Brugada syndrome (BS) is characterized by a typical ECG pattern leading to an increased occurrence of sudden cardiac arrest due to ventricular fibrillation. To carry out the diagnosis in patients without a spontaneous BS ECG pattern, sodium channel blocker (SCB) is currently used. However the value of this test remains poorly known and essentially based on genetic results. However as the penetrance and expressivity of BS in SCNA5 mutation carriers is low, genetic test can not be used as gold standard to define the disease. To clarify the value of SCB challenge, we analyzed a database of 137 families affected byBS, considering the obligatory transmitters (OT) as a true positive for the syndrome.
Methods: All consecutive families from 2001 to 2014 who have at least 2 subjects affected by the BS were screened. The OT were defined as an individual with at least one first-degree descendant and one ascendant presenting a BS or an unexplained sudden cardiac arrest. SCB challenge was performed according the 2nd consensus conference. ECG were reviewed by two experts.
Results: Eighty-five OT have been identified in the 137 selected families. Among the OT, 18 (21%) subjects had a spontaneous type 1 BS, 6 (7%) died from a sudden death, 6 (7%) died before the test was realized, 9 (11%) were not tested because deemed irrelevant in view of the low risk of sudden death and 46 (54%) underwent a SCB challenge. Among patients who underwent a SCB challenge, 42 presented an induced type 1 BS and 4 had a negative test. The sensitivity of the test is 91% (42/46). Thirty-four (74%) patients underwent an ajmaline test and 12 (26%) a flecainide challenge. For ajmaline challenge, 33 patients had a positive test and 9 patients for flecainide test. The sensitivity is significantly better for ajmaline than flecainide (97% vs 75% (p=0.048)).
Conclusion: This is the first study that demonstrates the excellent sensitivity of SBC using non-genetic criteria. Ajmaline appears to have better sensitivity than flecainide to unmask BS. This study reassures about the risk of presenting BS for patients with a negative test and so for their descendants.

P654 | BENCH
Exercise induced frequent atrial premature complexes: a portent of atrial fibrillation

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Background: Atrial premature complexes (APCs) are a common finding on electrocardiograms (ECGs) and have been regarded benign. We investigated clinical impact of frequent/short runs of APCs during exercise.
Methods: A total of 8520 consecutive patients undergone treadmill test from January 2007 to June 2010 were enrolled our registry. Among them, patients with prior ischemic and structural heart disease, and history of atrial fibrillation and flutter (AF/AFL) were excluded. Primary outcome was occurrence of newly developed AF/AFL during follow-up period.
Results: A total of 997 patients (mean age: 52.7±11.8 years old, male: 627 [63.1%]) were analyzed. Mean follow-up duration was 356.2±131.1 days. Patients with frequent/short runs of APCs during exercise were 144 (14.4%). There was no significant different between the two groups (APC group versus non-APC group) in baseline characteristics and medication, except the statin use (p=0.03). During the exercise, maximal heart rate were not significantly different between the two groups (p=0.21), but both systolic and diastolic blood pressure were higher in APC group than those were in non-APC group (p=0.13 and p=0.06, respectively). In univariate analysis, frequent or short runs of APCs during exercise was significantly associated with AF/AFL (hazard ratio [HR]: 23.6, 95% confidence interval [CI]: 2.6–21.4; p=0.01). After multiple adjustment with risk factors of AF/AFL, the APCs during exercise were also independent factor of AF/AFL during follow-up period (HR: 45.8, 95% CI: 4.4–47.6; p<0.01).
Conclusion: Frequent/short runs of APCs during exercise may be no more benign and closed monitoring for further AF/AFL progression in these patients will be needed.

P655 | BEDSIDE
Right bundle branch blocks in a general Chinese population: prevalence, incidence, risk factors, and association with all-cause mortality

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Background: The prognostic value of right bundle branch block (RBBB) is inconsistent across studies. There are no results from Chinese population previously.
Purpose: We aimed to determine the prevalence, incidence, risk factors and association with all-cause mortality of RBBB and incomplete RBBB (IRBBB) among a Chinese community-based population.
Methods: A total of 101,510 participants were included at baseline of the study (2006–2007). 100,157 subjects (79,972 men, and 20,185 women) having ECG recording at baseline free from left bundle branch block were followed up through 31 December 2014 for all-cause mortality. Prevalence and incidence of RBBB and IRBBB were calculated. Predictors of newly acquired RBBB were investigated by means of the logistic regression. Survival analysis regarding of RBBB and IRBBB with all-cause mortality was performed for multiple adjustments.
Results: The prevalence of RBBB/IRBBB was approximately two to three times in man as that in women (RBBB 1.77 vs. 0.84%; IRBBB 0.77 vs. 0.23%), as well as the incidence (RBBB 1.78 vs. 0.87/1000 person-years; IRBBB 0.98 vs. 0.35/1000 person-years). Prevalence and incidence increased with aging in RBBB, but displayed "U" shape in IRBBB. Predictors of newly-acquired RBBB were male gender, increasing age, IRBBB and sedentary/low activity, whereas predictors of IRBBB were male gender, increasing age, current smoking, history of hyperten-

sion, history of myocardial infarction, and elevated level of C-reactive protein. RBBB would increase 14% mortality risk after multivariable adjustments (95% confidence interval, 1.01–1.30). The presence of IRBBB was not associated with mortality.

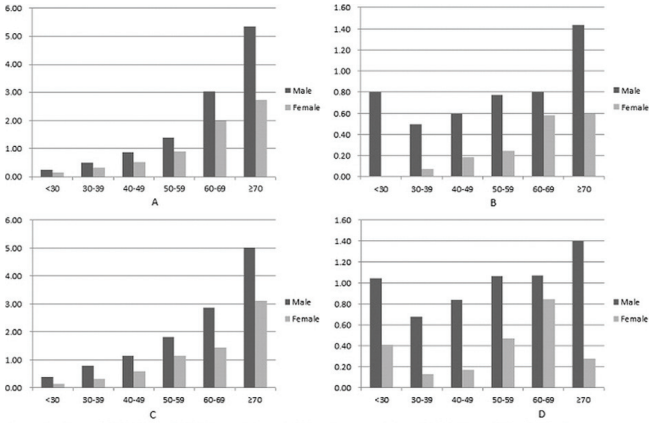

Figure. Prevalence of RBBB (A) and IRBBB (B) at baseline and 1000 person-year incidence of RBBB (C) and IRBBB (D) after 6 years

Conclusion: Prevalence and incidence of RBBB and IRBBB were two to three times more common among men than women. RBBB was associated with all-cause mortality, whereas IRBBB was not.

P656 | BEDSIDE
Evaluation of atrial dyssynchrony in patients with atrial fibrillation treated with catheter ablation: results from a prospective study using pulsed wave tissue Doppler imaging

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Introduction: Left atrial (LA) remodeling causing slower and asynchronous conduction is crucial for the maintenance of atrial fibrillation (AF).
Purpose: We propose a simple method to evaluate the LA asynchrony as a predictor for outcomes after catheter ablation for AF.
Methods: 130 patients with AF (mean age 59±12 years; 58% male; mean EF 64±7%) were examined prospectively using pulsed-wave tissue Doppler (PW-TDI). The time intervals from the onset of P-wave to A' (P-A') were measured at 4 different sites at mitral annulus (septal, lateral, anterior and inferior). The differences between the longest and shortest P-A' (DLS) as well as the standard deviation (SD) of all 4 values were used as measurements of LA asynchrony. Catheter ablation for AF with subsequent LA voltage mapping for scar characterization was performed in all patients. Follow-up visits were operated after 12 months including 7-day Holter-ECG. Patients with and without recurrences of AF after catheter ablation were compared with respect to the atrial activation pattern and atrial asynchrony. Additionally, patients with paroxysmal (PAF) and persistent AF (CAF), as well as with and without LA scar were compared with respect of asynchrony indexes (DLS and SD).
Results: The baseline echocardiographic characteristics, including LA dimensions, were comparable between both groups. 84 (64%) patients presented initially with PAF. The group with AF recurrence had longer DLS as compared to the one without: 38±16 ms vs 28±15 ms; P=0.017; SD was also bigger in AF recurrence group: 19±7 ms vs 16±5 ms; P=0.04. Patients with LA scar areas had significantly longer DLS as compared to those with normal LA: 49±26 ms vs 29±16 ms; P=0.01. Patients with PAF had significantly shorter DLS and SD as compared to those with CAF: 28±15 ms vs 39±22 ms; P=0.01 and 16±6 ms vs 19±5 ms; P=0.04, respectively. Distinct patterns of LA activation were observed with mostly showing upward LA activation (90%) in both groups. DLS was associated with increased probability for AF recurrence after catheter ablation (HR 1.04; P=0.23) independently from LA diameter.
Conclusions: Patients with persistent AF and presence of LA scar areas had greater asynchrony measured with PW-TDI. Also AF recurrences after catheter ablation showed greater LA asynchrony indexes, independently from LA diameter. These simply derived indexes can be useful to identify patients with more advanced LA remodeling who are at higher risk for AF recurrence after catheter ablation.

P657 | BEDSIDE
Effective magnetic dipole dynamics non-invasively assesses the electrophysiological properties of accessory pathways

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Multichannel magnetocardiography (MCG) is a unique contactless method for non-invasive characterization of cardiac electrophysiological events by mapping cardiac magnetic field (MF), which passes undistorted through intermediate human body tissues. MCG is more sensitive to initial electrophysiological (EP) derangements as compared to ECG, which is affected by the non-uniform, structurally complex and poorly conducting body tissues interposed between the heart and the skin, and by the contact resistance between the skin and the sensing electrodes. In addition, MCG contains information absent in ECG because MF measurements can detect circular (vortex) current in the heart, while electrical potential on the surface of the body from such a circular current must be identically zero. One appealing feature of MCG is the determination of the three-dimensional (3D) coordinates and the magnetic moments for the field sources based on the measured MF. This can be done through the solution of the "inverse problem" (IPS). The easiest solution is based on modelling the cardiac MF in terms of a single current/magnetic dipole. By the nature of relevant Physics laws, such solution is not unique because a number of possible field sources can satisfy the same measured MF distribution. Yet, one can successfully find the most probable and plausible approximate solution in terms of effective magnetic dipole model (EMD), at least for short segments of the cardiac cycle when the MF is dipolar. One clinical example of such is the "delta wave". We aimed at evaluating potential utility of MCG inverse solution with EMD to non-invasively characterize EP properties of ventricular preexcitation (VPx).
Method: MCG of 80 WPW patients were retrospectively analyzed. Proprietary software was used to solve the "inverse problem" with the EMD. All calculations were repeated setting reference baseline before the P wave and before the delta wave. The reproducibility was assessed by the intraclass correlation coefficient (ICC=0,86). The spatial-temporal analysis of EMD dynamics provided quantitative assessment of 3D activation trajectory (3D EMD) during the first 10 msec of the delta wave. A correlation was attempted with shortest preexcited RR interval (SPERRI) at EP study.
Results: Two patterns of EMD dynamics were observed during first 10 msec of delta waves: one with short (<1.5 cm) (Fig. 1A) and the other with longer 3D EMD (Fig. 1B). Pts with risk SPERRI (≤200 msec) had significantly shorter 3D EMD than pts with no-risk SPERRI (>240 msec) (1.77±1 vs 2.91±1.9 cm, respectively). Compared with that of EP study/ablation, accuracy of 3D VPx localization was 94% with MCG (vs 67% with ECG algorithms). In cases with unclear MCG localization (6%), complex/multiple VPx was found at the EP study resulting if ablation failure.

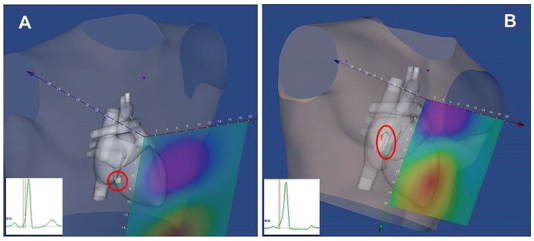

Figure 1. 3D delta wave EMD dynamics

Conclusions: EMD dynamics calculation from MCG provide unique information for non-invasive EP assessment of patients with WPW syndrome.

P658 | BEDSIDE
Assessment of deceleration capacity from short-term recordings predicts mortality after myocardial infarction: prospective validation study

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Background: Deceleration capacity (DC) of heart rate is a strong predictor of mortality after myocardial infarction (MI). DC is a measure of deceleration-related oscillations of heart rate and is usually assessed from 24-hour Holter recordings. Post-hoc analysis from the Autonomic Regulation Trial revealed that DC assessed from short-term recordings (≤30 minutes) can identify high-risk patients after an acute myocardial infarction, without the need to perform a 24-hour ECG-recording. This is a prospective validation study of the predictive power of DC in pos-t-MI patients.
Methods: We included 488 survivors of MI in sinus rhythm aged ≤80 years. All patients underwent a 15-minute ECG recording at 2,048 Hz (TMS, Porti System). The primary endpoint was 3-year all-cause mortality. DC was calculated from the short-term recordings using previously established technologies and was dichotomized at the established cut-off value of ≤2.5ms. We estimated survival curves by the Kaplan-Meier method and compared them with the log-rank test. We finally tested the incremental prognostic value of DC to established risk predictors, including reduced left ventricular ejection fraction (LVEF ≤35%) and presence of diabetes mellitus (DM) using Cox regression analysis. Multivariable models were adjusted for age and gender.
Results: 51 patients died within the first 3-years of follow-up. Median short-term DC was significantly lower in non-survivors compared with survivors (1.40 vs. 4.05, p<0.001). Figure shows the 3-year cumulative mortality rates in patients

stratified by DC ≤2.5ms. The 331 patients with DC >2.5ms had a 3-year mortality rate of 6.8% compared to a 27.4% 3-year mortality rate among the 157 patients with DC ≤2.5ms. In multivariable Cox regression analysis DC ≤2.5ms was the strongest predictor of mortality (HR 2.48, 95% CI 1.34–4.58, p=0.004) followed by LVEF ≤35% (HR 2.39, 95% CI 1.31–4.33, p=0.004).

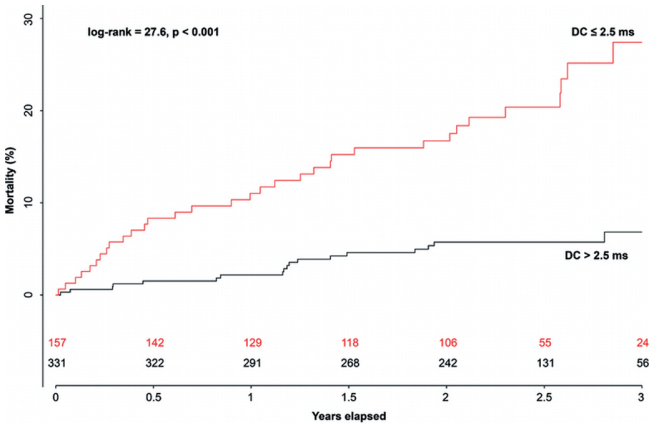

Figure 1

Conclusion: DC assessed from short-term recordings is a strong and independent predictor of 3-year mortality after myocardial infarction.

P659 | BENCH
Investigating inherited HCM caused by SCO2 and PRKAG2 mutations using the patients' induced pluripotent stem cell-derived cardiomyocytes

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Mutations in PRKAG2 gene encoding the γ subunit of AMPK cause hypertrophic cardiomyopathy (HCM) and familial Wolff-Parkinson-White syndrome (WPW). Patients with R302Q mutation in PRKAG2 suffer from sinus bradycardia, escape rhythms, atrial fibrillation and supraventricular tachycardia. This mutation affects AMPK activity and causes elevated glycogen storage in cardiomyocytes. The link between glycogen storage and WPW syndrome, HCM and arrhythmia remains unknown. A mutation in SCO2 gene encoding for mammalian cytochrome-c oxidase, a crucial part of the mitochondrial electron transport-chain, causes HCM and infants deaths.

To investigate the pathological mechanisms underlying these HCM-causing mutations and search for novel pharmaceutical and genetic therapeutic modalities, we generated induced Pluripotent Stem Cells-derived cardiomyocytes (iPSC-CMs) from patients' somatic cells, attempting to recapitulate the disease phenotype in vitro. The diseases we explored are: (1) HCM with familial WPW caused by R302Q mutation in PRKAG2 gene. (2) Concentric HCM caused by G192S mutation in SCO2 gene. Successful reprogramming of respective patients' skin-derived fibroblasts resulted in iPSCs colonies expressing R302Q or G192S mutations. Action potentials were recorded from cardiomyocytes and extracellular electrograms from beating cardiomyocytes clusters using patch clamp and Micro Electrode Array (MEA) techniques, respectively. $[Ca^{2+}]_i$ transients and contractions were recorded by means of fura-2 and video edge detector, respectively. The major findings were: (1) PRKAG2: mutated iPSC-CMs exhibited spontaneous delayed afterdepolarizations (DADs), slow firing rates and irregular rhythms (the latter two at the single cell and network level). Further, these phenomena were intensified with culture age, suggesting inter-relations between glycogen storage and electrophysiological abnormalities. (2) SCO2: mutated iPSC-CMs exhibited attenuated inotropic response to isoproterenol as well as DADs and irregular rhythms. Importantly, transmission electron microscopy analysis of SCO2-mutated iPSC-CMs displayed abnormal mitochondria size and morphology.

Conclusions: PRKAG2 and SCO2-mutated iPSC-CMs displayed abnormal functional features resembling the clinical phenotype expressed in patients carrying the mutations. In these cases of life threatening arrhythmias the cause is neither mutations in structural proteins nor ion channels; the cause for arrhythmias involved with hypertrophic cardiomyopathy, here, lies within mutated metabolism regulators.

P660 | BEDSIDE
Non-invasive testing cannot identify a typical substrate for life-threatening re-entry VTs in athletes

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Introduction: Two electroanatomical (EA) scar pattern for VT from the RV have been identified: a dominant subtricuspid and an isolated epicardial RVOT scar, typical for endurance athletes with inferior axis VT. The latter pattern may not be identified by non-invasive testing.

Methods: Consecutive symptomatic patients (pts) with scar-related re-entry VT from the RV, who underwent endocardial ± epicardial EA mapping (2006–2015) were included. Non-invasive evaluation included medical, family and endurance training history, ECG, Holter, exercise test, imaging studies (echocardiography, cardiac MR, CT), and genetic testing (NGS for 55 genes). Endurance training >6 hours/week, >5 years qualified as endurance athlete.

Results: Among 57 pts (48±15 years, 83% male, 95% Caucasian) 46 (81%) had a dominant subtricuspid scar; 6/46 presented with OHCA, 11/46 had (pre)syncope, 26/46 palpitations. All had features suggestive for structural heart disease (SHD); T-wave inversion (TWI) >V2 in 17 (37%), prolonged TAD 25/35, epsilon waves 10 (21%), wall motion abnormalities (WMA) on echocardiography/CMR 27 (59%), and 25/45 (56%) had an ARVC associated pathogenic mutation. Based on non-invasive testing the diagnosis was definite ARVC in 33 (72%), borderline ARVC in 3 (7%), cardiac sarcoidosis in 5 (11%), scar of unknown origin in 4 (9%) and myocarditis in 1 (2%).

All 11 pts with isolated RVOT scar were endurance athletes (15 [IQR 10–20] hours/week for 13 [IQR 10–18] years; 9/11 (82%) presented with exercise related palpitations including syncope in 6 (55%). All had spontaneous LBBB/inferior axis VT. Only 1 had increased TAD, 2 (18%) TWI V1-V2, but none TWI > V2, epsilon waves, WMA, or a pathogenic mutation. Based on non-invasive testing the diagnosis was idiopathic RVOT VT in 8/11 (81%) and possible SHD based on additional minor criteria in 3. Catheter ablation was successful in 10/11 (91%), none had VT recurrence during 30±37 months.

Conclusion: The majority of endurance athletes with isolated RVOT scar has no features for SHD on non-invasive testing and may be misdiagnosed as idiopathic VT. Considering the potentially life threatening VT EA mapping should be considered in symptomatic athletes.

Acknowledgement/Funding: The department of cardiology (LUMC) receives unrestricted grants from Biotronik, Medtronic & Boston Scientific

P661 | BEDSIDE
Blunted heart rate turbulence is a novel predictor at risk of developing heart failure in patients with diabetes mellitus

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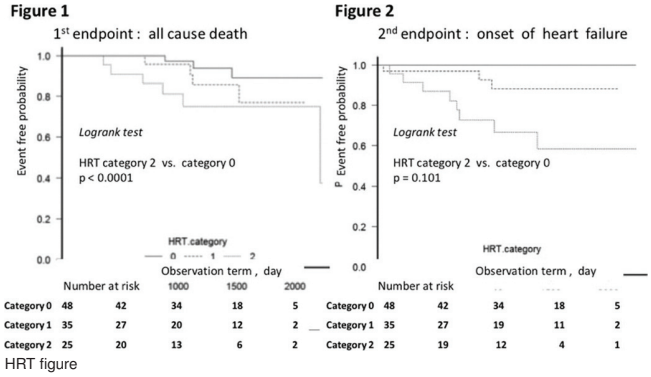
Background: Heart rate turbulence (HRT) is a parameter of the cardiac autonomic dysfunction. Although previous reports showed that the relationship between cardiac autonomic dysfunction and diabetes mellitus (DM), there is no data whether the blunted HRT concerns the prognosis of diabetic patients.

Methods: Consecutive diabetic patients without previous heart failure (HF) who underwent 24hr-Holter ECG were included to this study between Jan. 2009 and May 2014 (N=108, age 70 (62–78)y, HbA1c 7.0 (6.5–8.1)%, LVEF 70 (65–75)%, BNP 49.2 (18.5–118.6)pg/ml). In HRT analysis, turbulence onset (TO) and turbulence slope (TS) were obtained according to the international consensus and TO >0% and/or TS <2.5ms/RR were defined as blunted HRT based on the previous reports. We classified the patients into 3 groups as followings; category 0: normal HRT, category 1: blunted TO or TS, category 2: blunted both TO and TS. The follow-up period was 1142 (798–1560) days after 24hr-Holter recording. We investigated basic characteristics of the patients, all cause mortality and hospitalization due to HF among the groups.

Results: During the follow-up period, 13 (12%) patients died due to HF, malignancy, infectious disease, trauma and unknown causes. However, there was no



HRT figure

significant difference among the categories (p=0.101, Logrank test). On the other hand, 11 (10.2%) patients were hospitalized due to HF and the morbidity rate was significantly higher in the category 2 (8/25 cases) than in the category 0 (0/48 cases) (p<0.0001, Logrank test). In multivariable Cox regression analysis revealed BNP>100pg/ml and blunted both TO and TS (category 2) were independent predictors of developing HF (HR: 5.7, 95% CI: 1.1–29.2, p=0.03 and HR: 4.3, 95% CI: 1.0–17.7, p=0.04, respectively).
Conclusion: In the present study, we demonstrated that blunted HRT would be a strong predictor of developing heart failure in diabetic patients with preserved ejection fraction.

P662 | BEDSIDE
Age and lead specific distribution and prognostic implications of early repolarization parameters in a healthy korean population

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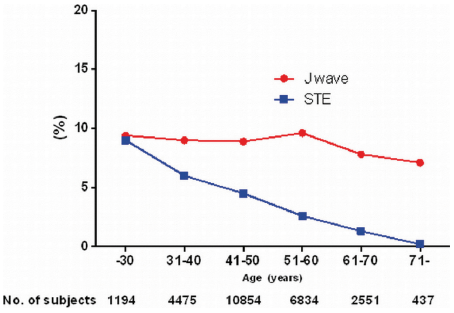
Background: The prognostic implication of components of electrocardiographic early repolarization (ER) patterns has not been well evaluated.
Purpose: We tested the hypothesis that the two fundamental component of ER, J wave and ST elevation (STE), might show different prevalence and prognostic implications.
Methods: A total of 26,345 healthy Korean population (mean 48.0±10.2 years old, 53.2% male) underwent medical check-up form January, 2002 to December, 2002. ER was found in 2,950 subjects (11.2%) and they were divided into the 3 study groups (J [J wave only, n=1874, 7.1% of total population], JST [both J wave and STE, n=463, 1.8%], ST group [STE only, n=595, 2.3%]) according to the presence or absence of J wave or STE.
Results: The prevalence of STE tended to be lower in the aged subjects, whereas the prevalence of J waves was at a constant level throughout the age groups. Most common pattern of ER was J waves with horizontal/descending ST segment in the inferior leads, while J waves with ascending ST segment was more common in the lateral lead. During mean follow-up of 126.0±11.1 months, 710 mortalities (2.7%) occurred. Only subjects in J group were at a higher risk than the control group (hazard ratio [HR] 1.60, 95% confidence interval [CI] 1.27–2.01, p<0.001 for total mortality; HR 1.82, 95% CI 1.11–2.99, p=0.017 for cardiac mortality), while JST and ST groups showed survival outcome similar to that of subjects without J or STE. Further stratification according to the pattern of the ST segment showed that the J group with descending/horizontal ST pattern was at higher risk than control groups (HR 1.63, 95% CI 1.28–2.08, p<0.001 for total mortality; HR 1.96, 95% CI 1.17–3.28, p=0.011 for cardiac mortality), whereas J group with ascending ST pattern was not.



Conclusion: J wave and STE showed different prevalence and prognostic implications.

P663 | BEDSIDE
Microvolt T-wave alternans assessed by 24-hour continuous 12-lead ECG in healthy subjects and in patients immediately after cardiac arrest: how to exclude pseudo T-wave alternans

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Background: Little has been reported on microvolt T-wave alternans (TWA) assessed by the modified moving average (MMA) method using 24-h continuous 12-lead electrocardiogram (ECG) in normal individuals.
Purposes: 1) To assess peak TWA values in healthy subjects; 2) to compare them with those in high risk patients; and 3) to describe "pseudo" TWA detected by visual inspection of the automated TWA output in healthy controls.
Methods: 24-h continuous 12-lead ECG was recorded in 15 healthy subjects (9 men; median age, 24) and 8 patients (5 men; median age, 60) including 2 patients with J-wave syndrome and 6 with long QT syndrome who had a history of cardiac arrest (high risk group). ECG monitoring was performed within 24 hours onset of cardiac arrest in the high risk group. Peak TWA values were determined by the MMA method.
Results: Peak TWA values in healthy controls were significantly lower than those in high risk group [29 (26.5–32.5, 17–39) vs 55 (46.5–66, 45–77) μV, median (interquartile range, minimum-maximum), p<0.001]. Pseudo TWA [53.5 (51.5–68.3, 37–96) μV, median (interquartile range, minimum-maximum)] was observed in 80% (12/15) of the healthy subjects. The leading cause of pseudo TWA was resulting from T-wave morphology change accompanied by deformation of the QRS complex, probably due to change in heart position or activation sequence of the ventricle. Pseudo TWA could be differentiated by the presence of the QRS deformation during the episode and by the absence of repeating ABAB pattern of the T-wave shape.

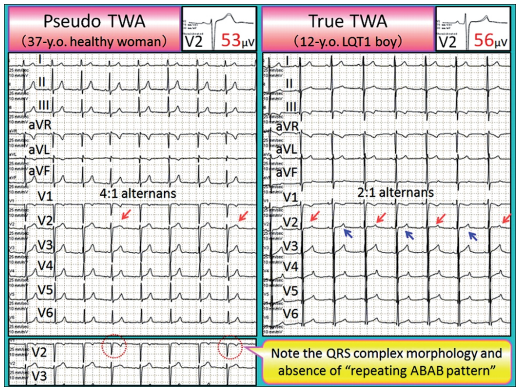

Figure 1

Conclusions: MMA-based TWA can identify high risk patients. However, change in the T-wave morphology accompanied by the QRS deformation, suggesting a component of depolarization effects in the repolarization changes, may disrupt automated TWA measurement. Thus, relying only on the automated interpretation may lead to an overestimation of arrhythmia risk in 80% of healthy subjects. Visual inspection of the automated TWA output and verifying QRS morphology during the "TWA episode" are essential to exclude pseudo TWA.

P664 | BEDSIDE
High-sensitivity cardiac troponin levels in supraventricular tachyarrhythmias

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Introduction: High-sensitivity cardiac troponin assays have provided a significant contribution for the early diagnosis of cardiovascular events. However, elevated cardiac troponin levels may occur in other clinical situations as supraventricular tachyarrhythmias with concerns about the mechanism of this elevation.
Objectives and methods: The goal of this study was to describe the performance of high-sensitivity cardiac troponin T (hs-cTnT) assay in patients presenting to the emergency department with a primary diagnosis of supraventricular tachyarrhythmia and to evaluate its relation with cardiovascular events during follow-up.
Results: 100 patients were included; mean age was 64±12 years and 59.8% were men. The most common arrhythmia at admission was atrial fibrillation

Variable	Value
1st troponin determination, ng/l	11 (5.5-22.5)
2nd troponin determination, ng/l	14 (5-39)
Delta troponin > 7, %	24.6
1st troponin determination > 14 ng/l, %	44.2
2nd troponin determination, > 14 ng/l, %	50.7

Variable	Value	p
1st troponin determination, ng/l		0.090
AF	10 (5-19.7)	
Atrial flutter	13(4.5-34.5)	
Reentrant mechanism	18.5 (8.2-50.5)	
2nd troponin determination, ng/l		0.231
AF	13.5 (5-32.7)	
AFL	10 (4-33)	
Reentrant mechanism	49 (12-145)	
Delta troponin > 7, %		0.002
AF	15.5	
AFL	9.1	
Reentrant mechanism	61.5	

(68%), followed by atrial flutter (16%) and reentrant tachycardia (16%). The results of the first determination of hs-cTnT were positive (>14 ng/l) in 44.2% of the patients and the second determination was positive in 50.7% of the cases. The variation between the first and the second troponin levels was 1 (0–5) ng/l, and was >7 ng/l in 24.6% of the cases, with a clear trend toward higher troponin values in reentrant tachycardias. Four events were reported at 30 days; in all the cases the patients had presented AF and there were no significant differences in hs-cTnT values.
Conclusions: There is a significant number of patients with supraventricular tachyarrhythmias who present elevated hs-cTnT levels. The association of this elevation with cardiovascular events seems to be very low.

P665 | BEDSIDE
Effect of liver transplant on autonomic neuropathy in patients with familial amyloid polyneuropathy

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Background: Transthyretin familial amyloid polyneuropathy (TTR-FAP) V30M is an autosomal dominant disease characterized by progressive sensorimotor and autonomic neuropathy. The 24-hour Holter recording allows characterization of cardiac autonomic function in these patients and seems to have prognostic value. Liver transplantation has been widely used to attenuate the progression of the disease. However, there is little information about liver transplantation's impact on heart rate variability (HRV) parameters on the 24-hour Holter recording.
Purpose: To evaluate the impact of liver transplantation on the progression of cardiac autonomic dysfunction in FAP patients (pts).
Methods: Prospective study of consecutive TTR-FAP pts evaluated between September 1998 and November 2015. Evaluation was performed annually and included a 24-hour Holter recording. Progression HRV parameters of pts submitted to liver transplantation was compared with that of non-transplanted pts. For that purpose, we performed a nested case-control analysis with patient matching according to the neurophysiological score measured prior to transplantation (<5% absolute difference).
Results: From a total population of 284 TTR-FAP pts, 88 pts (44 transplanted, 44 non-transplanted) with a mean age of 47±15 years, 52% male, with identical median neurophysiological (25; IQR 9 to 51) and clinical (24; IQR 12–34) scores were selected for analysis. During a median of 72 months after the matching-time point, 257 Holter exams were performed. At baseline, the transplanted group exhibited higher HR (83±11 vs. 75±14 bpm; P=0.001) and maximum HR (122±14 vs. 112±17 bpm; P=0.004). Autonomic parameters significantly improved at 48 months post-transplant, including the minimum HR (80±9 vs. 57±4 bpm, P<0.001), mean night-time RR (86±11 vs. 76±11 ms, P=0.02), daytime PNN-50 (7, IQR: 2 to 13 vs. 1, IQR: 0 to 4; P=0.011), daytime PNN-30 (17, IQR: 4 to 26 vs. 3, IQR: 1 to 11; P=0.008), daytime RMSSD (30, IQR: 17 to 59 vs. 16, IQR: 13 to 24; P=0.008), daytime SDNN (100, IQR: 77 to 115 vs. 69, IQR: 50 to 77; P<0.001), 24h VLF (1872, IQR: 760 to 2576 vs. 385, IQR: 248 to 866; P=0.002) and in daytime VLF (621, IQR: 411 to 951 vs. 312, IQR: 211 to 593; P=0.002). In contrast, non-transplanted pts showed progression of dysautonomia with a significant decrease of night RMSSD (25, IQR: 16 to 46 vs. 20, IQR: 12–33; P=0.028).
Conclusion: Liver transplant not only allows clinical stabilization of TTR-FAP but it also has a beneficial effect on autonomic function parameters as evaluated by 24-hour Holter recording.

P666 | BEDSIDE
A risk factor of thrombus in left atrial appendage by transesophageal echocardiography, comparison between warfarin and non-vitamin K antagonist oral anticoagulants

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Background: Warfarin and Non-vitamin K antagonist oral anticoagulants (NOACs) are used for the prevention of ischemic stroke in patients with atrial fibrillation (AF) and atrial flatter (AFL). CHADS2 and CHA2DS2-VASc score are popular for risk stratification of embolism. However effectiveness of echocardiography is still unknown.
Objectives: The objective of this study is to assess a risk factor of left atrial thrombi.
Methods: Consecutive 160 patients performed transesophageal echocardiography (TEE) due to AF or AFL were retrospectively analyzed (79% men; age 62.3±1.8; 42% paroxysmal AF; 35% persistent and long standing AF; 23% AFL). Anticoagulant therapy has been continued at least three weeks before TEE.
Results: Thrombi were observed by TEE in 3.6% (6/160) patients (1 in AFL, 1 in paroxysmal AF, 4 in persistent and long standing AF). Two patients were treated with NOACs, 4 with Warfarin. In patients treated with warfarin, LAA inflow and outflow velocity were significantly reduced in patients with thrombi compared to that without thrombi (0.2 vs 0.5 m/s, p=0.002 and 0.2 vs 0.5 m/s, p=0.004, respectively). Moreover the size of LAA measured by TEE was large in patients with thrombi compared to that without thrombi (8.0 vs 4.2 cm^2, p=0.0001). However, in patients treated with NOACs, there were no different on LAA velocity and the size of LAA between patients with and without thrombi.
Conclusions: The size and flow velocity of LAA in patients treated with NOACs did not become a risk factor of thrombus appearance. In patients taking NOACs, to pay attention to other factors shoud be more required for thromboprophylaxis.

P667 | BEDSIDE
Systematic use of an external loop recorder in patients with no documented palpitation improves care efficiency

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External loop recorders (ELR) devices are useful to study patients with no documented palpitations. However, its efficiency in clinical practice has not been deeply studied.
Methods: Retrospective cohorts study. All consecutively patients referred to outpatient arrhythmias clinics who had at least two episodes of palpitations in the last year and that after an initial assessment the diagnosis was not reached, were included. A cohort of patients where an ELR (SpiderFlash T, Sorin) was systematically indicated was compared with an historical cohort prior to the implementation of this exploration.
Results: One hundred fifty-five patients were included (96 in ELR group, 58 in control group). There were not significant differences either in the basal characteristics (Female: 73.9% vs. 74,1% p=NS; Age: 47.5±21.9 y.o. vs. 45.2±17.1 y.o p=NS) or in the clinical presentation form. The diagnostic yield was higher in ELR group (83 (86.5%) definitives diagnosis were reached in the ELR group vs. 12 (20.7%) in the control group, p<0.01). The average number of explorations made to accomplish the diagnosis was lower in the ELR group. (24 hours Holter: 0.1±0.3 vs. 1.10±0.8, p<0.01; electrophysiological study 0 vs 0.17±0.38, p<0.01; Stress test 0 vs. 0.31±0.56, p<0.01), as well as the number of visits made in outpatients clinics (1.37±0.25 vs. 4±2.87, p<0.01). In the patients that a diagnoses were reached, the follow-up time until diagnosis was 27.6±36.3 days in ELR group vs 204±293.6 days in control group (p<0.01).
Conclusion: Systematic use of an ELR for the study of patients with no documented palpitations improves care efficiency. It improves the diagnosis yield, decreases the number of explorations and visits to outpatient clinics as well as the time to reach a final diagnosis.

P668 | BEDSIDE
Coronary sinus to aid diagnosis of atrial flutter in patients with narrow complex tachycardia (NCT)

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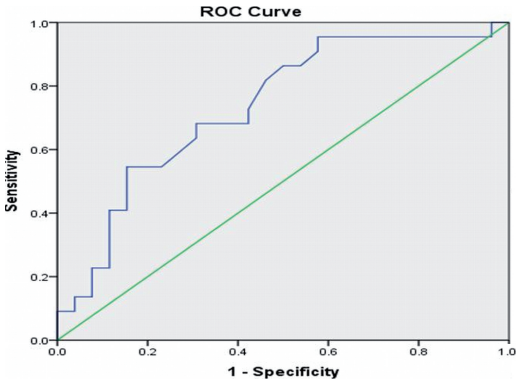
Background: Manoeuvres, like adenosine, could not be applied in short burst of NCT on telemetry or holter monitoring. Therefore, precise diagnosis of underlying rhythm may not be identified until invasive electrophysiology study (EPs) is performed. Such delays may put patients with undiagnosed atrial flutter at significant risk of developing thromboembolism.
Purpose: We sought to establish whether coronary sinus (CS) is a useful predictor for diagnosis of atrial flutter.
Methods: A retrospective analysis of all consecutive patients who were referred to EPs following an episode of NCT between April 2013 and March 2014. CS size was measured blindly and was recorded in end diastole. Patients were divided into two groups: flutter and non-flutter group. Statistical analysis was performed using SPSS 22.0.
Results: Total of 85 patients were identified and coronary sinus was identified in 84% of patients. Patients who have potential risk of developing thromboembolism (CHA2DS2-VASc ≥1) were only included. Mean age was 54±21, 62% females with mean CS of 7.4 mm. There was no significant difference between flutter and non-flutter groups in RV size and function, LV EF, LVEDD or symptoms duration. Atrial flutter group were older and less likely to be females. They also have larger coronary sinus (8.3 versus 6.7 mm, p=0.006).
On univariable logistic regression analysis age, female gender, CS and RA size were all predictors of atrial flutter (see Table). However, CS was the only independent predictor of atrial flutter diagnosis (OR 1.56 CI 0.99- 2.45, p=0.054) using multivariable logistic regression analysis.
ROC area under the curve was 0.73 (p=0.006) for the mean coronary size diameter of 7.4 mm to identify the flutter group.

Echo predictors of atrial flutter

	Univariable analysis		Multivariable analysis	
	OR (95% CI)	P value	OR (95% CI)	P value
Age	1.06 (1.02–1.11)	0.003	1.055 (0.99–1.12)	0.075
Female gender	0.25 (0.07–0.86)	0.028	0.56 (0.09–3.26)	0.519
Ejection fraction	0.94 (0.86–1.03)	0.17	–	–
Left ventricle end diastolic diameter	1.23 (0.4–3.77)	0.72	–	–
Right atrium size	20.8 (2.38–182)	0.006	0.2 (0.018 -2.3)	0.197
Right ventricle size	7.35 (0.79–68.6)	0.08	0.04 (0.001–1.31)	0.071
Right ventricle systolic pressure	1.06 (0.99–1.14)	0.077	1.025 (0.93–1.13)	0.616
CS	1.59 (1.1–2.29)	0.013	1.61 (1.01–2.57)	0.045

OR, odds ratio; 95% CI, 95% confidence interval.



ROC area under the curve

Conclusion: CS might be a useful tool to predict atrial flutter in patients with NCT who are at risk of developing thromboembolism.

P669 | BEDSIDE
Use of Bazett's formula could produce false positive responses to epinephrine test in patients with low heart rates

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Introduction: Only 50% to 60% of patients with genetically proven long QT syndrome (LQTS) have a diagnostically prolonged QTc at rest. Thus, infusion of epinephrine has been used to unmask patients with suspected LQTS. Although Bazett formula is the most universally utilised method to correct QT interval for heart rate, this method underestimate and overestimate the duration of cardiac repolarization at extreme low and high heart rates respectively.
Purpose: Our aim was to assess if the use of different formulas to correct the QT could modify the results of epinephrine test.
Methods: Fifteen patients with normal baseline QTc interval and suspected LQTS for recurrent syncope and/or family history of sudden death or LQTS, underwent to epinephrine test using the protocol previously described by Shimizu (bolus injection of 0.1μg/kg/min followed by continuous infusion at 0.1μg/kg/min). QTc was calculated using Bazett, Fridericia and Framingham formulas at baseline, at peak of epinephrine effect (when the RR interval was the shortest) and in the steady state (3 to 5 minutes after the start of infusion). ΔQTc steady-baseline (QTc steady state - QTc baseline) and ΔQTc peak-baseline (QTc peak – QTc baseline) were calculated. ΔQTc steady-baseline ≥35ms was considered diagnostic of LQT1 and if the ΔQTc steady-baseline was <35ms a ΔQTc peak-baseline ≥80ms was diagnostic of LQT2. The results of genetic testing for LQTS were not available when epinephrine test was performed.
Results: The mean values of QTc using the different formulas of QTc correction are shown in Table 1. RR intervals were: RR baseline 962±162 ms, RR peak 628±110 ms, RR steady-state 794±111 ms. 13 (87%) patients showed a positive test using Bazett formula (11 LQT1, 2 LQT2), and 6 (40%) with Fridericia and Framingham formulas (5 LQT1 and 1 LQT2). In the subgroup of patients with heart rate <60 beats per minute (n=7), the test was positive in 6 (86%) with Bazett formula and in 2 (29%) with both Fridericia and Framingham formulas.

Table 1

Formula	$QTc_{baseline}$ (ms)	QTc_{peak} (ms)	$QTc_{steady-state}$ (ms)	$\Delta QTc_{steady-baseline}$ (ms)	$\Delta QTc_{peak-baseline}$ (ms)
Bazett	402±19	496±46	444±29	41±24	93±41
Fridericia	399±18	458±44	427±28	28±22	59±34
Framingham	399±18	449±40	426±25	28±27	50±31

Values expressed as mean ± standard deviation.

Conclusion: Underestimation of the duration of cardiac repolarization at low heart rate using Bazett formula could produce false positive response to epinephrine test. Future studies that evaluate the role of other formulas of QT correction are necessary.

P670 | BEDSIDE
Computerized dynamic pupillometry indices correlates with heart rate variability parameters: the eyes are the mirror of the heart

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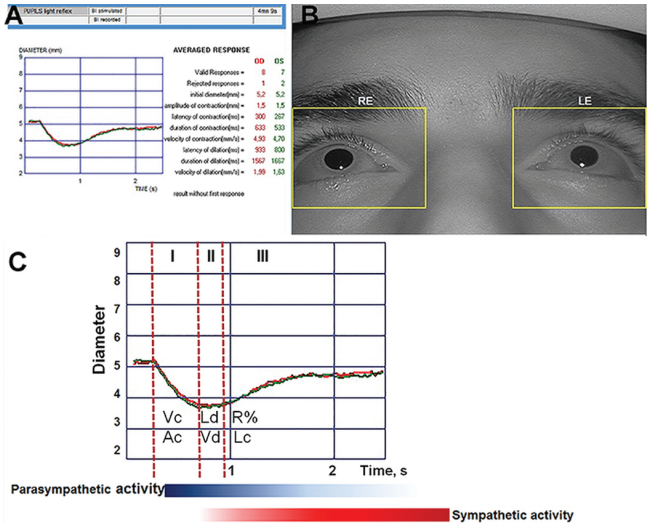
Background: Dynamic pupillometry (DP) is a simple, non-invasive computerized assessment of pupillary light response which provides data concerning both branches of autonomous nervous system (ANS). Heart rate variability (HRV) analysis assess cardiac health and the ANS modulation on heart.
Purpose: In this study, we aimed to evaluate utility of DP as a predictor of cardiac autonomic activity assessed by HRV.
Methods: A total of 44 consecutive healthy subjects (mean age= 35.9±7.4 years, 24 males) were enrolled. Pupil diameters (R0, R1, R2 and R%): latency (Lc), amplitude (Ac), velocity (Vc) and duration of pupil contraction (Tc): latency (Ld), velocity (Vd) and duration of pupil dilatation (Td) were measured in DP. Time and frequency domain indices of HRV were obtained from 24-h ambulatory electrocardiographic monitoring.
Results: Pupil sizes were determined 4.40±0.86mm for R0, 4.90±0.80mm for R1, 3.36±0.76mm for R2, respectively. There were strong significant correlations of Vc with LF/HF (r=-0.672, p=0.001) and RMSDD (r=0.654, p=0.001). R% significantly correlated with PNN50 (r=-0.432, p=0.003) and RMSDD (r=-0.422, p=0.004) and LF/HF (r=0.340, p=0.024). Vc (β=0.647, p=0.011) and Ac (β=0.320, p=0.013) were found as independent predictors of RMSSD. Vc (β=0.578, p=0.036) was found to be only significant predictor of PNN50. Vc (β=-0.617, p=0.008) and R% (β=0.309, p=0.038) were found to be significant predictors of LF/HF



Dynamic pupillometry analysis

Conclusions: Pupillary autonomic functions assessed by DP correlates with cardiac autonomic functions evaluated by HRV. Among the DP parameters analyzed, Vc was predictor of parasympathetic indices, and R% was predictor of sympathetic indicators of cardiac autonomic functions.

P671 | BEDSIDE
What does LF/HF of heart rate variability in ambulatory ECG mean? Effect of time in lying position during monitoring

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Background: Low-frequency-to-high-frequency ratio (LF/HF) of heart rate variability (HRV) has been used as a maker of sympathetic predominance in cardiac autonomic activity. In most of major prospective studies on the prognostic value of 24-hr HRV after acute myocardial infarction, however, have reported that decrease, rather than increase, in LF/HF is associated with increased mortality risk, which is contrary to the general concept of cardio-protective effects of sympathetic suppression.
Purpose: Laboratory studies have reported that LF/HF increases with standing and decreases with lying. We therefor hypothesized that decreased LF/HF in ambulatory ECG monitoring is associated with the length of time when patients spent in lying position during the monitoring. We examined this hypothesis with ambulatory ECG big data built by Allostatic State Mapping by Ambulatory ECG Repository (ALLSTAR) project, which has started since 2009 and is gathering >50,000/year of 24-hr ECG data from the entire Japan. Among >300,000 data accumulated, we could estimate patient's posture during the monitoring in 47,624 data recorded with Holter recorders having a built-in 3-axis accelerometer (Cardy303pico,SuzukenCo., Japan).
Method: Out of 47,624 ECG data with 3-axis accelerogram, we used 42,483 data that were recorded in patients ≥25 yr and the ECG showed sinus rhythm for >19.2 hr (80% of 24 hr) for this study. These data were recorded between April 2012 and July 2014 in 18,944 men (age,67±14 yr) and 23,539 women (68±15 yr). From 3-axis accelerograms, we estimated the ratio of time in lying position (%lying time) during the monitoring, by which the patients were divided into four quartile groups (Q1–4, Table). We compared LF/HF and other indices of HRV among the quartile groups.
Results: Table shows HRV indices in the quartile groups. LF/HF decreased progressively with advancing quartile of %lying time. LF/HF correlated negatively with

age in both genders (r=-0.50 and -0.43 for men and women, respectively) and %lying time positively with age (r=0.21 and 0.26 for men and women, respectively). Also, there is significant gender differences in both LF/HF (least-square mean ± SEM adjusted for age,0.59±0.01, 0.58±0.01 for men and women, respectively; P<0.001) and %lying time (47.4±0.1, 43.7±0.1; P<0.001). Nevertheless, the decrease in LF/HF with advancing %lying time quartile was significant (P<0.001), even when the effects of age and gender were adjusted (Figure).

Table. Heart rate variability indices in quartile groups by %lying time

	Quartiles by %lying time (N)				P
	Q1 <36% (10640)	Q2 36-43% (10705)	Q3 43-52% (10594)	Q4 >52% (10544)	ANOVA/chi^{2}test
Age (yr)	63 ± 14	67 ± 14	69 ± 14	72 ± 14	< 0.001
Females (%)	6684 (63%)	6280 (59%)	5794 (55%)	4781 (45%)	< 0.001
%Lying time (%)	31.1 ± 4.1	39.2 ± 1.9	46.9 ± 2.7	64.5 ± 10.6	< 0.001
Mean NN (ms)	828 ± 119	847 ± 124	856 ± 130	863 ± 147	< 0.001
SDNN (ms)	135 ± 40	138 ± 40	138 ± 45	127 ± 51	< 0.001
ULF (ln [ms^2])	11.51 ± 0.40	11.53 ± 0.42	11.55 ± 0.46	11.48 ± 0.52	< 0.001
VLF (ln [ms^2])	12.39 ± 0.44	12.39 ± 0.46	12.39 ± 0.52	12.35 ± 0.59	< 0.001
LF (ln [ms^2])	12.55 ± 0.63	12.58 ± 0.67	12.60 ± 0.73	12.61 ± 0.82	< 0.001
HF (ln [ms^2])	13.11 ± 0.84	13.19 ± 0.88	13.26 ± 0.90	13.32 ± 0.96	< 0.001
LF/HF	0.63 ± 0.28	0.60 ± 0.26	0.57 ± 0.25	0.54 ± 0.24	< 0.001
LF/HF during lying	0.59 ± 0.23	0.58 ± 0.23	0.57 ± 0.23	0.55 ± 0.23	< 0.001
LF/HF during standing	0.66 ± 0.28	0.63 ± 0.27	0.60 ± 0.27	0.57 ± 0.27	< 0.001

Data are mean ± SD or N (%)

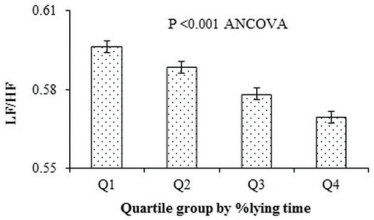

Fig. Low-frequency-to-high-frequency ratio (LF/HF) of heart rate variability adjusted for the effects of age and gender in quartile groups by %lying time during the ECG monitoring. Data are least-square means and standard error of the mean (error bar).

Conclusion: Decreased LF/HF in ambulatory ECG monitoring could be the result at least partly of the fact that patients spent longer time in lying position during the monitoring.

Acknowledgement/Funding: The Knowledge Hub of AICHI, The Priority Research Project, Japan; Toyoaki Scholarship Foundation, Japan

P672 | BEDSIDE
Distribution of the atrial fibrillation substrate in left atrium detected and quantified with integrated backscatter values

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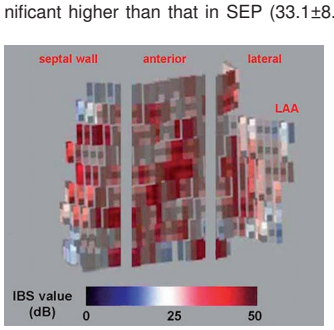
Introduction: Ablation of complex fractionated atrial electrograms (CFAE) is an important adjunctive therapy in atrial fibrillation (AF). And it has been suggested areas of CFAEs correlate with the AF substrate.
Purpose: The purpose of this study was to evaluate the distribution of the AF substrate in left atrium (LA) detected and quantified with integrated backscatter (IBS) values.
Methods: We measured IBS values of 15 LA specimens obtained from 10 autopsied hearts. After tissue was stained with Masson's trichrome, percentages of interstitial area were calculated. IBS values were acquired with transesophageal echocardiography. We measured IBS values of the LA wall (except the posterior wall) at 5 mm intervals in 24 patients with AF. For comparison of distribution of substrate, LA was divided into 4 segments: septum (SEP), anterior wall (ANT), lateral wall (LAT) and left atrial appendage (LAA). IBS values were calculated as the average power of the backscattered signal from regions of interest. Each IBS value was color-coded to construct three-dimensional maps.
Results: There was a significant correlation between the percentages of interstitial area and IBS values (r=0.45, p<0.05). The average IBS values of total voxels in SEP, ANT, LAT and LAA were 33.1±8.9 dB, 35.1±9.2 dB, 34.2±9.9 dB and 35.3±7.2 dB, respectively. The average IBS values in ANT (35.1±9.2) was significant higher than that in SEP (33.1±8.9) and LAT (34.2±9.9) (p<0.0001 and p<0.05, respectively). The average IBS values in LAA (35.3±7.2) was significant higher than that in SEP and LAT (p<0.0001 and p<0.01, respectively). The average IBS values in LAT was significant higher than that in SEP (p<0.05). There was no significant difference between the average IBS values in ANT and LAA.
Conclusions: The distribution of the AF substrate in LA was mainly observed in ANT and LAA in this study. Ablation to the AF substrate evaluated by IBS values might be complementary strategy in AF ablation.



Three-dimensional IBS LA map

P673 | BEDSIDE
Day-to-day variation of J-wave predicts life-threatening arrhythmias in patients with myocardial infarction

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Background: The J-wave has been reported to be related with life-threatening ventricular arrhythmias. Amplitude of J-wave is modulated by various clinical factors. Some reports have emphasized the importance of its dynamicity, however the clinical implication of day-to-day variation of J-wave in patient with old myocardial infarction (OMI) remains unclear. This study aimed to clarify the relation between day-to-day variation of J-wave and ventricular tachycardia or fibrillation (VT/VF) events in OMI patients.
Methods: The study population consisted of 54 patients with OMI and ICD (implantable cardioverter defibrillator) implantation. Various clinical characteristics, including the presence of J-wave and day-to-day variation of J-wave, were retrospectively analyzed. J-wave was defined as the appearance of notching or slurring of the QRS complex (≥0.1 mV) in at least 2 contiguous inferior/lateral leads on the 12-lead ECGs. Day-to-day variation of J-wave was defined as the temporal change in J-wave amplitude (≥0.1mV) on ECG recorded during daytime. VT/VF events were checked via ICD interrogation.
Results: Out of 54 patients, 22 patients (42%) experienced VT/VF events during 34±28 month observation. Day-to-day variation of J-wave was observed in 6 patients (11%). VT/VF events were more frequently observed in patients with day-to-day variation than those without (p=0.024). In the multivariate Cox proportional hazards models, day-to-day variation of J-wave (HR: 4.578, 95% CI: 1.351–14.056 p=0.017) was an independent predictor of VT/VF events. In patients with an EF>35%, day-to-day variation of J-wave was observed in 5 patients (28%). VT/VF events were more frequently observed in patients with day-to-day variation than those without (p=0.031)
Conclusion: Day-to-day variation of J-wave was considered to be an independent predictor for future VT/VF events in patients with OMI.

P674 | BEDSIDE
Insight into site-specificity of J wave arrhythmogenesis

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Introduction: Similarities and differences in the electrophysiological substrates of Brugada and early repolarization syndromes (BrS, ERS) have been proposed with few data about site-specific arrhythmogenesis and value T-wave alternans (TWA) in both syndromes.
Purpose: 1- To determine whether detailed assessment TWA using of 12-lead holter ECG can identify the arrhythmogenic site of J-wave origin and
2- To test whether the traditional cut-off value of abnormal TWA is applicable for ERS patients risk stratification.
Method: 12-lead holter ECG-based TWA was analyzed in 11 ventricular fibrillation (VF)-survivor patients with J-wave syndrome (8 BrS and 3 inferior ERS patients, age: 52±12 years) and 13 control subjects with Brugada type (BT) ECG (age 53±15 years). Furthermore; signal average ECG (SAECG) was assessed in all J-wave group.
Results: BrS patients had larger TWA than BT and ERS groups (83±27 vs. 51±12 vs. 44±9 μV, respectively, P=0.001). Importantly; in 88% of BrS patients, the max TWA was positive (>65μV) in right precordial leads while all ERS patients had negative TWA; however, the max TWA values, even negative, were seen in the inferior leads. Additionally; 75% of BrS had positive late potential on SAECG while it was negative in all ERS patients.
Conclusions: (A) TWA Assessment using 12-lead ECG can be a useful simple tool to determine the site specific arrhythmogenesis (right precordial leads in BrS and inferior leads in inferior ERS). (B) Large TWA values with positive LP in BrS might indicate a combination of both depolarization and repolarization abnormalities; which was not the case in ERS. (C) The conventional cut-off value of TWA (>65μV) is not applicable in ERS and a cohort-based analysis is necessary to define a better value for risk stratification.

P675 | BEDSIDE
Prediction of atrial fibrillation after ischemic stroke or transient ischaemic attack using PR interval

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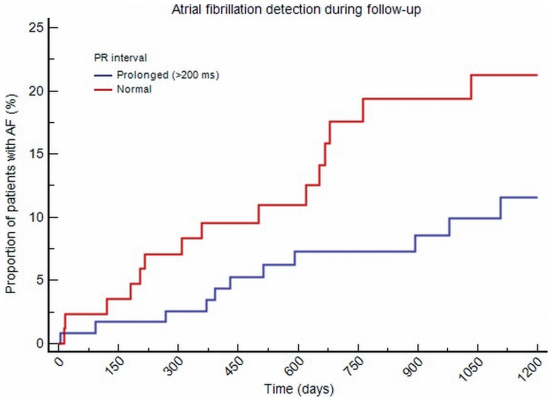
Introduction: Twenty-four hour Holter monitoring (24HM) is commonly performed after ischaemic stroke and transient ischemic attack (TIA) in order to detect paroxysmal atrial fibrillation (AF). However its diagnostic yield is low. Identifying patients at high risk of developing AF would be useful to prevent new events. Prolongation of the PR interval (>200 ms) has been associated with an increased risk of AF and it has been included in risk scores for AF.
Purpose: To investigate whether prolongation of PR interval detected by 24HM could predict the development of AF in patients with ischemic stroke or TIA.
Methods: Consecutive 24HM routinely performed during initial evaluation of patients with ischaemic stroke or AIT were analysed. Patients with known AF were excluded. Primary endpoint was the presence of paroxysmal or persistent AF (on twelve-lead electrocardiogram or 24HM) during follow-up. Study group included patients with prolongation of PR interval on initial 24HM. A group of patients with normal PR interval was randomized to the control group.
Results: During a median follow-up period of 1068 days, 202 patients were evaluated. Eighty-five patients had prolongation of PR interval; AF was detected in 18 (21,1%); median time for detection was 561 days (P25: 204; P75: 763). One hundred and seventeen patients with normal PR interval were randomly included in control group; AF was detected in 12 (10,2%); median time for detection was 472 days (P25: 319; P75: 936) (p=0,046; image). There were no significant differences between the two groups with respect to age, gender, cardiovascular risk factors and left atrial enlargement.



AF detetion during follow-up

Conclusion: In our study, prolongation of PR interval was associated with an increased risk of developing AF in patients with ischaemic stroke or TIA. It is important to monitor these patients more closely since detection of AF imposes anticoagulation in order to prevent recurrent stroke.

P676 | BEDSIDE
Analysis of QT intervals in healthy children 7–17 years old during Holter monitoring

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The QT interval one of the important markers of risk of lifethreatening arrhythmias and sudden death. The modern commercial systems of AECG automatically evaluate of QT intervals, however, the normal values of these parameters are still not known.
The aim of study was to define the normal limits of of the QT interval during 24 hr Holter monitoring (HM) in healthy children 7–17 years old. We evaluated 60 healthy children from 7 to 17 years old (10.6±7), 28 girls (10.3±2) and 32 boys (10.5±3). They were free from any chronic diseases, and were not on any medication and had normal values of QTc interval in ECG (QTc<440ms). All subjects underwent 24hour AECG monitoring in three modified chest leads (V2, V5, aVF). Analysis of QT interval included manual investigation with evaluation of QT interval at minimal HR, an automated analysis with evaluation of maximal QT interval length (QT max), average daily QT interval and corrected QT (QTc) interval, calculated according by Bassett's (QTc = QT/$\sqrt{}$RR) and Frederica's (QTc = QT/3$\sqrt{}$RR) formulas, average daily QTpeak (QTp) interval, and corrected QTp (QTpc) interval. The manual measurements of QT interval at the minimum HR were 426.5±22.1 (383–475) msec in boys and 418.2±17.7 (368–480) msec in girls without gender difference.
The results of automatic analysis is present in the table.

The autonomic analysis of QT intervals

Parameters (msec)	Total (n=60)	Boys (n=32)	Girls (n=28)
24 hour average QT interval	363±20 (327–401)	366±18 (342- 401)	358±23 (317–386)
24 hour average QTc (Bazett) interval	427±13 (401–444)	425±15 (396–447)	430±9 (408–442)
24 hour average QTc (Fridericia) interval	403±13 (382–421)	404±12 (384–421)	401±16 (375–421)
24 hour average QTp interval	285±18 (255–314)	286±16 (263–318)	281±21 (241–312)
24 hour average QTpc (Bazett) interval	335±15 (305–359)	333±16 (303–359)	339±13 (310–360)
24 hour average QTpc (Fridericia) interval	315±15 (291–342)	314±13 (291–342)	317±14 (285–343)
QT max.	433±23 (392–480)	433±20 (400–464)	433±28 (380–480)
QTp max.	349±16 (312–384)	345±19 (312–384)	357±8 (344–376)

Conclusion: The average QTc interval during HM in healthy children 7–17 years old did not exceed 450 ms and QTpc did not exeeced 360 ms.

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A noninvasive imaging modality for evaluation of repolarization dispersion abnormalities in patients susceptible to ventricular arrhythmias

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Background: Experimental studies provided evidences of close temporal correlations between ischemia-induced alternans, dispersion of repolarization and susceptibility to ventricular arrhythmias. Novel magnetocardiography (MCG) variables have been recently developed based on new MCG 3-D imaging modality to reconstruct measures of spatial repolarisation dispersion (SRD).The purpose of this study was to evaluate SRD abnormalities noninvasively in patients susceptible to ventricular arrhythmias.
Methods: A total of 101 subjects were included in the study: 40 (39%) patients had a history of ischemic heart disease and frequent (≥30/h) premature ventricular contractions (PVC group); based on the coronary angiogram, there were 28 (28%) patients with angiographically significant CAD (>70% luminal stenosis) and without PVCs (CAD group); 33 (33%) healthy subjects served as Control. All subjects underwent 9-channel MCG recordings in non-shielded MCG laboratory, yielding 3-D current density mapping during ventricular repolarization. The SRD was automatically defined as the time interval between the earliest terminal portion of the T-wave to the latest terminal portion of the T-wave in the different regions of myocardium by using the time evolution of current density variables map.
Results: SRD was significantly higher in patients with presence of PVCs in comparison to those with significant CAD and without PVCs (132.7±27.6 vs. 115.6±30.8 ms, p<0.001) and Control (132.7±27.6 vs. 73.6±20.8 ms, p<0.001). In addition, CAD patients had higher SRD than controls (115.6±30.8 vs. 73.6±20.8 ms, p<0.001) and the diagnostic sensitivity and specificity were 82% and 79% for SRD>90 ms. For identification of patients prone to PVCs, selection of cut-off values SRD >110 ms gave sensitivity of 78% and specificity of 97% (p<0.0001, AUC=0.95). MCG SRD was a significant predictor of PVCs (odds ratio, 1.12; 95% confidence interval, 1.05 to 1.18, p=0.0001)
Conclusions: In our knowledge, the present study is the first to use new MCG 3-D imaging modality to reconstruct images of spatial repolarization dispersion in high-risk patients. Study demonstrated the spatial repolarization heterogeneity detected by MCG may be a new predictive tool for patients susceptible to ventricular arrhythmias.
Acknowledgement/Funding: STCU and Oxford Cardiomox Ltd (UK) Partner Project grant P-624

P678 | BEDSIDE
ECG-predictors of ventricular tachyarrhythmias in patients with left ventricular systolic dysfunction

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The purpose of the study was assessment of high-precision ECG markers of myocardial electric instability in patients with systolic dysfunction; parameters of microvolt T-wave alternation (mTWA), heart rate turbulence (HRT: TO/TS), index R-wave asymmetry (Ras), intervals QTd and JTd dispersion, indexes deceleration (DC) and acceleration (AC) of heart rate were analysed to predict ventricular tachyarrhythmias (VTAs) in patients with heart failure (HF).
Materials and methods: The study enrolled and followed up 36,8±16,4 months 394 pts with NYHA III (204 pts who had dilated phenotype HF: aged 49,6±11,5 years; LVEF 27,5±11,2%; and 190 pts who had ischemic phenotype HF: aged 55,4±13,2l; LV EF 35,3±9,93%). All patients were examined by echocardiography, Holter monitoring (HM) ECG, 7-min ECG (Intekard-7/7) and telemetry of the implanted device (DDD, CRT-P/D, ICD) in the presence. Primary endpoints were VTAs such as sustained VT, successful resuscitation, ICD-shock, SCD.
Results: 117 (29,7%) patients developed VTAs including 37 (9,39%) syncope, 19 (4,82%) successful resuscitation, 22 (5,58%) with documented SCD; according to HM and device telemetry were revealed 76 (19,3%) pts with sustained VT. By correlative analysis were detected a positive correlations VTA events with mTWA, AC index, HRTO (p=0,004), male (p=0,01), left ventricular dysfunction (p=0,001) and heart rate (p=0,002). As a result of univariate regression analysis positive

test mTWA: both are mean and percentage values (Fmean = 30,4; F% =34,5; p=0,0001); HRTO (F = 29,9; p=0,0001); index Ras (F = 7,42; p=0,007); JTd (F = 9,65; p=0,002) and QTd (F = 15,8; p=0,001) were associated with endpoints. On multivariate analysis, only HRTO (HR 4,3: 95% CI: 1,17–13,4; p=0,014) and mTWA%: pathological percentage alone (HR 3,2: 95% CI: 1,12–10,3; p=0,026) remained significant as independent predictors of VTAs. By ROC curve analysis the prognostic value of HRTO (sensitivity 79%, specificity 70%; S = 0,786; 95% CI: 0,649–0,948, p=0,027; cut-off TO≥1,36%) and mTWA% (% of pathological mTWA: sensitivity 73%, specificity 67%; S= 0,714; 95% CI: 0,621–0,874, p=0,032; cut-off mTWA% ≥27,8%) were confirmed.
Conclusion: Early detection of ECG-predictors VTAs (pathological HRTO and mTWA%) in pts with systolic dysfunction determines the need for a more active management (implantation of cardioverter-defibrillators, resynchronization therapy, more aggressive antiarrhythmic therapy or surgical correction).

P679 | BEDSIDE
The relationship between the spatial distribution of late gadolinium enhancement on cardiac MRI and maximal T-wave alternans sites on the 12-lead Holter ECG in hypertrophic cardiomyopathy

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Background: Recent evidence has suggested that late gadolinium enhancement (LGE) on cardiac MRI (CMR) predicts the mortality in hypertrophic cardiomyopathy (HCM) patients, and T-wave alternans (TWA) is a potential cardiac mortality predictor. However, the relationship between LGE localization and TWA has not been fully elucidated in HCM. [Purpose]: To clarify the localization relationship between the LGE and maximal TWA lead (TWAmax-lead) and maximal TWA voltage (TWAmax) using 12-lead Holter ECGs (Holter12) in HCM.
Methods: Holter12s and CMR were performed in 46 HCM patients. TWA was assessed using a modified moving average method and the TWAmax was determined in each lead. The average transmural LGE extent was scored using a 4 point score (Score 0:no LGE, 1:1–25%, 2:26–50%, 3:51–75%, 4:76–100%) in 12 left ventricular segments and the sum (LGEtotal) was calculated. Left ventricular LGE sites were classified into anterior, septal, inferior, and lateral. Corresponding ECG lead groups were defined as V3–4 for anterior, V1–2 for septal, II, III, and aVF for inferior, and I, aVL, and V5–6 for lateral. The TWAmax was analyzed depending on the Score of the 5 stages, and the coincidence between the LGE distribution and TWAmax-lead was investigated. Furthermore, the differences in the TWAmax, LGEtotal, and left ventricular ejection fraction (LVEF) in the presence or absence of ventricular tachycardia (VT) were also studied.
Results: The TWAmax was 50±11μV for Score=0, 54±13μV for Score=1, 61±18μV for Score=2, 67±20μV for Score=3, and 47±16μV for Score=4. The TWAmax for Scores 2 and 3 was significantly greater than for Score=0 ($p<0.001$, $p<0.001$, respectively), but there was no significant difference between Scores 1 and 4, and Score=0 (p=0.14, p=0.41). The TWAmax-lead revealed scores ranging from 1 to 3 in all segments. The LGEtotal and TWAmax were significantly greater in patients with VT (n=23) than without (17±7 vs. 10±7 [$p<0.01$], 83±17μV vs. 64±18μV [$p<0.001$], respectively). The LVEF did not statistically differ between the two groups (48±16% vs. 54±10%, p=0.21).
Conclusions: The LGE distribution correlated with the TWA, i.e., a 26–75% transmural extent of the LGE yielded the maximal local TWA. The spatial distribution of the LGE may be closely linked to myocardial repolarization abnormalities, which lead to VT substrates in HCM.

P680 | BEDSIDE
The characteristics of sleep apnea in candidates for catheter ablation of atrial fibrillation

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Background: Sleep apnea (SA) and atrial fibrillation (AF) are highly correlated and regarded as risk factors for each other, however, the prevalence of SA as well as the clinical determinants of SA-related parameters in AF patients for catheter ablation are not well elucidated.
Purpose: The aim of this study was to clarify the prevalence and types of SA and to investigate whether there was any relationship between the SA-related parameters and the clinical background, echocardiographic parameters, or biomarkers in patients for AF ablation.
Methods: A total of 202 consecutive AF patients (age: 60±9 years, paroxysmal AF: 114, male: 192, CHADS2 score: 0.7±0.8) for catheter ablation were evaluated with polygraphy, echocardiography, and plasma BNP measurements. In patients with an apnea-hypopnea index (AHI) ≥5, the proportion of the obstructive and central apnea indexes were compared and it was determined whether the AHI was obstructive or central dominant.
Results: The mean AHI was 17.7±11.7 and 177 patients (87.6%) had SA (AHI ≥5). Out of them, 108 (61.0%) had an AHI ≥15, 31 patients (17.5%) had an AHI ≥30/h, and 142 patients (80.2%) had obstructive SA. The patients with an AHI ≥15 had a significantly larger body mass index (AHI <15 vs. AHI ≥15: 24.3±2.7 vs. 26.6±10.3, P=0.046), higher serum BNP level (74±68 vs. 109.8±88.5 pg/ml, P=0.003), higher prevalence of hypertension (29.8% [n=28] vs. 46.3% [n=50], odds ratio [OR]: 2.032, 95% confidence interval [CI]: 1.136 - 3.636), and larger LA size (3.9±0.6 vs. 4.2±0.6 cm, P=0.019), regardless of the type of AF (P=0.159). In the components of the AHI, the obstructive apnea index was significantly correlated with the plasma BNP level (r=0.313, $P<0.001$) and age (r=0.155, P=0.028), however, the central apnea index was not. In the patients with obstructive SA, the age (60.6±8.6 vs. 57.2±8.5 years, P=0.028), prevalence of hypertension (66 [47.5%] vs. 6 [17.1%], OR: 4.370, 95% CI: 1.707 - 11.186), and CHADS2 score (0.8±0.9 vs. 0.4±0.7, P=0.021) were significantly higher compared to those with central SA.
Conclusions: The incidence of an AHI ≥5 was quite common in the AF ablation candidates and obstructive SA was more frequent than central SA.

PREVENTION SUDDEN CARDIAC DEATH AND ICD THERAPY

P681 | BEDSIDE
Electrocardiographic (ECG) screening of 1-month-old infants for identifying prolonged QT intervals to prevent sudden infant death

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Background: Approximately 10% of victims of sudden infant death syndrome have disease-causing mutation(s) of long QT syndrome (LQTS)-related genes. Two studies have reported the prevalence and prognosis of LQTS infants in Italy and Japan. The prevalence was approximately 1/2000 when diagnosed based mainly on data of genetic testing and was approximately 1/1000 based mainly on data of ECG findings. Prognosis is good in individuals with LQTS who are treated, but prognosis is unknown in those who have normal ECG findings.
Purpose: This study aimed to investigate the usefulness of ECG screening of 1-month-old infants for identifying prolonged QT intervals to determine the prevalence of LQTS and the prognosis in all infants.
Methods: In eight areas in Japan, an ECG was recorded in 5994 infants at 1-month medical checks in maternity hospitals. In infants with a corrected QT interval (QTc) ≥450 ms, the ECG was repeated within 2–4 weeks. Subjects with a QTc ≥460 ms in follow-up ECGs were diagnosed with LQTS (Circ Arrhythm Electrophysiol, 2013).
Results: Six infants (two boys and four girls) were diagnosed with LQTS. Of these, three (one boy and two girls) were treated with propranolol alone or a combination of propranolol and mexiletine because they showed prolongation of a QTc of ≥500 ms. They had no family history. Genetic testing showed a mutation in the KCNH2 gene (K897T, 2690A>C) in one infant, and the remaining two are under investigation. The study screened four infants (two boys and two girls) with Wolff-Parkinson–White syndrome. Among infants who showed normal ECDs at the time of the 1-month medical check, two infants (one boy and girl each) were found dead during sleeping at the 2nd and 3rd months after birth. Autopsies and postmortem genetic testing were not performed. The prevalence of sudden infant death might be approximately 1:3000 excluding LQTS-related events.
Conclusion(s): The prevalence of LQTS in infants in the present study is the same as that of a previous study in Japan; it was approximately 1/1000 and that of LQTS infants who needed medication was 1/2000. The prevalence of LQTS based on ECG screening closely corresponds to that based on genetic testing because the yield of genetic testing in LQTS patients is 55% to 60%. Prospective studies of ECG examinations at 1 month after birth and follow-up studies can identify infants likely to be affected by LQTS and will provide important information on sudden infant death.
Acknowledgement/Funding: Funded by the Ministry of Health Labour and Welfare of Japan.

P682 | BEDSIDE
Long term follow-up of patients with ventricular arrhythmias due to coronary artery spasm

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Introduction: Cardiac arrhythmias are known to be associated with coronary artery spasm (CAS). Ventricular arrhythmia is a well-recognised complication and sudden cardiac death has also been documented. However, the role of primary prevention with the use of ICD is controversial. We aimed to report the long-term follow-up of patients with VA due to documented CAS.
Methods: Multicenter retrospective study performed in 8 Spanish hospitals. Patients with VA due to documented CAS (distinctive ECG elevation pre-VA and/or

reproducibility of the clinical VA with provocation tests of coronary artery spasm) were included.
Results: Eighteen patients with VA were identified. Mean age was 50.3 (± 15.8), of which 4 (22.2%) were women. Mean BMI was 25.45 [20–35] kg/m^2, 7 patients (38.9%) had previous diagnosis of arterial hypertension, 4 (22.2%) dyslipidemia, 2 (11.1%) diabetes mellitus, 8 active smokers (44.4%) and 2 patients had history of autoimmune diseases. Of them 17 patients (94.4%) had rescue cardiac arrested due to ventricular fibrillation (94.4%) and 3 documented episodes of bradiarrhythmias (16.7%). All of them underwent coronariography (plus provocation test in 6) documenting coronary lesion in 3 patients. Over a mean follow-up of 2376.3 days (± 1879.9), 3 patients (16.7%) received appropriate ICD intervention despite optical medical treatment (calcium-channel blockers and/or nitrate derivatives in 10 patients). On multivariate analysis, none clinical factor was found to be predictive of appropriate ICD intervention.
Conclusions: In patients with life-threatening ventricular arrhythmias due to CAS, an implantable defibrillator should be considered because of the risk of recurrence despite optimal medical management.

P683 | BEDSIDE
Validation of the good outcome following attempted resuscitation score on in-hospital cardiac arrest in southern Sweden

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Background: There is a great need for a simple and clinically useful instrument to help physicians estimate the probability of survival to discharge with a good neurological outcome (cerebral performance category, CPC = 1) in cases of in-hospital cardiac arrest (IHCA).
Purpose: To validate the "Good Outcome Following Attempted Resuscitation" (GO-FAR) score in a different country with different demographics than previously investigated.
Methods: A retrospective observational study including all cases of IHCA who were part of a cardiac arrest registry at Skåne University Hospital in Sweden 2007–2010.
Results: Two-hundred-eighty-seven patients suffered IHCA during the period. A majority were male and mean age was 70 years. Overall survival to discharge independent of neurological function was 20.2%; 78% of the survivors had CPC=1 and survival to discharge with CPC=1 was 15.7%. The area under the receiver operating characteristics curve for the GO-FAR score was 0.85 (CI: 0.78–0.91, $p<0.001$), consistent with very good discrimination. Patients in the group with low or very low probablility of survival had a likelihood of 2.8% (95% CI 0.0–6.7), whereas the groups with average and above average probabilities had likelihoods of 8.2% (3.7–13) and 46% (34–58), respectively, for good neurological outcome. This compares with likelihoods of 1.6%, 9.2% and 27.8% in the original study.
Conclusions: The GO-FAR score accurately predicted the probability of survival to discharge with CPC=1, even when applied to a different population in another country.
Acknowledgement/Funding: European Research Council, the Swedish Heart and Lung Foundation, Swedish Research Council, the Novo Nordisk Foundation

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Progressively increased QTc dispersion can predict sudden cardiac death in patients with end stage renal disease on hemodialysis - Korean Multicenter Study

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Purpose: Patients with end stage renal disease (ESRD) on hemodialysis (HD) have a high risk of sudden cardiac death (SCD) due to serious ventricular arrhythmias. We performed an electrocardiogram wave pattern analysis of patients with ESRD on HD to find risk factors for predicting SCD.
Methods: We conducted a retrospective study involving 36 HD patients who died from SCD (SCD-HD) and 314 HD patients well controlled (Non-SCD) from January 2010 to June 2015 in multi-centers. The QT interval, QT dispersion, and QT peak-end interval on all 12 leads, as well as some other 12-lead ECG parameters, were measured. We evaluated the first and last ECGs in 350 patients on HD.
Results: The SCD-HD patients were older (69.0±12.2 vs. 60.8±13.8 years, p=0.001) than the Non-SCD patients, however, there was no significant difference in the gender, underlying disease, or body surface area between the two groups among the enrolled 350 patients (50.0% male, 61.7±13.9 years) ($p>0.05$). But, a decreased QT peak-end interval (OR 0.961, $p<0.001$) in all pre-cordial leads (V1-V6) and a prolonged QTc dispersion (OR 1.023, $p<0.001$) were associated with an increase in SCD. The QTc dispersion increased progressively more in the ESRD patients than those undergoing a first HD during an average of 2.5 years. (49.5±25.0 vs. 38.8±15.2, p=0.037). A multivariate analysis also revealed that prolonged QTc dispersion (OR 1.1, p=0.003) was an independent predictor of SCD in HD patients. In the receiver operator curve (ROC) analysis, the area under the curve (AUC) for QTc dispersion was 0.653.
Conclusion: A decreased QT peak-end interval and prolonged QTc dispersion were independent predictors of SCD in patients with ESRD on HD. So serial ECG monitoring may have important clinical implications in patients with ESRD on HD.

P685 | BEDSIDE
Predictive factors for a positive response to sodium channel blockers in Brugada syndrome

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Introduction: Brugada syndrome (BS) is characterized by a typical ECG pattern leading to an increased occurrence of sudden cardiac arrest due to ventricular fibrillation. The typical pattern required for the diagnosis is transient over time. To carry out the diagnosis in patients without a spontaneous ECG pattern, sodium channel blockers (SCB) are currently used. The objective of the study is to identify predictive factors of a positive response to the SCB challenge.
Methods: We analysed the pre and post-test ECG of 657 individuals. The diagnosis of BS was done according to the consensus conference. ECGs were reviewed by two physicians blinded to the clinical and genetical status. PQ interval, QRS, QT peak, QTend and QTc duration (corrected by the Bazett's formula) were measured in V1. Additional parameters were measured in DII (PQ interval, QRS, terminal S wave duration and QTend duration), DIII (terminal S wave duration), V5 (terminal S wave duration) and aVR (terminal R wave duration).
Results: Among the 657 patients, the SBC challenge was positive for 313 patients (48%). At baseline, patients positive for the SBC challenge had a longer P (91±17 vs 95±18; p=0.009), PQ (161±27 vs 171±30; $p<0.001$) and QRS interval (83±17 vs 91±17; $p<0.001$) in DII than negative patients. The terminal S wave was significantly larger in the group of positive patients in lead DII (24±22 ms vs 35±24 ms; $p<0.001$), DIII (20.5±25 ms vs 33±28 ms; $p<0.001$) and V5 (29±18 ms vs 42±19 ms; $p<0.001$) and had higher amplitude in lead DII (1.3±1.5 vs 1.72±1.7; $p<0.001$), DIII (1.4±2.5 vs 2±2.8; $p<0.001$) and V5 (2.7±2.9 vs 3.5±3; $p<0.001$). The R wave was also significantly larger in positive patients in aVR (23±20 vs 32±22; $p<0.001$) and had higher amplitude (1.78±1.47 vs 2.36±1.47; p=0.036).
Conclusion: Larger and higher amplitude of S wave in DII, DIII and V5 and the R wave in aVR are predictor of the occurrence of BS during SCB challenge. This study highlights the role of cardiac conduction disorders in BS patients. These parameters could be used to better select the patient who need SCB test.

P686 | BEDSIDE
Long-term follow-up of patients with unexplained cardiac arrest: insights from the FIVI-Gen Study

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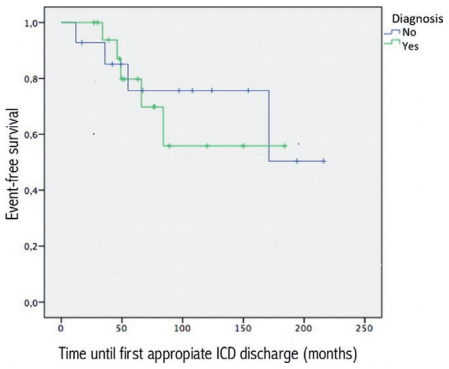
Background and objectives: The FIVI-Gen Study enrolled patients with apparently unexplained cardiac arrest. It assessed the usefulness of a new diagnostic protocol including pharmacological tests, assessment of family members and genetic testing with next generation sequencing, including 126 genes potentially involved in cardiac arrest. Our aim is to study the clinical outcome of patients included in the FIVI-Gen Study after a log-term follow-up.
Methods and results: 32 survivors of unexplained cardiac arrest from 9 centers across Spain were retrospectively analyzed to evaluate clinical events (age, 37.94±17.02 years, 31.3% females). With the diagnostic protocol, a diagnosis was achieved in 56.3% of the patients (6 Brugada Syndrome, 6 Catecholaminer-

Patients with appropriate shocks

	Age – sex	Diagnosis	Genetic test	Time to first appropriate ICD shock (months)	Follow-up (months)
Case 2	61 – Male	IVF	Negative	12	217
Case 7	27 – Male	IVF	Negative	36	56
Case 8	45 – Male	BrS	–	49	141
Case 9	32 – Male	LQTS	KCNq1, RYR2	34	48
Case 11	27 – Male	BrS	Negative	46	161
Case 16	34 – Male	BrS	Negative	84	164
Case 21	50 – Female	IVF	Negative	55	77
Case 23	29 – Male	IVF	KCNH2	171	186
Case 26	63 – Female	CPVT	RyR2	66	93

IVF, Idiopatic Ventricular Fibrillation; BrS, Brugada Syndrome; CPVT, Catecholaminergic Polymorphic Ventricular Tachycardia; LQTS, Long QT Syndrome. ICD: Implantable Cardioverter Defibrillator.



Time to first appropriate shock

gic Polymorphic Ventricular Tachycardia, 4 Long QT Syndrome and 2 Early Repolarization Syndrome). During a mean follow-up of 100.5±59.4 months, 28.1% of the patients suffered appropriate shocks, with no statistically significant difference between diagnosed and undiagnosed patients (table and figure). During follow-up, 4 patients presented an implantable defibrillator-related complication (2 inappropiate shocks and 2 infection of the system). The mean time from cardiac arrest to the first appropriate shock was 55.5±47.1 months (range 2–171 months). None of the patients died and none of the family members had an event during the follow-up.

Conclusions: Approximately half of previously unexplained cardiac arrest patients were diagnosed with this systematic advanced testing protocol. Appropriate ICD interventions occurred with a relatively low incidence both in diagnosed and undiagnosed cases, and in some cases >4 years after the initial episode.

P687 | BEDSIDE
Incidence and predictors of life-threatening ventricular arrhythmias in patients admitted to the cardiology department

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Background: In-hospital life-threatening ventricular arrhythmias (LT-VA) are a potential complication of patients admitted to the cardiology department. Telemetry monitoring may reduce mortality due to LT-VA but appropriate arrhythmic risk stratification of hospitalized patients is necessary for proper utilization of this resource.
Aim: To assess the incidence, characteristics of patients and outcome of in-hospital LT-VA occuring in the cardiology department in order to identify the high risk profile and help clinicians in prescribing appropriate levels of monitoring.
Methods: We enrolled all 10,741 consecutive patients (65±15 years, 67.7% males) admitted to our cardiology department in 2009–2014. Terminally ill patients and those with primary arrhythmia diagnosis were excluded. The composite end-point included the occurence of a life-threatening LT-VA defined as sudden arrhythmic death, ventricular fibrillation (VF), unstable ventricular tachycardia (VT) and appropriate ICD shock unrelated to invasive interventions.
Results: During the 6-year study period there were 68 events, including 1 unwitnessed death of presumed arrhythmic origin, 61 VF/unstable VT and 5 ICD shocks on VF/fast VT, with an incidence of LT-VA of 0.6% (95% CI: 0.5–0.8). There were no differences in the incidence of LT-VA according to age, gender and primary diagnosis of coronary artery disease. The incidence of LT-VA was significantly higher (1.2% versus 0.1%, p<0.001) among urgent compared with elective admissions and among patients with moderate to severe left ventricular systolic dysfunction (1.7% versus 0.2%, p<0.001). At multivariable analysis, urgent admission and left ventricular ejection fraction <45%, but not primary diagnosis of coronary artery disease, remained independent predictors of LT-VA. At the time of the event, 97.1% fulfilled either class I or class II indications for telemetry monitoring according to the American Heart Association guidelines. Survival to discharge with good neurological status was 70.6%.
Conclusions: Acutely ill patients with heart failure and LV systolic dysfunction showed the highest rate of LT-VAs, regardless of the underlying cardiac disease (ischemic or non-ischemic). Current American Heart Association guidelines demonstrated high sensitivity in identifying patients at risk, provided that both class I and class II indications are considered. These findings may favor proper utilization of telemetry monitoring resources.

P688 | BEDSIDE
Association of anemia with the risk of sudden cardiac arrest in general population

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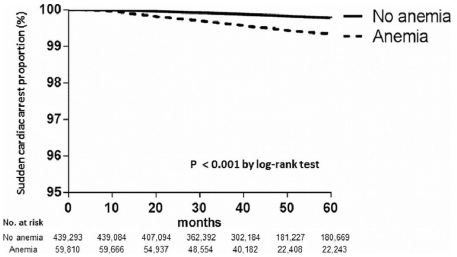
Introduction: Anemia might be associated with an increased sudden cardiac arrest (SCA) in cardiovascular disease. However, the relationship between anemia and SCA is still unclear in general population.
Purpose: The aim of this study was to assess the effect of anemia on SCA in general population.
Methods: In Korean National Health insurance Service - National Sample Cohort (NHIS-NSC), 499,103 subjects who received national health check-up after 2009 were enrolled, and follow up until 2013. We defined anemia according to WHO criteria. (Mild anemia – men: 11 ≤ Hb <13 g/dl, women: 11 ≤ Hb <12 g/dl, Moderate anemia - men, women: 8 ≤ Hb <11 g/dl, Severe anemia – men, women: Hb <8.0 g/dl)
Results: Of the 499,103 subjects, 11.98% were anemic. During the mean follow-up period of 45.5±14.9 months, 0.5% of anemic patients died compared with 0.15% of nonanemic patients. Crude mortality risk of anemia was hazards ratio (HR) 3.24 (95% confidence interval (CI): 2.83 to 3.71, p<0.001). Lower baseline hemoglobin values (> moderate anemia) were associated with increased crude mortality rates (r=–0.396, p=0.025). Adjusted HRs showed an increased adjusted risk for anemia (HR 1.99 [95% CI: 1.73 to 2.30, p<0.001]). Especially, anemia increased risk of sudden cardiac arrest in young age (HR 2.83 [95% CI: 2.23 to 3.6, p<0.001]) and subgroup without comorbidities (HR 2.09 [95% CI: 1.65 to 2.64, p<0.001 in no hypertension], HR 2.01 [95% CI: 1.66 to 2.44, p<0.001 in no diabetes mellitus], HR 2.05 [95% CI: 1.75 to 2.4, p<0.001 in no congestive heart failure]).



Conclusion: Anemia was associated with increased risk of SCA in general population. Lower baseline hemoglobin values were associated with increased crude mortality rates. Anemia should, therefore, be considered as a useful prognosticator, and therapeutic strategies aimed to increase hemoglobin levels in general population should be investigated.

P689 | BEDSIDE
Impact of age, weight and sex on motivation and interest on resuscitation training in 8-13-years-old schoolchildren: a randomized controlled trial

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Background/Purpose: The World Health Organization, the European Resuscitation Council and the American Heart Association emphasize the importance of resuscitation training in school. However, due to the lack of evidence, teaching chest compression skills is limited to children who are 13 years or older. Therefore, we examined the impact of age, weight and sex on motivation and interest in resuscitation training in younger children for the first time.
Methods: Children (n=322) between 8 and 13 years were included in a randomized, single-blind controlled trial. All children received 40 minutes basic life support training in small groups. We used two optically identical resuscitation manikins with different thoracic resistances: control group with standard resistance (45kg), intervention group with lower resistance (30kg). Children where not informed about the existence of different resistances of the manikins and were told that the randomization is for uniform distribution, in order to prevent distraction from the actual training. After training, we assessed each child with a questionnaire and measured weight and height. The six-item questionnaire with four possible answers assessed the enjoyment and the interest in the training, if the training was easy for them, how well they judged their performance, if they wanted to repeat the training and if they thought resuscitation skills are important.
Results: Of 322 participants, 164 were assigned to the intervention group and 158 to the control group. The mean age was 10.1 (±1.4) years in the interventions group, respectively 10.5 (±1.5) years in the control group (p=0.19). The mean body weight was 40.1 (±11.5) kg in the intervention group, while it was 41.4 (±11.8) kg in the control group (p=0.32). 98% of the participants in the intervention group and 99% in the control group had fun or a lot of fun, (p=0.32). Glad or very glad to train resuscitation again in the future were 89% of the participants in the intervention group and 91% in the control group (p=0.89). 99% of the participants in the intervention group and 98% in the control group (p=0.65) were interested or very interested in the training. In the intervention group, 96% believed to perform good or very good chest compression, while in the control group 93% believed this (p=023). For 81% of the participants in the intervention group, and 79% in the control group, it was easy or very easy to perform chest

compressions (p=0.39). For the whole sample independent of the group it was important to know how to help in case of emergency (p=0.81). There was no significant between-group difference in any of the items.
Conclusion: The results of this trial show that school children experience a lot of fun when being trained for resuscitation and have a strong desire to practice it again in the future. The findings support the concept of an early resuscitation training and refute the view that children are discouraged or uninterested during CPR training.

P690 | BEDSIDE
Subsequent shock delivery in paediatric out-of-hospital cardiac arrest with initial non-shockable rhythms: a nationwide population-based observational study

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Background: The most common initial cardiac rhythm in paediatric out-of-hospital cardiac arrest (OHCA) is non-shockable rhythm (i.e., asystole and pulseless electrical activity). Prognostic implications of defibrillation for children with a conversion to shockable rhythms from initial non-shockable rhythms in OHCA remain unclear. We hypothesized that survival and survival with favourable neurological outcomes, corresponding to a score of 1 or 2 on the Cerebral Performance Category scale (CPC 1–2), in paediatric OHCA would improve with subsequent shock delivery.
Purpose: We aimed to determine the relationship between subsequent shock delivery by emergency medical services (EMS) personnel and outcomes in children with OHCA.
Methods: We analysed the records of 1,706 OHCA children (age, 7–17 years) who had an initial non-shockable rhythm due to internal causes and were treated by EMS providers. Data were obtained from a prospectively recorded Japanese national Utstein-style database from 2005 to 2012. Patients were divided into subsequently shocked (n=103) and subsequently non-shocked (n=1,603) cohorts. The endpoints were prehospital return of spontaneous circulation (ROSC), 1-month survival, and 1-month CPC 1–2 after OHCA.
Results: The rates of overall prehospital ROSC, 1-month survival, and 1-month CPC 1–2 were 5.9%, 9.4%, and 2.2%, respectively. In the subsequently shocked cohort, the rates of prehospital ROSC, 1-month survival, and 1-month CPC 1–2 were significantly higher than those in the subsequently non-shocked cohort (14.5% versus 5.4%, 17.4% versus 8.9%, and 6.8% versus 2.0%, respectively; all $P<0.01$). Multivariate logistic regression analyses using 11 prehospital variables revealed that subsequent shock delivery was significantly associated with an increased odds of prehospital ROSC (adjusted odds ratio [aOR], 2.40; 95% confidence interval [CI], 1.08–5.00) and 1-month survival (aOR, 2.52; 95% CI, 1.28–4.73) when subsequent shock was delivered ≤20 minutes after initiation of cardiopulmonary resuscitation (CPR) by EMS personnel. However, subsequent shock delivery was not significantly associated with prehospital ROSC (aOR, 1.77; 95% CI, 0.48–5.04) and 1-month survival (aOR, 0.52; 95% CI, 0.08–1.85) when subsequent shock was delivered >20 minutes after CPR initiation by EMS personnel. Moreover, subsequent shock delivery was not significantly associated with 1-month CPC 1–2 whether subsequent shock was delivered ≤20 minutes (aOR, 2.29; 95% CI, 0.82–5.73) or >20 minutes (aOR, 0.00; 95% CI, 0.00–2.49) after initiation of CPR by EMS personnel.
Conclusions: In paediatric OHCA with initial non-shockable rhythm, prehospital ROSC and 1-month survival improved when subsequent shock was delivered ≤20 minutes after initiation of CPR by EMS personnel. However, subsequent shock delivery was not associated with improved 1-month survival with favourable neurological outcomes.
Acknowledgement/Funding: The Japan Society for the Promotion of Science (KAKENHI Grant Number 15K08543)

P691 | BEDSIDE
Implantable cardioverter-defibrillator shock failure in long QT syndrome patients

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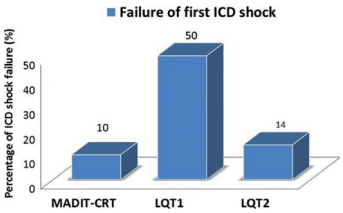
Background: Implantable cardioverter-defibrillator (ICD) is currently indicated in a high risk subgroup of patients with long QT syndrome (LQTS). The efficacy of first ICD shock to terminate life-threatening ventricular arrhythmias has not been reported in this cohort.
Methods: The study population comprised 284 LQTS patients from the Rochester LQTS ICD Registry who had ICD implantation. We evaluated the efficacy of first ICD shock for Ventricular Tachycardia/Ventricular Fibrillation (VT/VF). Clinical and genetic predictors of failed first ICD shock were studied.
Results: During 9.4 years of median follow-up, the cumulative event rate of first ICD shocks for VT/VF was 27% (85 patients). Failure of first ICD shock was 23% in all registry patients. LQT1 patients had a significantly higher rate of ICD shock failure than LQT2 patients (50% vs. 14%, p=0.02) or a historical cohort of MADIT-CRT (Figure), despite similar delivered defibrillation energy. Failure of first ICD shock was predicted by LQT1 vs. LQT2 genotype (OR=6.73; CI: 1.27–35.70, p=0.025), and an increased QTc at baseline (OR=2.45; CI: 1.01–5.97, p=0.048 for each 10 msec increase in QTc). β-blockers did not predict ICD shock efficacy. No difference in mortality was noted in LQTS patients with failed ICD shocks.
Conclusions: Among LQTS patients, first ICD shock failure is higher than in primary prevention ICD patients. LQT1 patients had higher ICD shock failure than LQT2, potentially driven by differences in autonomic nervous system modulation. An increased QTc at baseline predicted ICD shock failure.



Failure of first ICD shock

P692 | BENCH
Radiotherapy can cause serious malfunction of modern implantable cardioverters-defibrillators (ICD) and cardiac resynchronization device and defibrillator (CRT-D)

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Background: With rapidly aging population it is estimated that the number of cardiac implantable electronic devices (CIEDs) will grow dramatically. The number of patients with the implanted CIED with concomitant cancer is expected to rise by about 70%, from 14 million in 2012 to 22 within the next 2 decades. Treatment of most of these tumors and tumor metastases is often associated with radiation therapy. There is no recent data about an impact of modern radiotheraphy on CIEDs especially ICD and CRT-D devices.
Aim: We aimed to evaluate the impact of radiotherapy with a helical tomotherapy on ICDs and CRT-Ds function and integrity in-vitro.
Material and methods: The CIEDs were placed in the subclavian area of an anthropomorphic dosimetric phantom. A total of 24 devices were tested produced by three different manufacturers. All pre-radiation preparation was mimicked to the one used routinely in-vivo. All devices were tested according to radiotherapy plan for a patient with prostate cancer. A total dose of 78 Gy was delivered in 39 daily fractions. Each device was interrogated before radiotherapy and after every fraction. Full interrogation report was recorded for analysis. Measurements of the scattered radiation was performed with thermoluminescent dosimeters (TLD-100) and compared with values calculated by the treatment planning system (TPS).
Results: A total of 984 interrogation reports were available for analysis. In two devices serious malfunctions were observed. In one the left ventricle (LV) pulse amplitude was spontaneously changed after radiation with total of 12 and 16 Gy but returned to the predefined values the next day. In another device of another make, a partial reset of the device memory was observed with patient data loss and inadequate detection of ventricular tachyarrhythmia but without defibrillation after delivery of 42 Gy. After 56 Gy the same device detected a nonexisting ventricular tachyarrythmia and delivered an inappropriate shock of 40 J. In three devices significant increase of battery charge time (image 1). The mean maximum dose and mean average dose delivered to the devices varied between 9.31–11.11 cGy, and 7.9–8.38 for phase I and 3.75–3.8, and 3.32–3.43 cGy for phase II, respectively. The maximum doses calculated by the TPS ranged between 3 and 4 cGy for phase I and 0 for phase II, the mean doses: 2–3 cGy for phase I and 0 for phase II.

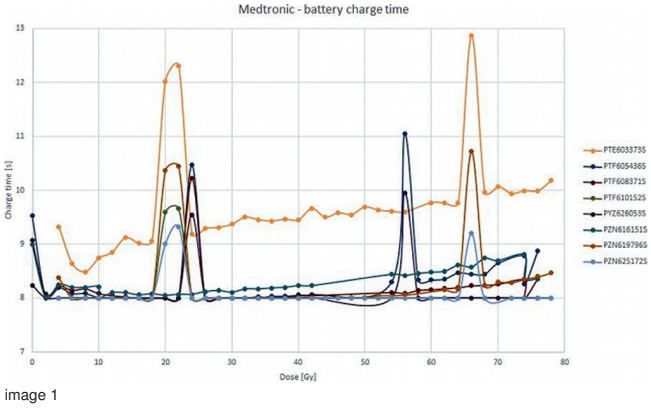

image 1

Conclusions: In spite of low energy of ionizing radiation and trace doses of scat-

tered radiation delivered to modern CIEDs, the helical tomotherapy machine may cause serious devices malfunction and influence their integrity. Further studies are needed to define clear and precise guidelines for both: oncologists and cardiologists for safe radiation therapy in patients with CIEDs and a creation of an Onco-Heart Teams in high-volume oncology centers similar to currently functioning Heart Team should be considered.

P693 | BEDSIDE
Is there a role for ICDs in LVAD patients? A meta-analysis

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Introduction: Ventricular arrhythmias (VA) are common in patients with left ventricular assist devices (LVAD) but may be well tolerated. The role of implantable cardioverter defibrillators (ICD) in LVAD-supported patients is controversial.
Purpose: The aim of this meta-analysis is to explore the association between ICDs and survival in LVAD patients.
Methods: An electronic search was conducted. We included studies that reported outcomes in LVAD patients stratified by the presence or absence of an ICD. The primary outcome was all cause mortality. Odds ratios (OR) were reported for dichotomous variables.
Results: Seven studies (6 retrospective and 1 prospective non-randomized) including 1124 adult patients were identified. An ICD was present in 499 LVAD patients. Baseline characteristics were similar between LVAD with ICD versus LVAD only groups (age: 56±4 vs. 53±5 years, p=0.3; male gender: 86% vs. 78%, p=0.6; ischemic heart disease: 42% vs. 59%, p=0.5 and left ventricular ejection fraction: 17±2% vs. 15±3%, p=0.5). Observed all cause mortality was lower in the LVAD with ICD group, compared with the LVAD only group (21% vs. 36%, OR 0.57 (95% confidence interval [CI] 0.40; 0.81), p=0.002). No significant heterogeneity was noted for the comparison (I2=16%, P=0.30). The rate of inappropriate therapies among ICD patients was 10% out of all delivered therapies.
Conclusions: Concomitant use of ICDs is associated with greater survival in observational studies of LVAD patients. This association may be due to confounding or represent a protective effect of ICD therapy in LVAD patients. A randomized controlled trial is required to define the role of ICDs in LVAD patients.

P694 | BEDSIDE
Incidence and timing of heart failure decompensation after the first ICD shock: the influence of beta-blocker therapy

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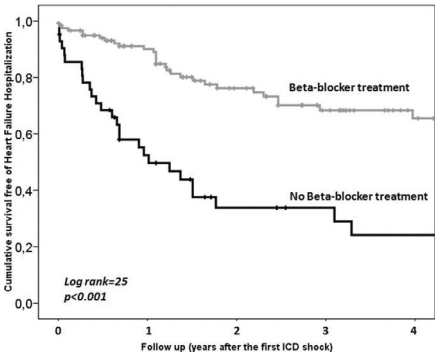
Shocks (SH) are associated with an increase in heart failure (HF) mortality among ICD patients with left ventricular dysfunction (LVD). This negative effect could be secondary to myocardial damage, in part due to the activation of the sympathetic nervous system following the SH, which produces tachycardia, ischemia and endothelial dysfunction. Were this the case, the beta-blocker treatment (BB-t) may have a beneficial impact on ICD patients presenting with SH.
Methods: In this prospective study we followed-up 435 ICD patients with LVD (age: 66±11; LVEF: 30±8; functional class II-III: 62%; primary prevention: 64%; ischemic etiology: 61%; BB-t: 79%). ICD programming was standardized. We determined the BB-t at each ICD intervention. We correlated the impact of BB-t at the first ICD shock with the subsequent occurrence of HF decompensation (HF-D): HF hospitalization or death due to HF.
Results: During the follow-up (3.4±2.1 years) 162 patients (37%, 91 appropriate, 44 inappropriate, 27 both) presented at least one SH (median=2). The crude incidence of HF-D was higher in patients with SH: 35.8 vs. 18.3% (p=0.006, log-rank test).
Focusing on the 162 individuals having SHs, the timing of HF-D with respect the first SH was: 9.9% before; 21% between days 1–180 after; 14.2% between days 181–365 and 54.9% one or more years later. The crude incidence of HF-D was lower in patients on BB-t: 25.8% vs. 64.3% (p<0.001, figure). By multivariate analysis (Cox-regression) we identified four independent predictors of HF-D after a SH: Functional Class (NYHA): HR=2.2 (p=0.003); Creatinine Serum Level (mg/dl): HR=2.4 (p=0.036); Number of SHs: HR=1.07 (p=0.008) and BB-t: HR=0.35 (p<0.001). The effect of BB-T was only significant in the year following the index SH, especially in the first 6 months (table).

Time interval from first SH	Incidence of HF-D with BB-t	Incidence of HF-D without BB-T	P value
6 months	6±0.02	32±0.07	<0.001
7–12 months	4±0.02	16±0.05	0.03
13–18 months	10±0.02	8±0.08	ns
19–24 months	4±0.01	10±0.08	ns
25–36 months	6±0.01	4±0.07	ns
	2±0.05	2±0.08	ns



Conclusions: 1- One-fifth of ICD patients experience a HF-D during the first 6 months following a SH. 2- The incidence of HF-D after a SH is lower in patients on BB-t, its beneficial effect being especially relevant in the first 6 months. 3- The sympathetic nervous system could play a central role in the SH-related myocardial damage.

P695 | BEDSIDE
Avoidance of primary preventive ICD implantation by intensified optimized heart failure therapy protected by the wearable cardioverter/defibrillator - The PROLONG registry

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Introduction: The wearable cardioverter/defibrillator (WCD) has been shown to be an effective tool for temporary prevention of sudden cardiac death (SCD) in patients with transient or unspecified risk for ventricular tachyarrhythmias. Patients with newly diagnosed heart failure and severely reduced left ventricular ejection fraction (LVEF) represent an indication for the WCD. After initiation of heart failure therapy and during optimization of medication dosages a WCD is prescribed for 3 months and re-evaluation of LVEF is scheduled. The aim of the PROLONG registry was to analyse the reasons for prolongation and outcome of this extended WCD wearing period.
Methods: 265 patients were prescribed a WCD between 06/2012 and 02/2016 in our center. Time from first wear date to last wear date (raw count of days) was determined for each patient. Patients wearing the WCD for more than 90 days with the indication of newly diagnosed heart failure and severely reduced LVEF were included in the study. Baseline characteristics and follow-up data were collected.
Results: 88 patients (mean age 54 years, 54 male) wore the WCD for more than 90 days, median 120 days, range 91 to 548 days. Indications for WCD use were non-ischemic cardiomyopathy (48%), ischemic cardiomyopathy (35%), peripartum cardiomyopathy (9%), myocarditis (6%) and other (2%). Mean follow-up duration was 12±10months. Median LVEF was 26% at baseline, 31% after 90 days and 36% at last follow-up.
After 90 days, 23 patients (26%) revealed recovery of LVEF >35% and 65 patients (74%) met the LVEF criteria for primary preventive ICD implantation. After prolonged WCD wearing and further optimization of heart failure medication, another 20 patients showed reverse remodelling to LVEF >35%. At last follow-up, 39 patients (44%) had received an ICD. 2 patients refused ICD implantation after prolonged WCD use despite a definite indication. Median duration from WCD prescription to ICD implantation was 126 days.
2 patients experienced 3 adequate WCD shocks for ventricular fibrillation. One of them received the shock after 122 days, i.e. during his prolongation period. The other one received 2 shocks within the first month of WCD use but refused ICD implantation and wore the WCD for more than 1 year.
Conclusions: By prolongation of WCD period to optimize heart failure therapy for more than 3 months ICD implantation was avoided in about one third of the patients (20 out of 65). One patient was protected from SCD by adequate WCD therapy during extended WCD period. Our data show that WCD protected optimization of heart failure therapy up to 6 months can avoid unnecesseray primary preventive ICD implantation.

P696 | BEDSIDE
Evaluation of alternative implant techniques for the subcutaneous implantable cardioverter-defibrillator

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Introduction: Alternative techniques to standard three-incision subcutaneous implantation of the subcutaneous implantable cardioverter-defibrillator (S-ICD) have been proposed, which may offer both operative and cosmetic advantages.
Purpose: We evaluated four implantation techniques in a large cohort of S-ICD patients for clinical outcomes.
Methods: Consecutive patients from two hospitals with ample experience with the S-ICD between 2009 and 2016 were included. Physician preference and

patient characteristics determined the implant technique. The two- and three-incision techniques place the pulse generator (PG) subcutaneously, but the two-incision technique omits the superior parasternal incision for lead positioning. Submuscular implantation places the PG underneath the Serratus Anterior muscle. Subfascial implantation positions the PG underneath the fascial layer on the anterior side of the Serratus Anterior muscle. Devices were tested intra-operatively at operator's discretion.

Results: 236 patients were included (table 1). First-shock efficacy and shock lead impedance during testing did not differ among the groups. A total 18 complications occurred, of which seven were infections requiring extraction. All infections occurred in subcutaneous implants (three-incision: n=3, two-incision: n=4, submuscular: n=0, subfascial: n=0). Skin erosion occurred in two patients, both implanted subcutaneously (three-incision: n=1, two-incision: n=1, submuscular: n=0, subfascial: n=0). Both appropriate shocks and inappropriate shocks did not differ significantly.

Table 1

	Subcutaneous 3 incisions (n=54)	Subcutaneous 2 incisions (n=114)	Submuscular (n=38)	Subfascial (n=30)	P
Age (median [IQR])	48 [31, 60]	41 [26, 53]	51 [26, 66]	56 [40, 62]	0.001
Days follow-up (median [IQR])	1774 [153, 1979]	706 [245, 1284]	269 [40, 381]	40 [16, 74]	<0.001
LVEF (%) (median [IQR])	45 [30, 55]	49 [30, 57]	50 [29, 60]	30 [20, 33]	0.001
Female (%)	18 (33)	48 (42)	11 (29)	13 (43)	0.40
DFT Successful (%)	100%	96%	100%	100%	0.46
Shock impedance (median [IQR])	72 [53, 91]	65 [57, 79]	79 [63, 92]	58 [55, 60]	0.08
Appropriate shock (%)	7 (13)	7 (6)	2 (5)	1 (3)	0.38
Inappropriate shock (%)	8 (15)	13 (11)	1 (3)	0 (0)	0.06
Complications (%)	6 (11)	9 (8)	3 (8)	0 (0)	0.31
- Infections (%)	3 (6)	4 (4)	0 (0)	0 (0)	0.44

Conclusions: The presented implantation techniques are feasible alternatives to the standard three-incision subcutaneous implantation and may reduce the risk of pocket-related complications.

P697 | BEDSIDE
Eligibility for subcutaneous cardioverter-defibrillator in patients with Brugada syndrome

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Background: Subcutaneous implantable cardioverter-defibrillator (S-ICD) can avoid important complications associated with transvenous leads in subjects who do not need pacing therapy such as patients with Brugada syndrome (BrS). Very little information is available on the S-ICD eligibility of patients with BrS. Aim of this study was to analyze eligibility for S-ICD in a series of patients with BrS, and to compare it with age- and gender-matched patients with other indication to ICD therapy.

Methods: ECG screening of consecutive patients was performed by analysis of QRS complex and T wave morphology recorded in standing and supine position. In BrS patients without a diagnostic baseline ECG, S-ICD sensing analysis was repeated during ajmaline challenge. Ajmaline was administrated at a dosage of 1 mg/kg over 5 minutes. Eligibility was defined when $\geq$1 sense vector was acceptable in both supine and standing position.

Results: A total of 58 patients (37 males; mean age: 54±13 years; mean LVEF 47±16%) underwent S-ICD sensing screening before an ICD implantation procedure. Twenty-four patients (41%) presented with ischemic heart disease and 30 (52%) with a primary electrical disorder (BrS: 23 pts, long-QT syndrome: 2 pts; idiopathic ventricular fibrillation: 5 pts). The remaining 4 subjects (7%) had an inherited myocardial disease. Ten patients with BrS (43%) presented with spontaneous type 1 ECG. In the other 13 patients, type 1 ECG was unmasked by ajmaline. Six out of 10 patients (60%) with spontaneous type 1 ECG failed the sensing screening. All patients with drug-induced BrS had appropriate morphology analysis at baseline. However, in 3 of them (23%), morphology analysis was inappropriate after ajmaline administration. Individuals with BrS had a higher prevalence of S-ICD screening failure as compared with other candidates to ICD therapy (39% vs 8.6%, p: 0.007). In all patients with BrS, the reason for sensing inappropriateness was due to the presence of too high T-wave voltages.

Conclusions: S-ICD screening failure occurs in up to 40% of patients with BrS. In patients with non-diagnostic baseline ECG, morphology analysis should be repeated after ajmaline challenge, which may unmask sensing issues in 23% of cases previously considered suitable to S-ICD.

VASCULAR BIOLOGY AND REMODELLING

P698 | BENCH
Adventitial activation is critical for negative vascular remodeling

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Background: Deciphering the detailed pathophysiological course of vascular remodeling processes is of pivotal importance for the development of novel therapeutic strategies. Especially, the impact and the cellular contribution of the vascular adventitial layer on neointima formation are simply unknown.

Purpose: The aim of this study was to analyze the impact of the adventitial layer on vascular remodeling processes and to define the underlying cellular mechanisms.

Methods and results: We dilated the femoral artery of C57BL/6J mice with a straight spring wire and performed morphometric analysis of the lesion and immunohistochemical staining for the proliferation marker Ki-67 7, 14, and 21 days following injury. Formation of a profound neointimal lesion at 21 days was preceded by high adventitial proliferation rates and massive adventitial thickening at 7 and 14 days (adv. area: 0.036±0.015 mm^2 at 0d vs. 0.082±0.013 mm^2 at 7d vs. 0.102±0.029 mm^2 at 14d, n=15, P<0.0001). Further immunohistochemical characterization of the respective proliferating cells revealed them to be negative for the pan-leukocyte marker CD45 as well as for the progenitor cell marker Sca-1 and thus most likely to be fibroblasts.

Complete removal of the adventitial layer almost completely prevented neointima formation attributing pivotal importance to the adventitial layer (luminal stenosis: 71.73±3.77% vs. 7.44±1.71%, n=5, P<0.0001). Coating of the medial vascular layer of the femoral artery with the aortic adventitia of ubiquitously GFP expressing C57BL/6-Tg (CAG-EGFP) 1Osb/J mice restored the negative vascular remodeling process. Importantly, only very view GFP+ cells could be detected in the prominent neointimal layer, indicating that a direct contribution and transdifferentiation of adventitial cells to neointimal SMC represents an extremely rare event. To investigate a potential paracrine effect of the activated adventitial layer, we explanted adventitial grafts 14 days following injury and transplantation and incubated the respective samples in serum-free media for 24 hours. BrdU incorporation assays and scratch wound assays revealed significantly increased proliferation and migration rates of human coronary artery SMCs in response to the supernatant of adventitial transplants compared to the supernatant of appropriate controls. Further protein array analyses of adventital supernatants at 14 days after injury identified the up-regulation of several growth factors/cytokines previously described to trigger SMC proliferation and migration (especially interleukin-6 and -8). Moreover, we identified the non-canonical type II sonic hedgehog (Shh) signaling to be crucial for adventitial activation and cytokine release.

Conclusion: Dilation of the murine femoral artery is immediately followed by adventitial enrichment of cytokine-producing fibroblasts, whose paracrine function is essential for subsequent proliferation and migration of local SMC and neointima formation.

Acknowledgement/Funding: This study was funded by the German Research Foundation (Cluster of Excellence REBIRTH)

P699 | BENCH
Sonic hedgehog signalling in adventitial fibroblasts promotes inflammation and smooth muscle cell proliferation in neointima formation

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Background: Vascular proliferative diseases are characterized by the accumulation of inflammatory cells and the subsequent proliferation of smooth muscle cells (SMC). Adventitial cells have been suggested to contribute to these processes, but the functional relevance and the responsible signalling pathways are largely unknown. Sonic hedgehog (Shh) is a regulator of vasculogenesis and promotes angiogenesis in the adult. Smoothened (Smo) is a membrane-bound downstream protein of Shh and orchestrates signal transduction via the Gli family of transcription factors and other pathways.

Purpose: We analysed the functional impact of adventitial fibroblasts on neointima formation and defined the underlying signalling mechanisms.

Methods and results: Following wire-mediated injury of the femoral artery in C57BL/6 mice, the majority of inflammatory cells (CD45+) and proliferative cells (Ki-67+) was not detected in the neointima/media but within the adventitia 7 and 14 days after injury. Simultaneously, the expression of Shh and Smo were robustly increased within injured arteries, as indicated by immunoblotting and immunohistochemistry. In vitro, platelet-derived growth factor (PDGF)-BB was identified to upregulate the expression and the release of Shh in leukocytes and SMC, whereas Smo was upregulated especially in fibroblasts. Combined stimulation with Shh and PDGF-BB strongly induced the proliferation and migration of fibroblasts and SMC. Importantly, the specific Smo inhibitor GDC-0449 (Vismodegib) as well as Smo siRNA reversed the effects of Shh/PDGF-BB in fibroblasts but not in SMC. Mechanistically, we found that PDGF-BB selectively induced trafficking of Smo to the plasma membrane of fibroblasts but not SMC via activation of protein kinase A (PKA). After stimulation of fibroblasts or leukocytes with Shh/PDGF-BB, only the supernatant of fibroblasts strongly induced proliferation and migration of SMC. Also this effect was completely abolished by GDC-0449. Further proteomic analysis of the supernatant of stimulated fibroblasts using cytokine-arrays showed a strong upregulation of interleukin (IL)-6, IL-8 and the chemokine (C-X-C motif) ligand 1. Following wire-induced injury in C57BL/6 mice, perivascular application of GDC-0449 significantly reduced the inflammatory response to injury (CD45+ cells), proliferation of adventitial fibroblasts and the subsequent proliferation of neointimal SMC, which resulted in significantly reduced neointima formation and luminal stenosis.

Conclusions: The activation of fibroblasts represents a so far underestimated

key event in vascular proliferative diseases by releasing cytokines and growth factors. This activation is mediated by Shh and PDGF-BB induced activation of Smo-dependent signalling and the selective inhibitor GDC-0449 may serve as a novel and promising therapeutic strategy to prevent neointima formation.

P700 | BENCH

The novel mineralocorticoid receptor antagonist Finerenone attenuates neointima formation after vascular injury

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Background: Ischemic cardiomyopathy as a result of coronary artery disease is the leading cause for heart failure. In consequence, the effect of novel heart failure therapeutics on vascular function and remodeling processes is of pivotal importance. Finerenone, a novel nonsteroidal mineralocorticoid receptor (MR) antagonist, holds the promise to be safe and efficient in the treatment of patients with heart failure and/or chronic kidney disease. However, the effects on vascular function remain elusive.
Purpose: The aim of this study was to determine the functional effect of selective MR antagonism by Finerenone in vascular cells in vitro and the effect on vascular remodeling following acute vascular injury in vivo.
Methods and results: Finerenone dose-dependently and significantly reduced aldosterone-induced human coronary artery smooth muscle cell (HCASMC) proliferation as quantified by BrdU incorporation. Furthermore, Finerenone dose-dependently and significantly prevented aldosterone-induced apoptosis in human umbilical vein endothelial cells (HUVEC) as measured with a flow cytometry based FLICA-assay.
In vivo, oral application of Finerenone dose-dependently and significantly inhibited intimal and medial cell proliferation following femoral artery wire-induced injury in C57BL/6J mice as quantified by staining for Ki-67 10 days following injury (vehicle vs. 1 mg/kg/d vs. 10mg/kg/d; each $p<0.01$). Concomitantly, Finerenone attenuated neointimal lesion formation following femoral artery wire-induced injury 21 days following injury (luminal stenosis, vehicle vs. Finerenone 1 mg/kg/d vs. Finerenone 10mg/kg/d: 90.2±1.1% vs. 60.1±17.3%; p=0.1063 to vehicle, vs. 35.3±10.0%; p=0.0061 to vehicle; n=8). Furthermore, there was a trend towards an accelerated re-endothelialization of the injured vessel segments in Finerenone-treated mice three days following electric injury of the murine carotid artery.
Conclusion: Finerenone treatment significantly attenuates HCASMC proliferation while simultaneously preventing apoptosis of endothelial cells in vitro. This is reflected by a significantly reduced neointima formation and reduction of luminal stenosis as well as a trend towards an accelerated endothelial healing of the injured vessels. Thus, apart from its beneficial effects in heart failure therapy, Finerenone might provide favorable vascular effects through restoring vascular integrity and preventing adverse vascular remodeling.
Acknowledgement/Funding: This study is supported by Bayer HealthCare Pharmaceuticals, Wuppertal, Germany

P701 | BENCH

Endothelial protein tyrosine phosphatase-1B deletion enhances neointima formation in mice with diet-induced obesity

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Background: Obesity and metabolic dysfunction are associated with increased expression of protein tyrosine phosphate (PTP)-1B, a negative regulator of receptor tyrosine kinase signalling, and PTP1B overexpression may be causally involved in the development of insulin and leptin resistance in obesity. Previous studies have shown that systemic inhibition or genetic deletion of PTP1B protects against endothelial dysfunction in heart failure. However, the role of PTP1B expressed in endothelial cells for the cardiovascular risk in obesity has not been directly examined so far.
Purpose: To determine the effect of endothelial PTP1B deletion on the vascular response to injury in mice with diet-induced obesity.
Methods: Mice with loxP-flanked PTP1B alleles were mated with mice expressing a Cre recombinase-estrogen receptor fusion protein ER (T2) under control of the endothelial receptor tyrosine kinase (Tie2) promoter. Cre recombinase activity and endothelial-restricted PTP1B gene excision (End.PTP1B-KO) was induced by feeding mice tamoxifen-containing rodent chow for 6 weeks. Obesity was induced by feeding mice 45% high fat diet (HFD) for 4 weeks prior to vascular injury at the common carotid artery using 10% ferric chloride and continued until sacrifice 3 weeks later.
Results: HFD resulted in increased body weight, visceral obesity and total serum cholesterol, both in End.PTP1B-WT and End.PTP1B-KO mice and also was associated with elevated PTP1B protein levels in endothelial cells isolated from the lungs of obese mice (1.4-fold increase vs. lean; $P<0.05$). Morphometric analysis of serial sections through restenotic lesions revealed that deletion of PTP1B in endothelial cells was associated with a significant increase in the neointima area ($P<0.05$) and intima-to-media ratio ($P<0.05$). Because the total vessel area also was significantly enlarged in mice lacking endothelial PTP1B ($P<0.05$), the more pronounced lumen stenosis observed in End.PTP1B-KO mice (33±7.0 vs. 20±4.0% in End.PTP1B-WT) did not reach statistical significance. Analysis of re-endothelisation revealed significantly reduced numbers of luminal cell nuclei in End.PTP1B-KO animals ($P<0.05$), and (immuno-)histochemical analysis confirmed reduced luminal binding of endothelial lectin (10±4.4 vs. 25±5.1% in End.PTP1B-WT mice; P=0.065). Moreover, neointimal lesions of End.PTP1B-KO mice were characterised by an increased absolute number of cell nuclei ($P<0.05$ vs. End.PTP1B-WT mice) as well as elevated amounts of αSM-actin-positive SMCs (6315±2671 vs. 1729±496 μm^2; P=0.075).
Conclusion: Our findings suggest that endothelial PTP1B plays an important role for lesion re-endothelisation after vascular injury. The observed neointimal hyperplasia in mice lacking PTP1B in endothelial cells may be the consequence of failure to induce SMC quiescence resulting in uncontrolled neointimal SMC proliferation.

P702 | BENCH

Endothelial-Mesenchymal Transition: miR-101 as a new target to treat intimal hyperplasia

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Introduction: Endothelial-Mesenchymal Transition (EndMT) is a specific form of endothelial dysfunction wherein endothelial cells acquire a mesenchymal phenotype and lose their endothelial functions. We, and others, recently described that EndMT contributes to intimal hyperplasia and atherosclerosis.
Pro-fibrotic and inflammatory cytokines, such as IL-1β and TGFβ2 induce EndMT. We found that the mitogen activated protein kinase 7 (MAPK7, also known as Erk5) inhibits EndMT. MAPK7 activation decreases the expression of the histone methyltransferase Enhancer-of-Zeste homologue 2 (Ezh2) thereby maintaining endothelial quiescence.This decrease in Ezh2 expression may therefore be responsible for the protective effects of MAPK7 activation and may thus offer new therapeutic options for the treatment of endothelial dysfunction and intimal hyperplasia.
Ezh2 is the catalytic subunit of the Polycomb Repressive Complex 2 that methylates lysine 27 on histone 3 (H3K27me3). H3K27me3 is a repressive chromatin mark that inhibits gene expression. Currently, it is elusive how the crosstalk between MAPK7 and Ezh2 is regulated in the endothelium and if the balance between MAPK7 and EZH2 is disturbed during intimal hyperplasia.
Methods and results: We used in silico analysis to identify miRNAs that could evoke posttranscriptional silencing of Ezh2. In Luciferase reporter assays, miR-101 efficiently inhibited expression of the luciferase reporter by interacting with the 3'UTR of EZH2. Using a uniform laminar flow setup, we revealed that MAPK7 induced miR101 expression, which was blocked by the selective MAPK7 inhibitor BIX02189 ($p<0.05$). Furthermore, ectopic expression of miR-101 in endothelial cells reduced the expression of Ezh2.
In samples of human coronary artery stenosis Ezh2 levels are increased, whereas MAPK7 expression is reduced. Moreover, miR-101 expression is decreased, which associated with the increase of Ezh2 ($R^2=0.23$, p=0.051) and severity of the stenosis (Intima/Media Thickness, $R^2=0.45$, p=0.003).
Conclusion(s): Under uniform laminar flow MAPK7 inhibits Ezh2 expression via activation of miR-101. In coronary artery stenosis, endothelial cells are exposed by non-uniform shear stress which decreases MAPK7 activation, miR-101 expression and concurrently increases Ezh2 expression, which may cause EndMT and intimal hyperplasia. Therefore, the restoration of miR-101 expression or the silencing of Ezh2 in the endothelium might provide novel therapeutic approaches to treat intimal hyperplasia.
Acknowledgement/Funding: Mongolian Government Scholarship (BV)

P703 | BEDSIDE

TNF-antagonists improve arterial stiffness in patients with rheumatoid arthritis: a meta-analysis

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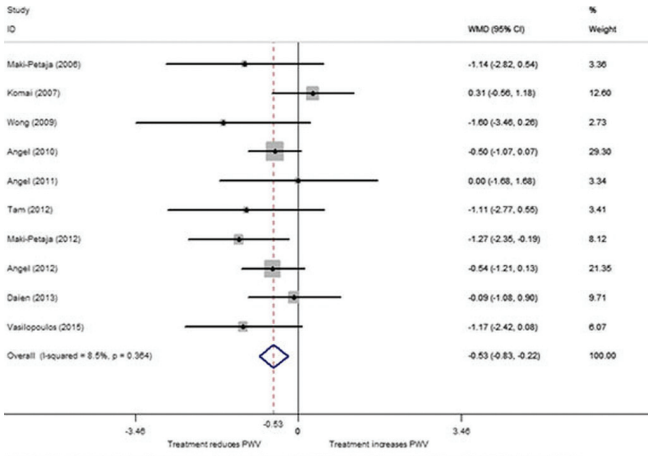
Background: Patients with rheumatoid arthritis (RA) have a higher arterial stiffness than their age-matched healthy counterparts and an increased inflammatory burden that might be associated with their increased cardiovascular risk. While tumor necrosis factor alpha (TNF)-antagonists have been found to reduce inflammatory markers in RA, it is debatable if they have favorable effects on surrogate markers of cardiovascular outcomes.
Purpose: We conducted a meta- analysis to assess the effect of TNF-antagonists on arterial stiffness, a predictor of cardiovascular events and mortality, in RA patients.
Methods: A search of PUBMED was conducted to identify studies into the ef-

fect of TNF- antagonists on arterial stiffness in RA patients. Studies matching the search criteria were included for analysis. Data were available on 3 TNF-antagonists: infliximab, adalimumab, and etanercept.
Results: 10 studies (n=208 patients) out of 13 eligible studies in total, measured changes in carotid-femoral PWV after treatment with anti-TNFs. Subjects under therapy with anti-TNFs significantly decreased their arterial stiffness (mean change in PWV: -0.53 m/s, p=0.001) (Figure). No significant heterogeneity was observed across the studies (I2=8.5%, p=0.364). By subgroup analysis, improvement in PWV after therapy was independent from age and clinical response to treatment (DAS reduction) but was less prominent in subjects treated with infliximab. Sensitivity analysis indicated consistency of our results.



Weighted mean differences (WMD) and 95% CI after treatment with anti-TNFs for PWV. Studies are listed by date of publication. Boxes represent the WMD and lines represent the 95% CI for individual studies. The diamonds and their width represent the pooled WMDs and the 95% CI, respectively.

Conclusions: The balance of evidence suggests that TNF-antagonists may have a beneficial effect on arterial stiffness in RA patients. Given the predictive role of aortic stiffness for adverse cardiovascular outcomes, TNF-antagonists might confer reduction of the cardiovascular risk of these patients beyond their anti-inflammatory effect. However, larger longitudinal studies are warranted to confirm recent findings.

P704 | BENCH
C1q/TNF-related protein 1 reduces vascular smooth muscle cell growth and neointimal thickening after vascular injury

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Background: Obesity is closely associated with the progression of various vascular disorders including pathological vascular remodeling. C1q/TNF-related protein (CTRP) 1 is an adipokine that is upregulated in association with metabolic syndrome, coronary artery disease and type 2 diabetes. Recently we have demonstrated that CTRP1 prevents myocardial ischemia-reperfusion injury in vivo. Here, we examined whether CTRP1 affects vascular smooth muscle cell (VSMC) proliferation and neointimal formation.
Methods/Results: We generated CTRP1-knockout (CTRP1-KO) mice by TALEN-based method. Under basal conditions, no differences were observed in morphometric and metabolic parameters between CTRP1-KO and wild-type (WT) mice. CTRP1-KO mice displayed the enhanced intima/media area ratio after femoral artery injury induced by wire insertion compared with WT mice. CTRP1-KO mice also showed the increased number of bromodeoxyuridine (BrdU) positive proliferating cells in the injured artery after surgery compared with WT mice. Systemic administration of CTRP1 using an adenoviral vector expression system to WT mice led to an increase in plasma CTRP1 level and a decrease in intima/media area ratio in the injured artery. Treatment with recombinant CTRP1 protein suppressed growth factor-stimulated proliferative activity and ERK phosphorylation in VSMCs. CTRP1 treatment increased cyclic AMP (cAMP) levels in VSMCs. The inhibitory effects of CTRP1 on proliferation and ERK phosphorylation in VSMCs were abolished by pharmacological inhibition of adenylyl cyclase. Furthermore, pretreatment of VSMCs with the antagonist for a sphingosine-1-phosphate (S1P) receptor reversed the actions of CTRP1 on VSMC growth and cAMP production.
Conclusion: These data suggest that CTRP1 protects against pathological vascular remodeling by suppression of VSMC proliferation through the cAMP-dependent mechanism.
Acknowledgement/Funding: This research is supported by Grant-in-Aid for Scientific Research and Grant-in-Aid for Challenging Exploratory Research.

P705 | BENCH
Obstructive sleep apnea causes aortic remodelling in a chronic murine model

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Background: Obstructive sleep apnea syndrome (OSA) promotes aortic dilation, increased stiffness and accelerated atherosclerosis progression. The mechanisms of deleterious vascular remodelling have not been studied in clinically relevant OSA animal models.
Purpose: To investigate vascular remodelling in a chronic OSA rat model involving both thoracic pressure swings and intermittent hypoxia.
Methods: 30 Sprague-Dawley male rats were randomized into 2 groups: OSA- rats (n=16) were subjected to 15-second obstructions (60/hour, 6 hours/day, 21 days). Sham-rats (n=14) were placed in the setup during 21 consecutive days without air obstructions. Descending thoracic aorta was dissected and fixed in OCT for morphometric measurements and histology, or frozen in liquid nitrogen for Western Blot analysis. Proteins involved in endothelial function, oxidative stress and Renin Angiotensin Aldosterone System (RAAS) were quantified. Remodelling of intramyocardial vessels was assessed in left and right ventricle paraffin-embedded heart sections.
Results: OSA induced aortic hypertrophic outward remodelling characterized by increased wall thickness (Fig.A), but had no effect in the lumen diameter. No changes in collagen deposition in the tunica media (Sirius Red) or collagen 1–3 protein levels were triggered by OSA. Chronic OSA upregulated ACE1 protein levels (Fig.B) and RAAS downstream effectors Erk1/2 and GTPase protein RhoA. Also, protein levels of NADPH oxidase subunits NOX1 (Fig.C) and p47phox were found to be increased, whereas endothelial nitric oxide synthase (eNOS) protein levels were decreased (Fig.D) in OSA compared to Sham rats. No differences were found in the lumen area, tunica media thickness or perivascular fibrosis of intramyocardial vessels.

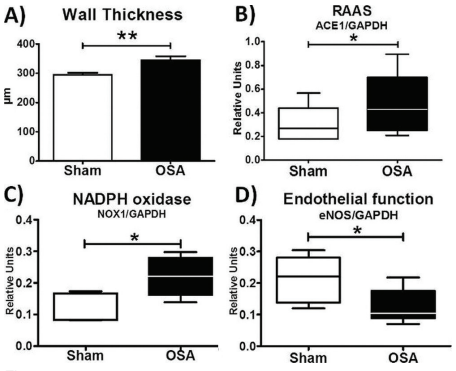

Figure 1

Conclusions: In this clinically relevant model, we show that OSA causes aorta hypertrophy and endothelial dysfunction in large elastic arteries. RAAS upregulation and increased oxidative stress likely mediate these effects. Our results provide valuable insights into OSA-promoted atherogenesis and potential future therapeutic targets. Confirmation in OSA patients is warranted.
Acknowledgement/Funding: Supported by a grant from the Instituto de Salud Carlos III and a personal grant (pFIS) from the Spanish Ministry of Economy and Competitivity.

P706 | BENCH
PI3Kdelta mediates growth factor induced PASMC proliferation and hypoxia induced pulmonary hypertension via non-catalytic mechanisms

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Introduction: Pulmonary hypertension (PH) is a devastating disease hallmarked by vascular remodeling processes in pulmonary arterioles. Peptide growth factor dependent activation of PI 3-kinase (PI3K) is crucial for these processes as it induces proliferation and migration of pulmonary arterial smooth muscle cells (PASMCs). Interestingly, we were able to demonstrate that the PI3K isoform PI3Kdelta which is primarily believed to be restricted to leukocytes is abundantly expressed in PASMCs.
Purpose: Here, we analysed the effects of PI3Kdelta deficiency on growth factor mediated PASMCs proliferation and chemotaxis as well as its impact on hypoxia induced PH in mice.
Methods: The effects of a PI3Kdelta specific inhibitor (IC87114) as well as siRNA mediated knockdown and genetic ablation of PI3Kdelta on growth factor induced PASMC proliferation and chemotaxis were investigated. Proliferation was anal-

ysed via BrdU-incorporation. Chemotaxis was quantified using modified Boyden chambers. Additionally, adult male p110delta deficient mice and wildtype were subjected to chronic hypoxia (21 days) or normoxia, respectively. RV systolic pressure (RVSP) was measured using a Millar pressure catheter inserted via the jugular vein. RV hypertrophy was demonstrated as the ratio of RV weight to LV + septum weight.
Results: siRNA knockdown as well as deficiency of PI3Kdelta significantly impaired platelet-derived growth factor (PDGF)-BB (30 ng/ml, n≥3) induced PASMC proliferation but had no effect on PDGF mediated PASMC chemotaxis. Additionally, proliferation induced by various growth factors (PDGF [30ng/ml], EGF [0,5ng/ml], bFGF [2ng/ml], insulin [0,5ng/ml], and FBS [5%]) was significantly reduced in PI3Kdelta deficient cells. However, pharmacological inhibition of PI3Kdelta using IC87114 even at high concentrations (3μM) affected neither PASMC proliferation nor chemotaxis. Interestingly, these in vitro data suggest that PI3Kdelta exerted kinase independent functions on PASMC proliferation. Further analysis of PI3Kdelta deficiency on hypoxia induced PH revealed that RVSP was significantly increased in wildtype mice but not in PI3Kdelta–/– animals. Consistently, hypoxia induced RV hypertrophy was only present in wildtype mice, demonstrating that PI3Kdelta deficiency ameliorated PH.
Conclusion: These data provide evidence for the first time that 1.) PI3Kdelta has a significant impact on cellular proliferation of non-hematopoietic cells and 2. that this effect is primarily mediated via non-catalytic mechanisms at least in PASMCs. These important findings have direct implications on the pathogenesis of PH as lack of PI3Kdelta expression leads to reduced proliferation of PASMCs in response to growth factors and to improved hemodynamics in hypoxia induced PH.

P707 | BENCH
Neutrophil extracellular traps: imaging, nanomechanics and their relevance for cardiovascular diseases

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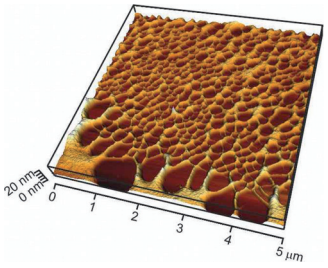
Neutrophils are immune cells that make the first line of defence against pathogens., and their relationship with cardiovascular disorders is often underappreciated. Recent studies have shown that neutrophils populate atherosclerotic lesions in a platelet-dependent manner, can contribute to an erosion of endothelial functions, atherosclerotic plaque destabilization and atherothrombosis. It has been found that neutrophils can also engage in a suicidal pathway that leads to the release of partially decondensed chromatin, or neutrophil extracellular traps (NETs). Through its binding to pathogens, the emergence of NETs, or NETosis, actively contributes to limiting the spread of an infection, but it can also elicit specific forms of collateral damage to the cardiovascular system. NETs have been identified in association with human and murine atherosclerotic lesions, and bind to coagulation factors that can lead to deep vein thrombosis. Despite the fundamental role of NETs as part of an immune system response and their repercussions to the cardiovascular system, we remain far from understanding how their nanoscale properties contribute to their macroscopic behaviour.
In this work, using a combination of fluorescence and atomic force microscopy, we set out to characterize NETosis with respect to its dynamics, as well as high detail imaging and mechanical properties of NETs. We found that NETs are a filamentous network with a reticulated appearance containing openings that span from tens of nanometers up to a few microns. Openings up to 500×500 nm^2 were the most frequently observed, indicating that NETs can potentially trap particles that are much larger, such as bacteria and host circulating cells. Statistical analysis of the contour length of NET branches typically revealed filament stretches equivalent to the unravelling of the DNA present in at least 2 nucleosomes. The presence of DNA could also be inferred from force spectroscopy data where force plateaus of ~65 pN are indicative of the DNA overstretch transition. We also found that the protein content of NETs is relevant for its structural integrity and its binding functionality. Proteolytic treatment of NETs combined with force mapping totalling 4096 probed sites, revealed a highly significant ($p<0.001$) 40% average drop in the maximal force of rupture events and 23% average decrease ($p<0.001$) in the work involved in the manipulation of NETs.



3D Topographic Image of NETs

We conclude that NETs comprise a porous filament network containing openings with a size distribution small enough to capture circulating cells. They consist of a DNA-protein assembly where proteins contribute both to the adhesion of foreign particles as well as to the structural integrity of NETs. We anticipate that NETs may work as microscopic mechanical sieves that segregate particles also as a result of their size. Such behaviour can help to explain their indiscriminate participation in capturing pathogens as well as in promoting thrombosis.
Acknowledgement/Funding: German Center for Cardiovascular Research (DZHK); German Ministry of Education and Research (BMBF); Land Mecklenburg-Vorpommern

P708 | BENCH
In vitro evience in support of a double-hit hypothesis for BMPR2 signalling in the development of pulmonary hypertension: role of hypoxia and the serotonin transporter

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Background: Pathologically, pulmonary hypertension is characterised by remodelling of the pulmonary arteries involving all three layers of the vessel wall. Previous studies have shown that pulmonary artery fibroblasts show an increase in proliferation in response to hypoxia and that this response is depended on activation of p38 MAP kinase. Genetic mutations leading to the disruption of BMP signalling have been identified in Heritable Pulmonary Hypertension (PH). However not all people with a BMPR2 haploinsufficiency develop PH, i.e. there is reduced gene penetrance. One hypothesis that may account for the low penetrance of the disease among BMPR2 mutation carriers is that additional environmental or genetic modifying factors are required which act in concert with BMPR2 deficiency to induce a pulmonary hypertensive phenotype. It is therefore important that potential "second hits" be identified. We choose to examine the serotonin pathway as a possible second hit as this pathway has also been implicated in the pathogenesis of Pulmonary Hypertension.
Purpose: To investigate in vitro whether a PH pro-proliferative phenotype would be observed in BMPR2+/– mice pulmonary artery fibroblasts where there was also serotonin transporter (SERT) over-expression and to investigate the role of the p38 MAP kinase pathway in the proliferative response to hypoxia in pulmonary artery fibroblasts.
Methods: BMPR2+/– mice were generated from the C57BL/6J strain at the University of Cambridge, UK. Transgenic mice that over express the gene for human SERT (SERT+ mice) were developed from the C57BL/6 x CBA background strain. The BMPR2+/– / SERT+ mouse was generated at the University of Glasgow, UK. SERT+ males were crossed with BMPR2+/– females. Pulmonary artery fibroblasts were isolated from all genotypes (wild type (WT), BMPR2+/–, SERT+ and BMPR2+/– / SERT+) and subjected to hypoxic conditions as an experimental model of pulmonary hypertension. Fibroblasts were cultured in the presence and absence of foetal calf serum as this has previously been shown to be necessary for the hypoxic response of pulmonary fibroblasts in vitro. Proliferation and migration of cells was studied. The MAP kinase signalling pathway was also examined as we have previously shown it to be important in the proliferation of pulmonary artery fibroblasts in experimental pulmonary hypertensive models.
Results: Fibroblasts lacking the BMPR2 gene and over-expressing the serotonin

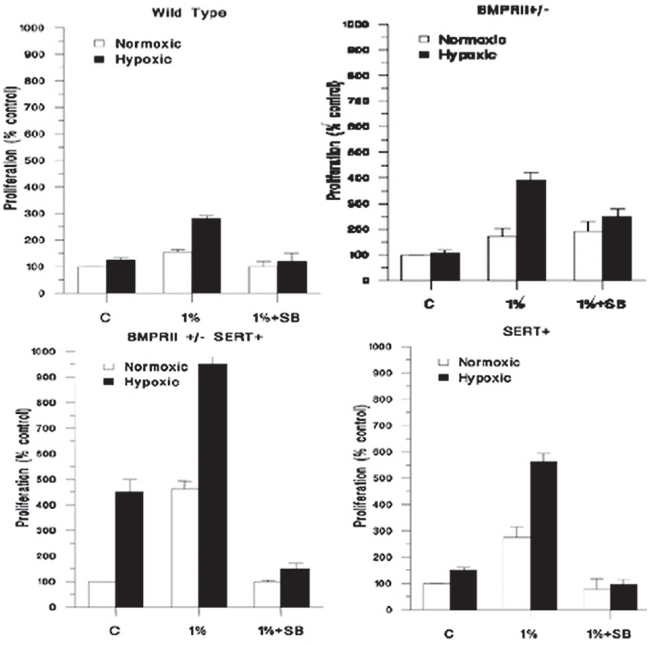

Figure 1 – Effect of Hypoxia, Serum and SB 203580 (p38 MAP kinase inhibitor) on WT, BMPR2$^{+/-}$, BMPR2$^{+/-}$/SERT+ and SERT+ on fibroblast proliferation.

transporter showed an increase in proliferation and cell migration compared to the other cell types when cultured in the absence of serum. This response could be abrogated by inhibition of p38 MAP kinase.
Conclusion: Pulmonary artery fibroblasts from BMPR2+/– / SERT+ mice show an increased proliferative response to hypoxia, supporting the "double-hit hypothesis". This response is a result of a p38 MAP kinase dependent pathway.

P709 | BENCH
molecular mechanism of worsening aortic dissection by high salt through IL-17 pathway

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Background: Aortic dissection (AD) is one of the fatal cardiovascular diseases, in which proinflammatory response is proposed to be important. High salt intake is an established risk factor of cardiovascular diseases, although the molecular mechanism has not been fully understood.
Method and results: In this study, we investigated the effect of high salt intake on a mouse AD model that was induced by continuous infusion of beta-aminopropionitrile (BAPN), a collagen/elastin crosslink inhibitor, and angiotensin II (AngII). High salt intake was achieved by giving 1% NaCl as drinking water 1 week prior to and during the BAPN+AngII infusion. BAPN+AngII caused thoracic and suprarenal AD in most of the mice within 2 weeks. The severity of AD as determined by lesion length was significantly higher in high salt group than in normal salt group, whereas systolic blood pressure or pulse rate showed no significant changes. Because recent studies have demonstrated that high salt activates TH17/IL-17 pathway that is central to the inflammatory response, we examined the effect of high salt on TH17/IL-17 pathway. High salt didn't increase plasma IL-17a, but increased IL-17 receptors in aorta, suggesting that high salt may increase the sensitivity of aortic tissue to IL-17. We next examined the involvement of IL-17 in AD using IL-17 knockout mice (IL17-KO). Significantly, deletion of IL-17 gene abolished the exacerbating effect of high salt on the severity of AD. Transcriptome analysis of aortae showed that strong induction of proinflammatory genes and suppression of extracellular matrix (ECM) genes precede the AD development after BAPN+AngII. Although IL-17 is central to inflammatory response in general, alteration of inflammatory response was not prominent in IL17-KO aorta at the baseline before the high salt or BAPN+AngII administration. Instead, genes for ECM were upregulated in IL17-KO. Immunofluorescence staining showed that Smad2, a central regulator of ECM metabolism, was activated in the medial layer of IL-17-KO aorta. Picrosirius red staining showed that the amount of medial collagen fibers, the major ECM to support the physical strength of aorta, was increased in IL17-KO compared to wild type mice. High salt intake downregulated ECM genes in wild type aorta, but upregulated in IL-17-KO. Analysis of physical properties in excised aortic tissue revealed that high salt intake weakened aorta in wild type, but not in IL-17 KO aorta.
Conclusion: These data uncovered the unexpected role of IL-17 and salt to suppress ECM metabolism in aorta. We conclude that high salt induces the weakening of ECM, which worsens AD in the IL-17-dependent manner. Salt intake and IL-17 represent therapeutic targets for AD, and salt restriction may be a practical and low cost strategy for prevention of AD.

P710 | BEDSIDE
Placement of a sheath during cardiac catheterization could influence on the pressure waveform

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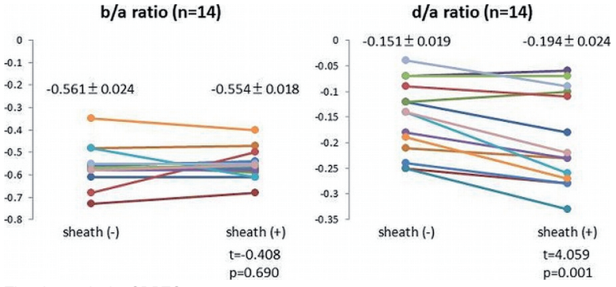
Background: Analyzing central arterial pressure waveform obtained by an invasive method is the gold standard for the pulse wave analysis. However, it is reported that the aortic pressure augmentation by the aortic pressure wave reflection occurs by external compression of the femoral arteries. Therefore, it is possible that the cardiac catheterization itself could influence on the pressure waveform.
Purpose: The purpose of this study is to clarify the influence of the sheath placement in a femoral artery on aortic pressure waveform.
Methods: This study enrolled 14 patients (11 men and 3 women) who underwent a cardiac catheterization. The mean age was 4 years (range 1 to 12 years). All patients were placed a sheath in their femoral arteries and the size of the sheath were 4F in 11 and 5F in 3. The change in the pulse pressure waveform induced by the placement of the sheath was investigated using a digital fingertip photoplethysmograph (SDP-100, Fukuda Denshi, Japan). The second derivative of the fingertip photoplethysmogram (SDPTG) has been verified as a useful non-invasive method for the pulse wave analysis. We assessed the SDPTG by the b/a ratio and the d/a ratio based on the height of the pulse wave components. The b/a ratio means the arterial stiffness and the d/a ratio represents the degree of the pressure wave reflection. That is to say, the high b/a ratio means the stiff aorta and the low d/a ratio represents the enhancement of the aortic pressure wave reflection.
Results: By the placement of the sheath in the femoral artery, the b/a ratio was not influenced (mean ± SEM, sheath (–): -0.561±0.024 vs. sheath (+): -0.554±0.018; p=0.690) and the d/a ratio significantly decreased (-0.151±0.019 vs. -0.194±0.024; p=0.001). Heart rate (94.1±4.0 mmHg vs. 91.6±3.7; p=0.215), systolic brachial cuff blood pressure (90.1±3.4 vs. 88.2±2.9; p=0.115), diastolic brachial cuff blood pressure (45.2±2.7 vs. 41.9±2.7; p=0.055) and pulse pressure (44.9±2.7 vs. 46.4±2.5; p=0.223) did not change.

Cardiovascular parameters

Parameter	Sheath (–)	Sheath (+)	p value
Heart rate (bpm)	94.1±4.0	91.6±3.7	0.215
Systolic brachial cuff BP (mmHg)	90.1±3.4	88.2±2.9	0.115
Diastolic brachial cuff BP (mmHg)	45.2±2.7	41.9±2.7	0.055
Pulse pressure (mmHg)	44.9±2.7	46.4±2.5	0.223

BP = blood pressure. Data are given as mean ± SEM.



The change in the SDPTG

Conclusions: The placement of the femoral arterial sheath enhances the pressure wave reflection and would lead to a change in the central aortic pressure waveform. The cardiac catheterization by femoral arterial approach itself could influence on the result of the pulse wave analysis

P711 | BENCH
Endothelial lectin-like oxidized low-density lipoprotein receptor-1 (LOX-1) exacerbates ischemia/reperfusion-induced cerebral injury

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Background: Vascular lectin-like oxidized low-density lipoprotein receptor-1 (LOX-1) promotes inflammation, apoptosis and oxidative stress, which are crucial components to ischemia/reperfusion (I/R) brain damage. In this study we investigate the role of endothelial LOX-1 in I/R-induced brain injury using a mouse model of ischemic stroke, primary human brain microvascular endothelial cells (HBMVECs) as well as peripheral blood monocytes (PBMs) from ischemic stroke patients.
Methods: Endothelial LOX-1 transgenic (LOX-1TG) (C57BL/6 background) and wild-type (WT) mice underwent transient (45min) middle cerebral artery (MCA) occlusion followed by 24hours of reperfusion; stroke volumes were assessed by serial TTC stainings and neurological deficits by neurological score and Rotarod tests. In addition, vascular LOX-1 responsiveness was investigated in MCAs of WT mice following I/R. To further investigate underlying mechanism, LOX-1 transfected HBMVECs were exposed to hypoxia/reoxygenation (4hours/4hours) and proapoptotic downstream targets of LOX-1 were investigated. Finally, in order to translate our findings to the human situation, LOX-1 responsiveness was determined in ischemic stroke patients using PBMs as surrogate cells and compared to age-, sex- and risk factor-matched control subjects.
Results: Following I/R, LOX-1 expression was enhanced in MCAs of WT mice, as compared with sham-operated animals. Furthermore, LOX-1TG mice revealed increased stroke volumes (WT, 46±10mm^3; LOX-1TG, 82±9mm^3, n=7 per group) and decreased neuromotor functions, compared with WT animals. Similarly, LOX-1 was upregulated in HBMVECs exposed to hypoxia/reoxygenation. LOX-1-transfected HBMVECs revealed increased cell death and caspase-3 activation, as compared with empty vector-transfected cells. At the clinical level, we found that PBMs of ischemic stroke patients exhibited increased LOX-1 expression levels 6 hours after symptom onset, which returned to levels of control subjects within 24 hours.
Conclusions: Brain ischemia/reperfusion induces vascular LOX-1 expression in WT mice as well as in primary human cerebrovascular endothelial cells and monocytes from patients with ischemic stroke. Endothelial LOX-1 overexpression in the mouse augments stroke volumes and neuromotor deficits suggesting its involvement in the pathogenesis of ischemia/reperfusion-induced brain damage.
Acknowledgement/Funding: Swiss National Science Foundation (310030_147017 to GGC) and the Foundation of Cardiovascular Research – Zurich Heart House, Zurich, Switzerland.

P712 | BENCH

Association of common genetics variants and their association with vascular organ damage in untreated 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 (cf-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. cf-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: 235TT homozygotes had significantly lower FMD compared with M allele carriers in controls (p=0.038) and c-fPWV was higher in TT homozygotes compared with MM+MT genotypes in hypertensive patients (p=0.025). With respect to other vascular properties we observed no other significant associations across genotypes. Regarding the CYP11B2 promoter genotype we have observed higher values of IMT in -344TT homozygosity, in the group of hypertensives (712.5±16.2 vs 781.6±33.5 μm, p=0.03). Notably, it was observed that T-allele carriage was significantly associated with higher prevalence of atherosclerotic plaques in the study population (OR: 0.32; CI 0.12 to 0.85, p=0.01), and 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=0.0008). 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 235TT homozygotes had significantly lower FMD in controls and c-fPWV 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.

CARDIOVASCULAR CELL BIOLOGY

P713 | BEDSIDE

Impact of alirocumab treatment on renal function

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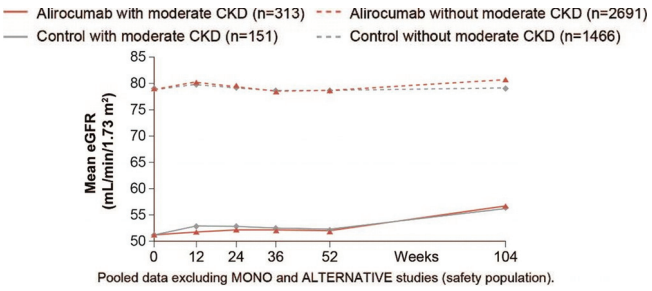
Background: Mesenchymal cells of the kidney express PCSK9, although PCSK9 function in the kidney is unclear. The effects of PCSK9 antibodies on renal function have not been fully characterised.
Purpose: To investigate impact of alirocumab (ALI) on renal function using pooled data from 10 Phase 3 ODYSSEY trials (24–104 weeks).
Methods: Patients (n=4983; most at high CV risk receiving maximally tolerated statin) were randomised to receive ALI 75/150 mg every 2 weeks vs placebo [PBO] 5 trials or ezetimibe [EZE] 5 trials. Patients were on background statin ± other lipid-lowering therapies except in 2 trials (no statin). Data were pooled by ALI dose or control; analyses were based on moderate chronic kidney disease (CKD) or proteinuria status.
Results: At baseline 10% of patients had moderate CKD (estimated glomerular filtration rate [eGFR]: 30–59 mL/min/1.73m^2) and 90% had mild/no CKD (eGFR: ≥60 mL/min/1.73m^2). 68% were negative, 23% had trace and 9% were positive for dipstick proteinuria. Mean eGFR (Fig), serum creatinine (Cr) and blood urea nitrogen (BUN) measurements were unchanged up to 104 weeks in ALI and control arms regardless of CKD severity. eGFR, Cr and BUN levels were stable in ALI and control arms, with or without presence of proteinuria (Table). At Week 24 reductions from baseline in elevated LDL-C were similar across all ALI treatment groups regardless of baseline moderate CKD or proteinuria status. Adverse events were similar in ALI and control groups, regardless of moderate CKD status. Haematuria developed in <2% of patients with no imbalance between groups.

Table 1. Mean change from baseline to Week 24

Proteinuria	ALI 75/150 mg and 150 mg vs PBO			ALI 75/150 mg vs EZE		
	n	PBO	ALI	n	EZE	ALI
eGFR, mL/min/1.73m^2						
Negative	1912	–0.1 (10.9)	0.5 (10.4)	796	0.1 (9.6)	0.3 (10.7)
Trace	620	–1.0 (9.7)	–0.2 (10.9)	267	–0.6 (11.7)	0.9 (10.1)
Positive	256	1.6 (9.4)	1.1 (12.7)	96	–0.3 (10.2)	–3.4 (13.5)
Cr, umol/L						
Negative	1920	–0.5 (19.1)	–0.3 (11.2)	797	–0.3 (8.7)	–0.4 (15.0)
Trace	621	0.3 (10.9)	–0.7 (11.9)	267	0.8 (21.6)	–0.9 (9.7)
Positive	257	–1.0 (11.2)	–1.3 (12.8)	96	3.0 (11.2)	3.4 (13.8)
BUN, mmol/L						
Negative	1916	0.07 (1.42)	0.07 (1.49)	796	0.03 (1.46)	–0.04 (1.50)
Trace	621	0.11 (1.74)	–0.11 (1.56)	267	–0.15 (1.63)	–0.16 (1.35)
Positive	257	0.23 (1.50)	0.15 (1.74)	96	0.65 (2.48)	–0.02 (2.45)



eGFR over time: baseline to W104

Conclusion: ALI did not impact renal function irrespective of the presence of moderate CKD or proteinuria. Renal function did not influence the LDL-C lowering efficacy or safety profile of ALI.
Acknowledgement/Funding: Sanofi and Regeneron Pharmaceuticals Inc.

P714 | BEDSIDE

The validity of a novel method for estimating low-density lipoprotein cholesterol levels in diabetic patients

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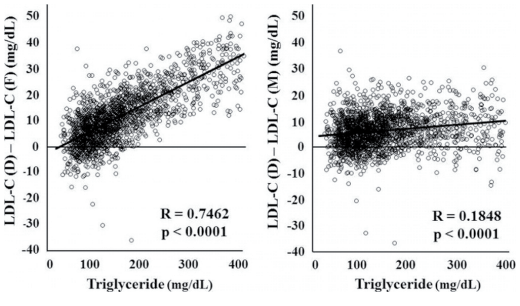
Background: Low-density lipoprotein cholesterol (LDL-C) plays an important role in the pathogenesis of atherosclerosis and is one of major risk factors of coronary artery disease. LDL-C is usually estimated by the Friedewald equation [LDL-C (F)]; LDL-C (F) = TC - (HDL-C+TG/5), where TC is total cholesterol, HDL-C is high density lipoprotein cholesterol, and TG is triglyceride. Friedewald equation used a fixed factor of 5 for the ratio of TG to very low-density lipoprotein cholesterol (TG:VLDL-C). Recently, Martin et al reported a novel method to estimate LDL-C [LDL-C (M)] using an adjustable factor for the TG:VLDL-C ratio based on strata of TG and non-HDL-C values (JAMA. 2013; 310: 2061–8). However, the validity of LDL-C (M) in different races and patients with type 2 diabetic mellitus (DM) has not been elucidated.
Purpose: The aim of this study is to validate this novel method comparing three LDLs; LDL-D (M), LDL-C (F) and directly measured LDL-C [LDL-C (D)] in Japanese patients with type 2 DM.
Method: We measured serum levels of TC, HDL-C and TG after more than 12 hours fasting in patients with type 2 DM. In the consecutive 1828 patients with TG <400 mg/dl, LDL-C (M) and LDL-C (F) levels were estimated by these lipid data. LDL-C (D) was also directly measured using the selective solubilization methods obtained from Kyowa Medex (Tokyo, Japan).
Results: The characteristics of 1828 patients as follows; male: 58.4%, age: 60.6±11.9 years, TC: 207.7±36.6 mg/dl, HDL-C: 59.5±16.3 mg/dl, TG: 148.8±80.9 mg/dl, LDL-C (F): 118.8±33.5 mg/dl, LDL-C (M): 122.0±32.0 mg/dl, LDL-C (D): 128.6±32.4 mg/dl, and HbA1c: 7. 6±1.7%. The linear regression analysis demonstrated that LDL-C (D) showed a stronger correlation with LDL-C (M) than LDL-C (F) [R=0.979 in LDL-C (M) and R=0.953 in LDL-C (F)]. Furthermore, we analyzed the effect of serum TG concentrations on the LDL-difference, such



as LDL-C (D) – LDL-C (F) or LDL-C (D) – LDL-C (M). Although LDL-difference showed a positive correlation with TG levels, the difference of LDL-C (F) and LDL-C (D) was getting larger depending on TG levels than that of LDL-C (M) and LDL-C (D) (Figure).
Conclusion: We for the first time demonstrated that the LDL-C estimated by Martin's method was suggested to be more accurate compared with the Friedewald equation in Japanese patients with type 2 DM. This novel method could be easily implemented in laboratory reporting systems at virtually no cost, and may be useful in clinical practice and studies.

P715 | BEDSIDE
Serum lipoprotein (a) is associated with the presence of ruptured plaque determined by optical coherence tomography in coronary artery disease

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Background: Elevated serum lipoprotein(a) [Lp(a)] is a risk factor for cardiovascular disease. There is a causal relationship between Lp(a) excess and risk for myocardial infarction. However, relationship between serum Lp(a) levels and coronary plaque vulnerability remains unclear.
Purpose: The aim of this study was to evaluate the relationship between Lp(a) and coronary plaque vulnerability assessed by optical coherence tomography (OCT).
Methods: We used OCT to determine plaque vulnerability in 179 patients with coronary artery disease (acute coronary syndrome, n=15; stable angina pectoris, n=164). At admission, Lp(a) and other lipid profile markers such as low-density lipoprotein (LDL), very low-density lipoprotein (VLDL), intermediate density lipoprotein (IDL), high-density lipoprotein (HDL), malondialdehyde-modified-LDL, remnant-like lipoprotein particles (RLP), Apoprotein B, and eicosapentaenoic acid (EPA)/arachidonic acid (AA) ratio were measured.
Results: Level of serum Lp(a) and other lipid profile markers were not significant between patients with thin-cap fibroatheromas (TCFAs; defined as lipid-rich with plaque cap thickness $<65\mu m$) and those with non-TCFA. In patients with ruptured plaque, we detected more TCFA, and more frequently lipid rich (94% versus 55%, $p<0.001$), and wider lipid arc (167±8.6° versus 129±4.7°, p=0.002). Serum Lp(a) levels was significantly higher in patients with ruptured plaque compared with those with non-ruptured plaque (25.4±3.7 versus 17.4±1.6, p=0.048), but not other lipid profile markers. Multivariable logistic regression analysis revealed that serum Lp(a) levels were associated with the presence of ruptured plaque (odds ratio, 1.03; 95% CI, 1.00–1.05; p=0.031) after adjusting some cofounding factors.
Conclusion: Serum Lp(a) levels might be associated with the coronary plaque vulnerability in the culprit lesion.

P716 | BEDSIDE
Decreased circulating omega-6 fatty acid levels are associated with total mortality in patients admitted to cardiac intensive care unit

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Background: Polyunsaturated fatty acids (PUFAs), especially omega-3 PUFAs, have several important roles in the pathogenesis of cardiovascular diseases. Recently, several studies have reported the anti-inflammatory and anti-atherogenic effects of omega-6 and omega-3 PUFAs. However, the clinical significance of PUFA metabolism in the acute phase of cardiovascular diseases remains unknown. Therefore, we investigated the association between circulating PUFA levels and clinical prognosis in patients admitted to the cardiac intensive care unit (CICU).
Methods: We recruited 456 consecutive patients (acute decompensated heart failure: 38.4%, acute coronary syndrome: 37.9%) admitted to CICU in our University Hospital from April 2012 to October 2013. Fasting plasma PUFA levels, including eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA), arachidonic acid (AA), and dihomo-gamma-linolenic acid (DGLA), were measured within 24 h after admission. After excluding patients with malignant diseases, 383 patients were followed up for 45 months.
Results: During the 2.0 year mean follow-up period, 67 patients died. The levels of AA (153.4±52.4 vs. 169.3±53.2 μg/mL, P=0.03) and DGLA (24.1±17.3 vs. 30.2±12.2 μg/mL, $P<0.001$), but not EPA (53.2±36.5 vs. 54.2±36.0 μg/mL, NS) and DHA (115.1±43.8 vs. 124.7±43.2 μg/mL, NS), were significantly lower in the non-survivor group compared with the survivor group. In addition, DGLA levels and DGLA/AA ratio were significantly and negatively correlated with BNP ($r=-0.43$, $P<0.001$; $r=-0.36$, $P<0.001$; respectively) and CRP levels ($r=-0.19$, P=0.002; $r=-0.11$, P=0.04; respectively). Kaplan–Meier survival analysis showed that both low AA and DGLA levels, but not EPA and DHA levels, were associated with all-cause mortality. Multivariable Cox regression analysis showed that a low DGLA level was an independent predictor for all-cause mortality (Hazard ratio, 2.21; P=0.01).
Conclusion: Decreased levels of circulating DGLA, AA, and DGLA/AA ratio in patients admitted to CICU were significantly associated with total mortality, suggesting that circulating omega-6 PUFA levels, rather than omega-3 PUFA levels, play a role in the pathogenesis of acute cardiovascular diseases.

P717 | BEDSIDE
Pitavastatin lowers plasma levels of CoQ10 less than equipotent doses of rosuvastatin or atorvastatin

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Background: The reduction of CoQ10 following statin therapy is considered a possible mechanism for muscle-related adverse events and may be related to risk of incident diabetes. CoQ10 has been found to be deficient in patients with diabetes and may be able to counteract various metabolic disturbances associated with insulin resistance. Recent meta-analyses have shown the increase in risk of incident diabetes following treatment with statins is dose-dependent and statin-dependent. Lipoprotein Insulin Resistance (LPIR) is a new biomarker strongly associated with increased insulin resistance and potentially incident diabetes and may be an early indicator of type 2 diabetes risk.
Hypothesis: In an impaired glucose tolerant adult patient population with dyslipidemia, pitavastatin will lower CoQ10 less and decrease LPIR more than equipotent doses of rosuvastatin or atorvastatin.
Method: Single site double blind study of 134 patients with impaired glucose tolerance randomized to pitavastatin (4 mg/qd), rosuvastatin (5 mg/qd) and atorvastatin (20 mg/qd) for 12 weeks. The primary endpoint was to determine the difference in plasma levels of total CoQ10, ubiquinol, and ubiquinone, before and after 12 weeks of therapy, between the three groups. A secondary analysis of the data measured serum LPIR at baseline and following treatment. Nine patients were unable to complete the study.
Results: Comparable LDL-C reduction was noted among the 3 groups, (p=0.2626), however, pitavastatin decreased CoQ10 levels, in particular ubiquinol, significantly less than atorvastatin and rosuvastatin (p=0.0401). No statistically significant treatment difference was observed in ubiquinone levels (p=0.6988), however the significant change in ubiquinol allowed total CoQ10 (p=0.0697) to be marginally significant. No statistically significant treatment differences were observed in the metabolic or lipid measures. Among the lipoprotein particles and apolipoproteins, LDL-particle number showed a significant difference between treatment groups (p=0.0087); as subjects in the rosuvastatin arm exhibited the smallest decrease in LDL-particle number, while those in the atorvastatin arm exhibited the largest decrease, followed by pitavastatin. In the LPIR data analysis, mean LPIR did not change significantly from pre- to post-treatment for any treatment arm, however, both pitavastatin and atorvastatin showed non-zero decreases in LPIR, with the greatest change being with pitavastatin.
Conclusion: Pitavastatin showed the smallest reduction in CoQ10 as well as greatest reduction in LPIR compared to atorvastatin and rosuvastatin. Pitavastatin may be preferred when considering a statin therapy for patients needing potent LDL-C and LDL-P reduction but at risk of developing diabetes. Further studies are necessary to determine the clinically relevant changes in levels of CoQ10 and in markers of insulin resistance and incident diabetes with statin therapy when considering treatment regimens.
Acknowledgement/Funding: Kowa Pharmaceuticals

P718 | BENCH
MicroRNA-19a reduces thrombogenicity in diabetes via targeting of tissue factor

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Background: Diabetes mellitus is characterized by chronic vascular inflammation and a main risk factor for cardiovascular mortality. In particular, elevated levels of circulating tissue factor (TF) lead to increased thrombogenicity in patients with diabetes and poor glycemic control. Recently, microRNA (miR)s, such as miR-19a, have been implicated in TF regulation. In the present study we sought to elucidate the role of miR-depending TF expression and procoagulability in diabetes.
Methods and results: Plasma samples of 44 patients with known Diabetes and poor glycemic control were assessed for the expression of miR-19a, TF protein, TF activity, and markers for vascular inflammation. High miR-19a expression was associated with reduced TF protein, TF-mediated procoagulability, and vascular inflammation as estimated by expression of vascular adhesion molecule-1 and leukocyte count. We found plasma miR-19a to strongly correlate with miR-126 ($r=0.92$, $p<0.0001$). Human microvascular endothelial cells were transfected with a miR-mimic or a control-miR. miR-19a transfection led to suppression of TF mRNA and protein. miR-19a and miR-126 in concert exhibited additive inhibition of TF expression and activity of a luciferase reporter construct containing the F3 3'UTR.
Conclusion: We conclude that miR-19a and miR-126 have anti-thrombotic properties via regulating post-transcriptional TF expression and, thereby, contribute to

the vascular homeostasis in diabetes. Modulating the post-transcriptional regulation of TF in diabetes may provide a new future anti-thrombotic and anti-inflammatory therapy strategy.

P719 | BEDSIDE
Carotid thermal heterogeneity and aortic stiffness: the heat is on

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Background: Microwave Radiometry (MWR) is a new validated method, which allows evaluation of thermal heterogeneity of carotid arteries and is associated with inflammation. Aortic elastic properties as assessed by aortic stiffness and wave reflections are important predictors of CVD.
Purpose: The aim of this pilot study was to determine if thermal heterogeneity in the carotid arteries is associated with aortic elastic properties in patients with dyslipidemia and whether treatment for dyslipidemia affects thermal heterogeneity.
Method: Twenty-nine patients with dyslipidemia (mean age 42±13 years, range 22–75, 19 men) without known cardiovascular disease, underwent assessment of carotid thermal heterogeneity (temperature difference — ΔT) using MWR. Mean common carotid intima-media thickness (CIMT) was also assessed. Aortic stiffness was assessed with carotid-femoral pulse wave velocity (cfPWV) and wave reflections with aortic augmentation index (AIx). Twenty-one patients were treated for 6 months with statin or/and ezetimibe and thermal heterogeneity was assessed after treatment.
Results: There was a negative correlation between ΔT in the carotid arteries and cfPWV (r=-0.397, p=0.033) as well as a positive correlation between ΔT and cIMT (r=0.474, p=0.009). In multivariate regression analysis, after adjustment for potential confounders such as age, sex and mean blood pressure, cfPWV showed a negative correlation with ΔT in carotid arteries (Adjusted R2=0.284, p=0.006). In multivariate regression analysis, after adjustment for potential confounders such as age, sex, mean blood pressure and body-mass index, cIMT showed a positive correlation with ΔT in carotid arteries (Adjusted R2=0.258, p=0.048). AIx showed no association with thermal heterogeneity. Thermal heterogeneity after 6 months of treatment was reduced statistically significant (0.88±0.42 to 0.58±0.29°C, p=0.021)
Conclusion: In a group of patients with dyslipidemia thermal heterogeneity in the carotid arteries was inversely associated with aortic stiffness but positively associated with carotid subclinical atherosclerosis. Moreover, dyslipidemia treatment reduced thermal heterogeneity after a short-term period, implying a beneficial effect of treatment on thermal heterogeneity.

P720 | BENCH
A non-steroidal antagonist of mineralocorticoid receptor (MR) protects from coronary reserve loss and diastolic dysfunction worsened by exercise in mice with cardiomyocyte-specific MR overexpression

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Introduction: Mice with cardiomyocyte-specific mineralocorticoid receptor overexpression (MR-Cardio) are characterized by arrhythmias (premature ventricular beats and tachycardia) (Circulation 2005) and by impaired endothelial dependent relaxation of isolated coronary arteries (Am J Physiol Heart Circ Physiol 2011). However, whether this affects exercise performance has not yet been evaluated.
Purpose: To test whether impaired heart functional parameters aggravated by treadmill exercise in MR-Cardio mice can be improved by 4 weeks oral treatment with the non-steroidal MR antagonist BR-4628 (1 mg/kg/day).
Methods: We assessed i) ECG telemetry at rest and during treadmill running (stepwise of 10 min at 19, 21 and 25 cm/sec), ii) measurements by magnetic resonance imaging (MRI) of left ventricular (LV) coronary reserve (difference between basal and maximal perfusion under stimulation of A2a adenosinergic receptor by ATL307 inducing vasodilatation), and iii) LV hemodynamic by invasive pressure-volume loops.
Results: MR-cardio mice were found to possess an increased prevalence of ventricular tachycardia after epinephrine injection (2mg/kg). Compared to control mice (Ctrl), ECG telemetry at baseline indicated increased ST-elevation, increased number of sinus arrests and ventricular extrasystoles in MR-Cardio mice. There was no difference between MR-Cardio and Ctrl mice in motility (rotarod device) and spontaneous locomotor activity (open-field test). However, during the running phase and the subsequent resting phase, ECG telemetry showed increased QTc duration (from speed 21 cm/sec) and exacerbation of the ST-elevation in MR-Cardio mice. Coronary reserve (measured by MRI) was decreased in MR-Cardio mice, but improved by 4 weeks treatment with BR-4628 (coronary reserve: Ctrl 5.2±0.7; MR-Cardio 2.4±0.7, $p<0.05$ vs. Ctrl; MR-Cardio+BR 3.9±0.8 ml.min-1.g-1, NS vs. Ctrl). Moreover, LV hemodynamic assessments showed impairments in Left Ventricular-End-Diastolic-Pressure (LVEDP) and LVEDP-Volume-Relation (LVEDPVR) in MR-Cardio mice, reflecting LV diastolic filling and LV compliance which were also improved with BR-4628 treatment [(LVEDP: Ctrl 5.10±0.57; MR-Cardio 8.94±0.88, $p<0.01$ vs. Ctrl; MR-Cardio+BR 6.06±0.56; NS vs. Ctrl) and (LVEDPVR: Ctrl 2.33±0.33; MR-Cardio 4.94±0.51, $p<0.001$ vs. Ctrl; MR-Cardio+BR 2.74±0.52, NS vs. Ctrl)].
Conclusion: The results suggest that increased cardiac MR expression as reported in several human cardiac pathologies, may cause coronary reserve impairment, diastolic dysfunction and arrhythmias, resulting in inability to exercise. Treatment of MR-Cardio mice with the non-steroidal MR antagonist BR-4628 improves coronary reserve and diastolic function.

P721 | BENCH
Uridine triphosphates analogues as inhibitors of platelet P2Y12: structure activity relationship

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Background and aims: Platelet P2Y12 is an important ADP receptor that is involved in agonists-induced platelet aggregation and is an important target for the development of anti-platelet aggregation drugs. The aim of the present study was to characterise the effects of uridine triphosphate (UTP) and its thio-(S)-analogues on ADP-induced platelet aggregation.
Methods: The experiments were performed on platelet rich plasma freshly isolated from blood donated by healthy human volunteers. The investigation of molecular characteristics of these derivatives possibly associated with the inhibition of P2Y12 receptor was also carried out via molecular docking simulations.
Results: UTP inhibited P2Y12 receptors and antagonised ADP-induced platelet aggregation in a conc.-dependent manner with an IC50 value of ~250 μM against ADP (10 μM). A 5-fold increase in the platelet inhibitory activity was observed by adding a thio (-S) group at position 2 (2S-UTP) of the nucleotide ring with an IC50 value of 30 μM. Interestingly, a 500-fold increase in anti-platelet aggregation activity was observed when a (-S) was introduced at position 4 of the nucleotide ring (4S-UTP) with an IC50 value of 7.5 μM. However, introducing an isobutyl group at the 4S- position reduced its activity by 2-fold with IC50 of 15 μM. A modeling study using FRED docking program was performed to dock these compounds into the ligand binding site of P2Y12 receptor. An excellent correlation was observed between the experimental findings and the docking results.
Conclusion: The novel data demonstrate for the first time that thio (-S) analogues of UTP, particular 4S-UTP, are potent P2Y12 receptor antagonists and can be useful candidates for therapeutic intervention.

P722 | BENCH
Glucagon-like peptide-1 (GLP-1) reduces microvascular thrombosis, systemic inflammation and platelet activation in endotoxemic mice

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Objective: Sepsis causes disseminated intravasal coagulation (DIC) and severe hypotension, accompanied by high mortality. Inhibition of dipeptidyl peptidase 4 (DPP4i) and supplementation with glucagon-like peptide 1 analogues (GLP1a) are new therapeutic approaches in diabetes. There is evidence for an immunemodulatory effect by DPP4i therapy and GLP1a supplementation. We investigated whether DPP4i and supplementation with GLP1a may improve sepsis associated vascular complications and disseminated intravasal coagulation.
Methods: C57/BL6j-, DPP4–/– and GLP1receptor–/– mice were used. DPP4i (linagliptin) and GLP-1a (liraglutide) were applied subcutaneously. Sepsis was induced by lipopolysaccharide (LPS) injection. Fluorescence-based imaging technique (IVIS Spectrum; using microbeads) was used to detect microvascular occlusion in lungs. Aortic vascular function was tested by isometric tension recording. Aortic tissue and isolated monocytes were used for RT-PCR. Blood samples were drawn for examination of platelet function (thrombin burst (CAT), aggregometry) in platelet-rich plasma (PRP), cell count and quantification iNOS-derived NO formation by ESR. Oxidative burst was quantified by chemilimunescence (L-012)
Results: In-vitro experiments of human and mouse platelets revealed antiaggregatory effects of GLP1 in response to ADP and thrombin. GLP1a-incubated platelets showed increased phosphorylation of VASPSer157 (cAMP-dependent) and increased cAMP levels. In cultured monocytes, oxidative burst was markedly suppressed by GLP1a and DPP4i. Pharmacological DPP4 inhibition and GLP1a supplementation of septic animals reduced iNOS activity, diminished the decrease in blood platelet count and microvascular occlusion of lung vessels. Platelet-reactivity of DPP4i and GLP1a treated animals was reduced, whereas isolated platelets of GLP1receptor–/– animals showed increased reactivity as envisaged by more pronounced tissue factor-induced thrombin-generation. DPP4 knockout revealed inverted effects. In GLP1receptor–/– mice, GLP1a therapy failed to improve both normalization of platelet count and microvascular occlusion. Endothelial function was impaired in LPS-induced sepsis and improved by

DPP4i, GLP1a therapy and DPP4-knock-out. DPP4i, GLP1a therapy and DPP4-knock-out reduced aortic mRNA levels of iNOS, P-selectin and IL-6 in endotoxemia.

Conclusion: The present studies demonstrates that DPP4i and GLP1a therapy ameliorates sepsis-induced microvascular occlusion by prevention of DIC and endothelial dysfunction. These beneficial effects are likely to be mediated by inhibitory effects of GLP1 on platelet function (cAMP-dependent) and activation of myelomonocytic cells. Future studies will be directed towards the translation of this concept to septic patients.

P723 | BENCH
Mean platelet volume and platelet reactivity in acute coronary syndromes: is there a correlation?

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Background: Previous reports shows that "young" (immature) platelets, on the average, have larger volumes, when compared with "older" platelets; moreover, it is known that the former are metabolically and enzymatically more active. On the other hand, in the setting of acute coronary syndromes (ACS) mean platelet volume (MPV) has been used in the literature as a surrogate for "young" platelets; however, the correlation between MPV and platelet aggregability (PA) is poorly understood in this population. To the best of our knowledge, this is the first study correlating MPV with PA utilizing VerifyNow® P2Y12 (VN), a point of care test, in ACS patients.

Purpose: To evaluate the association between MPV and PA at Coronary Care Unit (CCU) discharge, in patients with ACS.

Methods: From 247 patients with ACS submitted in a routine basis to a PA measurement with VN at CCU discharge, and included prospectively and consecutively in a dedicated databank, we selected retrospectively 170 patients that also had MPV measured at the CCU discharge (mean age 61.9±11.8 y.o., 69,2% men). All patients were on dual antiplatelet therapy. The median PA obtained was 170 PRU, and the population was divided in those with PA $\geq$ median (Group I, n=86) or $<$ median (Group II, n=84). Univariate and multivariable analyses were developed, with the utilization of chi-square (categorical variables), parametric/non-parametric (continuous variables) and stepwise logistic regression tests (VN as dependent variable and 27 other variables as independent ones, as age, platelet count, history of diabetes mellitus, smoking habit, ST-segment elevation myocardial infarction and creatinin peak during hospitalization).

Results: By univariate analysis, the MPV mean (±SD) value obtained was 7.95±1.24 fL for Group I and 7.36±0.82 fL for Group II (P-value=0.001). In the adjusted model only MPV, history of diabetes mellitus and statin use during hospitalization correlated significantly and independently with platelet aggregability at CCU discharge (Table).

Variables independently associated with platelet aggregability after ACS	OR	95% CI	P-value
MPV	1.86	1.29 to 2.67	0.001
History of diabetes mellitus	3.44	1.66 to 7.10	0.001
Statin use during hospitalization	0.14	0.02 to 0.72	0.019

Conclusion: The present study showed, in an ACS population, a highly significant association between MPV (as a surrogate endpoint to immature platelets) and platelet aggregability. The clinical importance of these findings should be addressed in studies with adequate sample size to analyze hard endpoints.

Acknowledgement/Funding: National Council for Scientific and Technological Development (CNPq) - Brazil

P724 | BEDSIDE
Is efficacy of platelet aggregation inhibition by endogenous endothelial platelet antagonists enhanced by oral ticagrelor mediated P2Y12 blockade?

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Background: Acute coronary syndrome (ACS) is a spectrum of cardiovascular conditions characterised by the presence of an unstable atherosclerotic plaque with overlying thrombus. P2Y12 receptor antagonists play a pivotal part in the management of ACS by inhibiting ADP-induced platelet aggregation. PURPOSE This study evaluated the effect of P2Y12 receptor antagonism by oral ticagrelor on the action of endogenous endothelial inhibitors of platelet activation, and overall endothelial function, in healthy subjects.

Methods: Samples were incubated for 2minutes with variable concentrations of S-Nitrosoglutathione (GSNO) (nitric oxide donor) or prostacyclin (PGI2) and then maximally activated with a PAR1 receptor agonist (10μM). As measures of platelet activation p-selectin, fibrinogen and platelet leukocytes aggregate (PLA) associated fluorescence was quantified using flow cytometry. Analysis was performed at baseline and following 3days of ticagrelor. Endothelial function was assessed using the validated EndoPAT method, generating a reactive hyperaemic index (RHI). Statistical analysis was performed using paired t-test on SPSS version 22.

Results: Ten healthy subjects (7 men) had a mean age 56±9 years; baseline investigations were all within normal limits. The results demonstrated that ticagrelor had a synergistic relationship with both endothelial vasodilators (GSNO and PGI2) as p-selectin expression was significantly inhibited. Prostacyclin 1nM generated a higher than threefold increase in inhibition compared to that expected by an additive effect (inhibition from ticagrelor alone added to that related to prostacyclin 1nM). Results for fibrinogen expression were consistent with the p-selectin findings. The PLA data supported the direct measures as no statistical response to prostacyclin prior to ticagrelor but a 50% reduction in aggregate formation seen with 10nM post ticagrelor. Endothelial assessment showed a mean RHI within normal limits pre ticagrelor (2.19±0.46) with an increase post ticagrelor (2.42±0.57), although this did not reach statistical significance (p=0.225).

Table 1. Cells positive for both leukocyte (CD45) and platelet (CD42a) markers following activation, representing PLA formation

	PLA (%) no PGI2	PLA (%) PGI2 0.1 nM	PLA (%) PGI2 1 nM	PLA (%) PGI2 10 nM**
Pre ticagrelor	83.3	83.0	81.5	81.2
Post ticagrelor	82.9	80.0	79.2	39.9

**p value = 0.005.

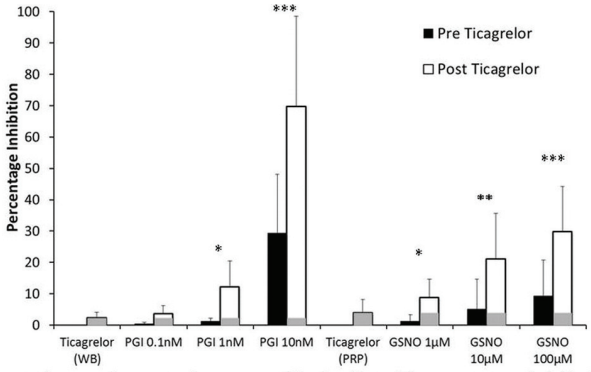

Figure 1: A histogram demonstrating the percentage of platelet inhibition following activation in whole blood (WB) with increasing concentrations of prostacyclin and in PRP with increasing concentrations of GSNO at baseline (solid bar) and post three days of oral ticagrelor (open bar). Significantly greater inhibition was seen following ticagrelor, statistically beyond the expected additive effect.
* p value <0.05 ** p value <0.01 *** p value <0.001. Grey box represents extent of inhibition by ticagrelor alone. Error bars to one standard deviation.

Conclusions: P2Y12 blockade by ticagrelor enhances the antiplatelet activity of endogenous endothelial vasodilators. There may also be a role in improving overall endothelial function. Future research is needed to explore this relationship and the effects of underlying endothelial dysfunction in patients.

Acknowledgement/Funding: This study was supported by funding from AstraZeneca.

P725 | BEDSIDE
Platelet activity recovery time is 48 hours slower than the platelet count recovery in hemorrhagic dengue fever infeceted subjects

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Background: Hemorrhagic dengue shock is associated with thrombocytopenia and platelet dysfunction. It is lethal especially when patients carry with comorbidity diseases, including coronary artery disease. Current practical guideline for dengue fever defines the "recovered platelet count" as greater than 150×10^9/L. However, no one test whether the actual "platelet activity" recovered at this time point. The timing of when to resume antiplatelet agents among these patients remained unanswered. We thus test the recovery timing of thrombocytopenia and platelet dysfunction in patients with hemorrhagic dengue virus infection.

Methods: We enrolled 12 patients (male in gender 83.3%; average in age: 55±25 years) who were diagnosed as hemorrhagic dengue fever between Sept. 01 and Oct. 20 in 2015, during which period an endemic outbreak of dengue fever happened in Southern Taiwan. Using the Multiplate® analyzer, a point-of-care impedance aggregometer, we test different timing of whole blood aggregation function, from the nadir stage of white blood cell count till the recovery time of total platelet count. All of the blood samples were collected with agreements. The reference intervals obtained in our laboratory were 60 (95% confidence interval was 32 to 104) area under curve (AUC).

Results: After the nadir stage of dengue virus infection, the average recovery period time for platelet counts to be greater than 150×10^9/L was 95±17 hours (4 days). However, the average recovery period time for platelet activity to be greater than 60 AUC was 146±20 hours (6 days) after the nadir stage.

Conclusion: Platelet activity recoveries later than the total platelet count during the hemorrhagic dengue fever nature course. For those who were indicated for antiplatelet long-term therapy, resuming antiplatelet therapy should be deferred

48 hour after the total platelet count greater than 150×10^9/L, which was recommended in current practical guideline.

P726 | BENCH
APJ expression in human platelets is related to cardiac troponin levels in patients with acute coronary syndrome

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Aim: Vessel injury and thrombosis, as a result of coronary plaque disruption, are the most important mechanisms by which atherosclerosis causes acute manifestations of vascular athero-thrombotic disease, such as acute coronary syndromes (ACS), including both non-ST-elevation myocardial infarction (NSTEMI) and ST-elevation myocardial infarction (STEMI). To our knowledge, the expression of the G protein-coupled receptor APJ in human blood cells has not been described.In the present study, we show for the first time that APJ is expressed on the surface of human platelets. Upon protease-activated receptor (PAR) -1-mediated activation, APJ is internalized and subsequently set free. Additionally, we investigated platelet-APJ expression in a small number of patients (n=27) undergoing PCI after myocardial infarction and compared the results to an age-matched control group (n=14).
Methods: In this study, we investigated the expression of APJ on human platelets by immunofluorescence staining, Western Blot analysis, and flow cytometry.In a pilot study, platelet-APJ expression was analyzed in 27 MI patients and 14 age-matched controls.Furthermore, troponin T levels in MI patients were determined.
Results: Immunofluorescence staining of resting platelets, partially activated platelets and fully activated platelets shows, that APJ is initially located at the cell membrane of resting human platelets. Upon activation with 30 μM thrombin activating peptide (AP1), the receptor is rapidly internalized. Western Blot analysis of AP-1-activated platelets and their supernatant revealed that APJ is not only internalized but is also released from activated platelets.Thereby, the receptor density on the platelet surface membrane drops below 50% of initial APJ expression in resting platelets (p=0.023). Furthermore, we determined the level of APJ expression in human platelets of MI patients and healthy controls. Our data show, that the expression of APJ is significantly reduced in MI patients when compared to the control group (Figure 1, 146.9±24 versus 258.4±50; p=0.029). Interestingly, the decreased APJ expression on platelets of MI patients negatively correlates with troponin T plasma levels (r=-0.46; p=0.03) suggesting that an elevated APJ expression correlates with a low plasma level of troponin T.
Conclusion: Our data show a negative correlation of APJ with troponin T levels in MI patients. In clinical practice, cardiac troponin T is the preferred biochemical marker for diagnosis and progression of MI.Since high troponin T levels are associated with a poor outcome, further studies are warranted for assessment of platelet-APJ expression as a diagnostic tool to further refine the course of the disease.

P727 | BENCH
Electrical reverse remodeling following pressure unloading in a rat model of left ventricular hypertrophy

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Introduction: Left ventricular hypertrophy (LVH) is the pathological response reaction of the heart to sustained pressure overload (hypertension, aortic stenosis) and it represents a major risk factor for the manifestation of malignant ventricular tachyarrhythmias and sudden cardiac death. On the other hand, pressure unloading often leads to myocardial reverse remodeling (reduction of increased left ventricular mass, attenuated myocardial fibrosis) which was previously reported to decrease LVH associated proarrhythmic vulnerability as well. However, the responsible mechanisms for the recovery of the adverse electrophysiological changes in LVH during reverse remodeling are still poorly explored.
Purpose: Therefore, we aimed at providing an electrocardiographic characterization of a rat model of LVH undergoing pressure unloading and in parallel indentify the underlying cellular and functional alterations.
Methods: Pressure overload was induced in rats by abdominal aortic banding for 6 or 12 weeks (AB 12th week), while sham operated animals served as controls. Pressure unloading was evoked by removing the aortic constriction after the 6th experimental week (debanded 12th week) to investigate the consequences of reverse remodeling. Serial echocardiography and electrocardiography were performed in order to investigate the development and the regression of LVH. Protein expression levels were detected by western blot technique. Myocardial fibrosis was assessed by Picrosirius red staining.
Results: Pressure unloading resulted in significant reduction of the prolonged QT interval (corrected QT interval: 69.9±2.0 vs. 91.5±1.6ms debanded 12th week vs. AB 12th week, $p<0.05$), in correlation with the regression of LVH (left ventricular mass: 1.64±0.10 vs. 2.48±0.14mg debanded 12th week vs. AB 12th week, $p<0.05$), and in association with restored Kv4.3 and SERCA2 expression. Furthermore, pressure unloading prevented the functional decompensation of LVH (ejection fraction: 64±1 vs. 45±4% debanded 12th week vs. AB 12th week, $p<0.05$) and simultaneously preserved adequate atrioventricular conduction (PQ interval: 48.1±1.4 vs. 54.0±2.5ms debanded 12th week vs. AB 12th week, $p<0.05$). Finally, pressure unloading effectively preceded the broadening of the QRS complex (QRS complex: 22.2±0.6 vs. 26.0±0.9ms debanded 12th week vs. AB 12th week, $p<0.05$) in parallel with attenuated interstitial collagen accumulation (Picrosirius score: 1.163±0.08 vs. 1.60±0.12 debanded 12th week vs. AB 12th week, $p<0.05$).
Conclusion: Regression of LVH with restored expression of Kv4.3 and SERCA2, maintained cardiac function and decreased myocardial fibrosis contribute to pressure unloading induced electrical reverse remodeling.
Acknowledgement/Funding: Land Baden-Württemberg, Germany, by the Medical Faculty of the University of Heidelberg, Germany; Hungarian Scientific Research Fund

P728 | BENCH
The MAGUK protein CASK negatively regulates NaV1.5 sodium channel in cardiac myocytes

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Introduction: Scaffolding MAGUK (Membrane Associated Guanylate Kinase) proteins are central organizer of ion channel complexes. Here, we investigated the expression and the role of a new cardiac MAGUK protein, CASK (CAlcium/calmodulin-dependent Serine protein Kinase).
Methods: The study was conducted in rat heart using multidisciplinary approaches including adenoviral transfer technology to manipulate CASK in adult cardiac myocytes, high resolution 3-dimensional deconvolution and Total Internal Reflection Fluorescence microscopy (TIRFm), RT-qPCR, biochemistry, and whole-cell patch clamp.
Results: In both atrial and ventricular rat myocytes, CASK was excluded from the intercalated disk and exclusively located at lateral membranes at the costamere in association with dystrophin. CASK co-precipitated and co-localized with Nav1.5 channels, the molecular basis of cardiac sodium current (INa). Silencing of CASK increased INa in both adult cardiac myocytes and HEK293 cells. TIRF microscopy and biotinylation assays showed that CASK-silencing increased the surface expression of NaV1.5 without changes in mRNA level. The protein transport inhibitor brefeldin-A prevented INa increase in CASK-silenced myocytes. In dilated/remodeled atria, CASK expression was reduced but its localization unchanged.
Conclusion: CASK regulates NaV1.5 surface expression by impeding the sorting of NaV1.5 at early stage of processing. Since CASK is restricted to the lateral membrane, it could participate in maintaining low levels of NaV1.5 in this domain.

HEART FAILURE LV DYSFUNCTION

P729 | BEDSIDE
Shift in relative contribution of longitudinal and radial motion to global right ventricular function in heart transplant patients

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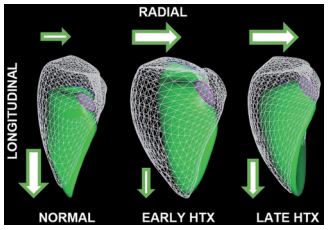
Longitudinal shortening is considered to be the most important motion determining right ventricular (RV) function. However, the radial direction ("bellows" effect) can gain particular importance in certain conditions.
Our aim was to quantify the longitudinal and the radial components of RV performance using three-dimensional (3D) echocardiography in patients after heart transplantation (HTX) and assess their relative contribution to RV function in time. Fifty-one ambulatory HTX patients (median of 226 days after HTX) and 35 age- and gender matched healthy volunteers were enrolled. Fifteen HTX patients also completed one-year follow up. Beyond conventional echocardiographic protocol, full volume datasets were acquired using multi-beat reconstruction from 4 or 6 cardiac cycles. Using dedicated software for RV 3D and speckle-tracking analysis (4D RV-Function 2), 3D beutel model was created and exported volume-by-volume throughout the cardiac cycle. Beside end-diastolic volume (EDV) and total ejection fraction (TEF), we quantified longitudinal (LEF) and radial ejection fraction (REF) by decomposing the motion of each vertex of the reconstructed 3D beutel model along three orthogonal axes and omitting the other two directions.
EDV was higher, TEF was mildly decreased in HTX patients compared to controls (HTX vs. control; EDV: 96±27 vs. 80±26mL, TEF: 47±7 vs. 51±4%, both $p<0.01$). In normal subjects, TEF was mainly determined by longitudinal motion (LEF β=0.64, REF β=0.54, R^2=0.52, $p<0.001$), however, in HTX patients the radial motion became far dominant (LEF β=0.49, REF β=0.84, R^2=0.87, $p<0.001$). After one-year follow up, EDV and TEF did not change significantly (EDV: 96±27 to 101±21mL, TEF: 47±7 to 52±9%, both NS). Notably, longitudinal function improved in time (LEF: 12±4 to 15±5%, TAPSE: 14±3 to 17±3mm, free wall longitudinal strain: -19±6 to -26±5%, all $p<0.05$). Nevertheless, radial function remained dominant (LEF β=0.48, REF β=0.66, R^2=0.65, $p<0.001$). TAPSE and free wall

longitudinal strain correlated with the time elapsed after HTX (r=0.57 and r=-0.48, respectively, both p<0.001).



Relative contribution to RV function

Our software allows to quantify longitudinal and radial motion of the RV separately using 3D analysis. Current results confirm the empirical phenomenon on the superiority of radial motion in determining RV function in HTX patients. In time, longitudinal function may recover, however, radial motion remains dominant.

P730 | BEDSIDE
Sex-mismatch interaction and prognosis after heart transplantation. A clarifying meta-analysis

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Background: Orthotopic heart transplantation is the treatment of choice in selected patients with terminal heart disease. Optimal donor allocation is essential due to the current shortness of grafts. When allocating a graft, donor and recipient relation is essential and includes several factors like blood group, size, serological and immunological factors. The possible role of donor and recipient sex has been discussed for years. Despite some contradictory results, it has been reported that survival after heart transplantation seems to be worse when donor-recipient gender is mismatched. There may be an interaction between sex mismatch and gender of the recipient.
Purpose: This systematic review and meta-analyses aimed to appraise the current evidence on the effect of gender mismatching after heart transplantation depending on sex of the recipient.
Methods: We searched PUBMED and EMBASE until February 2015. Comparative cohort and registry studies regarding survival after heart transplantation on both genders were included. Articles published were identified systematically and meta-analyses were performed. Primary endpoint was one-year mortality in both genders. 10-years mortality was appraised but meta-analyses were not possible as 10 years follow-up was not completed.
Results: After retrieving 510 articles, 10 studies (53.199 patients) were included. When analyzing recipients of both genders, significant differences were found for one-year survival between gender matched and mismatched recipients [odds ratio (OR) = 1.30, 95% confidence interval (CI) = 1.25–1.35]. In male recipients, we found that gender mismatch was a risk factor for one-year mortality (OR= 1.38, 95% CI = 1.31–1.44), but this was not valid for female recipients (OR= 0.92, 95% CI = 0.85–1.00). In this latter group, better survival was suggested (Figure 1).

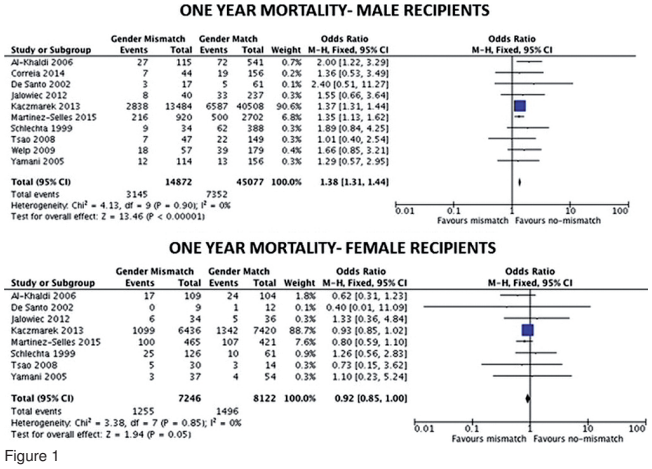

Figure 1

Conclusions: Sex mismatch increases one-year mortality after heart transplantation only in male recipients, while better survival is suggested in female recipients. Due to the current shortness of grafts, clinical protocols should be taken into account when allocating a graft.

P731 | BENCH
One year hemodynamics and long-term survival after heart transplantation

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Severe pre-transplant pulmonary hypertension (PH) has been associated with adverse short-term clinical outcome after heart transplantation (Htx). However, sparse data are available on the impact of post-transplant hemodynamic parameters on long-term survival.
Aim: To investigate the impact of pulmonary hypertension (PH) on mortality after HTx.
Methods: In this study we included all the adult patients (age >18 yrs.) who underwent first time HTx (period 1988–2009) and had available right heart catheterization (RHC) data at one year after HTx: 286 patients (175 men/111 women; age 48±11 years). RHC data were recorded at rest and during supine exercise. PH was defined as the mean pulmonary artery pressure (PAM) >25 mmHg at rest. Mortality was certifiedusing National Death Register. Kaplan Meijer and Cox proportional regression analysis were performed to investigate the association between PH, adjusted for relevant confounders
Results: During a mean follow-up of 8.2±5.8 years, there were 111 (39%) deaths and the death rate was 47.3/1000 patient yrs. There was a significant positive association between age and PAM (β=0.169 p=0.004) and no gender-differences was observed. Post transplant PH was found in 15 patients (5%) and in 8 cases had PCW >15mmHg. Kaplan Meijer for the survival of quartiles showed significantly lower survival of the highest quartile (p=0.021). Cox-regression analysis showed an increase of mortality with 5% for every 1mmHg increase in PAM after adjusting for age, gender, and donor's age (HR=1.05 95% CI 1.01–1.09). Post-transplant PH was a significant predictor of mortality (HR 3.52, 95% CI 1.72–7.18, p=0.001) Further adjustments for PCW showed an attenuation of the association that was still significant (HR=2.52 95% CI 1.09–5.82). Similar findings were done when all-cause mortality within 5 years was considered in the adjusted model (PAM HR=1.09 95% CI 1.03–1.16; PH HR=5.95 95% CI 2.55–13.91). PAM at exercise did not predict events. Cardiac index at rest did not predict all-cause mortality, however, high cardiac index during exercise was associated with better survival in the adjusted model (Highest quintile versus the rest HR=0.43 CI 0.21–0.89 p=0.023)
Conclusion: The development of PH during the first year after Htx predicted all-cause mortality in this large Swedish cohort. Further research is needed to better understand the mechanisms behind pulmonary vascular changes so as to improve the survival of the transplanted patients.

P732 | BEDSIDE
Predictors of long-term progression of cardiac allograft vasculopathy assessed by serial quantitative coronary analysis

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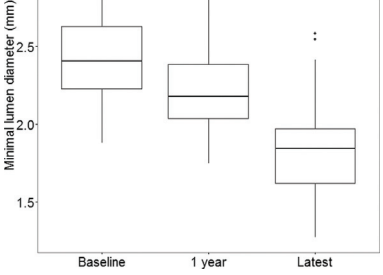
Background: Cardiac allograft vasculopathy (CAV) adversely affects the long-term prognosis after heart transplantation (HTx). Only limited data is available regarding the long-term progression of CAV by means of serial quantitative coronary angiography (QCA).
Purpose: The primary objective of our study was to investigate the progression and potential predictors of CAV assessed by 3-vessel QCA after HTx.
Methods: We enrolled 70 heart transplant recipients who underwent HTx between 1994 and 2014. The 3-vessel QCA was performed for every segment according to the modified AHA/ACC classification. Data was retrospectively collected at baseline (i.e. donor angiography or within 6 months after HTx), at 1 year and at the latest follow-up (FUP), if available. CAV was visually classified according to the definition of the International Society for Heart and Lung Transplantation (ISHLT-CAV 0 to 3).
Results: After mean angiographic follow-up duration of 6.65±3.95 years, 36 patients (51%) had visual signs of CAV (CAV-1 N=25 [69%]; CAV-2 N=10 [28%];



Serial angiography (N=40, 510 segments)

CAV-3 N=1 [3%]). Thirty-seven (53%) patients were on everolimus immunosuppressive therapy. At FUP, minimal lumen diameter (MLD) and maximal % diameter stenosis (%DS) were 2.06±0.35mm and 15.3±3.1% in patients with CAV-0, 1.98±0.45mm and 19.5±3.9% for CAV-1, 1.74±0.30mm and 24.0±5.7% for CAV-2, and 1.95mm and 29.7% in one patient with CAV-3, respectively. Higher %DS was significantly associated with higher recipient age (p=0.03), higher HbA1c (p=0.04), lower estimated glomerular filtration rate (eGFR) (p=0.002) and severe total rejection score (TRS) ≥2R (p=0.03). Predictors of ISHLT-CAV ≥1 were higher recipient age (p=0.02), higher donor age (p=0.01), previous coronary artery disease (p=0.04), lower eGFR (p=0.048) and severe TRS ≥2R (p=0.01).
Serial angiography at all three time points was available in 40 patients (57%, 510 matched segments) of whom 32 (80%) had CAV-0 at 1 year. MLD significantly decreased from baseline to 1-year follow up (Δ-0.22 mm/year [95% CI -0.28 to -0.16], p<0.001) and from 1-year to the latest follow-up (Δ-0.08 mm/year [95% CI -0.11 to -0.05], p<0.001) (Figure).
Conclusion: The predictors of CAV evaluated by QCA were in line with the findings from standardised visually angiographic ISHLT-CAV criteria. In the QCA analysis, prevailing lumen loss was observed already one year after HTx followed by a low but steady decrease in MLD up to 17 years, although 80% of patients had no visual signs of CAV at 1 year. Hence, QCA might be a more sensitive tool to detect early CAV changes after HTx.

P733 | BEDSIDE
Prognostic value of non-surgery related pericardial effusion in heart transplant recipients

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Background: Hemodynamically irrelevant pericardial effusion (PE) is a known predictor of negative outcome in heart failure patients. In contrast, the clinical relevance of non-surgery related PE in heart transplanted patients remains unknown. This study was designed to assess the prognostic value of PE occurring later than one year after heart transplantation.
Methods: All 313 patients who underwent heart transplantation in Zurich between August 1989 and July 2012 were retrospectively assessed for PE in our echocardiography database. Exclusion criteria were death within the first year after transplantation (64 patients), age <16 years at heart transplantation (8 patients), and lack of echocardiography follow-up (89 patients, mostly due to transfer to a different clinic after transplantation). Cox proportional hazard models were performed to analyze both mortality and unscheduled hospitalization for patients with and without PE. For analysis of mortality, the data was adjusted for gender and age at transplantation.
Results: A total of 152 patients was included, of which 25 developed PE. The median follow-up was 11.9 years with a PE incidence of 14.4 per 1000 patient-years. Absolute number of deaths was 6 in the PE group and 46 in the non-PE group. The occurrence of PE was associated with an increased risk of death (HR 2.49, 95%-CI 1.02 - 6.13, p<0.05). Cause of death was cancer (28.8%), infections (15.4%), heart failure (13.4%), cardiovascular events (11.5%), and transplant rejection (3.8%). Absolute number of unscheduled hospitalizations was 306. In patients with PE, the risk of hospital admission was increased (HR 2.53, 95%-CI 1.57 - 4.1, p=0.0002). The main reason for hospitalization was infection in 47.6% followed by cardiovascular events (10.4%) and cancer (6.9%).
Conclusion: This study reveals that the echocardiographic finding of PE in heart transplanted patients is associated with a 2.5 times higher risk of either death or hospitalization as compared to patients without PE. Thus, small PE which may be observed during routine echocardiography – even though hemodynamically irrelevant – are associated with a negative outcome.

P734 | BEDSIDE
Circulating chromogranin B levels and outcome in patients with cardiovascular related-acute respiratory failure

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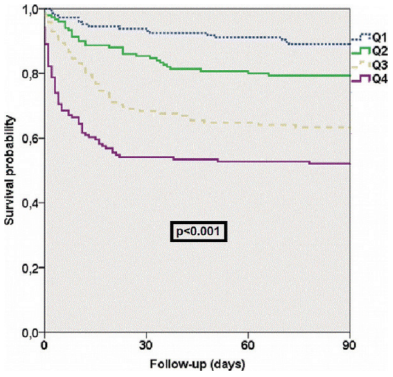
Background: Circulating chromogranin B (CgB) levels are elevated in conditions characterized by systemic and myocardial stress, but whether CgB provides incremental prognostic information to established risk indices in patients with acute respiratory failure (ARF) is unknown.
Methods: We included 584 patients with ARF, defined as ventilatory support >6 h, and with blood samples available on ICU admission. CgB levels were measured by radioimmunoassay on study inclusion and after 48 h, follow-up was 90 days, and the patients were categorized as either cardiovascular (CV)-related ARF (n=209) or non-CV-related ARF (n=375).
Results: CgB levels were similar in patients with CV- and non-CV-related ARF on ICU admission: 1.00 (95% CI 0.79–1.41) vs. 0.99 (0.79–1.32) nmol/L, p=0.47. Admission CgB levels were higher in 90 day non-survivors than in survivors, both for patients with CV-related ARF (median 1.32 [Q1–3 1.05–1.81] vs. 0.88 [0.76–1.13] nmol/L, p<0.001) and non-CV-related ARF (1.18 [0.96–1.65] vs. 0.93 [0.74–1.25] nmol/L, p<0.001). Stratifying patients according to CgB quartiles on ICU admission, CgB levels provided prognostic information across the spectrum of ARF (Figure). In multivariate Cox regression analyses, admission CgB levels (logarithmically transformed) provided incremental prognostic information to clinical and biochemical risk markers both regarding CV-related (HR 2.17 [95% CI 1.25–3.76], p=0.006) and non-CV-related ARF (HR 3.56 [2.20–5.77], p<0.001). The correlation coefficient between CgB and NT-proBNP levels on study inclusion was 0.34, p<0.001 and the AUC of admission CgB and NT-proBNP levels to predict 90 day mortality was 0.72 (95% CI 0.67–0.76) for both. CgB levels on ICU admission also provided incremental prognostic information to SAPS II and SOFA scores, which both were based on data recorded 24 h after admission. CgB levels after 48 h also provided additional prognostic information to established risk indices in CV-related ARF (HR 6.34 [95% CI 2.39–16.79]), while CgB levels after 48 h did not improve risk prediction in patients with non-CV-related ARF.



Survival according to CgB quartiles

Conclusions: CgB levels measured on ICU admission provided prognostic information independently of conventional risk markers across the spectrum of patients with ARF, while CgB levels after 48 h only improved risk stratification in patients with CV-related ARF.
Acknowledgement/Funding: University of Oslo

P735 | BEDSIDE
Omega-3 PUFAs supplementation favorably affect left ventricle strain and the inflammatory, fibrosis process

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Background: Omega-3 polyunsaturated fatty acids (PUFAs) exert anti-inflammatory properties and have been tested in patients with systolic heart failure (HF). Soluble suppression of tumorigenicity 2 (sST2) has emerged as a novel biomarker for HF, is a member of the interleukin 1 (IL1) receptor family and is released from cardiomyocytes and fibroblasts after mechanical strain and has been identified as a novel biomarker of cardiac stress, fibrosis and remodeling. Moreover, serum levels of sST2 are associated with prognosis of HF patients.
Purpose: To examine the short term impact of omega-3 PUFAs on novel indices of left ventricle function and on the cardiac stress and fibrinogenesis process.
Methods: The study was carried out on two separate arms (omega-3 PUFAs-2gr/day- or placebo for 8 weeks), in a cross-over double blind design with an 8-wash out period between the two arms. The study population consisted of 17 systolic stable HF patients of ischemic etiology. All subjects were under optimal medical therapy for a period of 6 months. All subjects were evaluated at baseline and after completion of each treatment arm. Left ventricular (LV) function before and after treatment was assessed using LV ejection fraction (LVEF), determined by the biplane modified Simpson method, and LV global longitudinal strain (GLS), using a commercially available software. Serum levels of sST2 were measured at each examined day as a biomarker of inflammation, myocardial stress and fibrosis.
Results: Seventeen subjects (age 65.7±5.7yr) were included in the study. In the PUFA group a significant improvement in sST2 levels were observed at the end of the treatment period compare to pre-treatment levels [219 (161–362)ng/ml vs. 212 (158–315)ng/ml, p=0.006]. In the placebo group there was no improvement at the end of the treatment period compare to pre-treatment levels [215 (155–325)ng/ml vs. 211 (160–340)ng/ml, p=0.22]. Importantly, a significant improvement in LV function as assessed by LVEF and GLS was observed only after PUFA treatment (35.4±7.6% vs. 33.4±6.8%; p=0.032, and -11.6±3.3% vs. -10.1±2.9%; p=0.022, respectively) as well as a marginal improvement in LV diastolic and systolic dimensions (55.7±6.0mm vs. 57.1±6.2mm; p=0.245, and 45.1±6.7mm vs. 47.6±5.2mm; p=0.09, respectively). Interestingly, in the PUFA group there was as

significant correlation between the improvement in sST2 levels and the improvement in GLS (rho=0.6, p=0.01) while there was no such correlation concerning the improvement in FMD and the LVEF.
Conclusions: In systolic HF patients, short term treatment with omega-3 PUFAs downregulates levels of sST2 with a parallel improvement in left ventricle ejection fraction and global longitudinal strain. These findings shed lights on the possible favorable mechanisms of omega-3 PUFAs in patients with ischemic heart failure.

P736 | BEDSIDE
Fontan patients with high N-terminal pro-brain natriuretic peptide fall into not only low cardiac output but also venostasis

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Background: For Fontan patients ventricle and atrium exist only in systemic circulation. Therefore, secretory stimulation for n-terminal pro-brain natriuretic peptide (NT-proBNP) and characteristics of patients with high NT-proBNP levels (hNT-proBNP) would differ from those in patients with biventricular heart. We investigated strains affecting NT-proBNP levels and features of patients with hNT-proBNP.
Methods: The medical records of 161 Fontan patients were reviewed aged from 1.7 to 42.9 years. They underwent cardiac catheterization and measurement of NT-proBNP between 2010 and 2015. We defined hNT-proBNP as NT-proBNP 400pg/ml or over (by Japan heart failure society, n=31). First, cardiac performances and clinical characteristics were determined which would act on secretion of NT-proBNP. Second, we compared clinical features between patients with hNT-proBNP and without hNT-proBNP.
Results: In monovariate analysis hNT-proBNP was significantly related to following clinical factors: study age (≥19.0 years), age at Fontan (≥5.9 years), levels of creatinine (≥0.70 mg/dl), mild or over regurgitation of aortic valve, and mild-to-moderate or over regurgitation of atrio-ventricular valve. Similarly, hNT-proBNP was significantly related to cardiac performances: ventricular volumes on end-systole (≥60%) and end-diastole (≥155%); driving pressure of pulmonary artery (≤5 mmHg); end-diastolic pressure of ventricle (≥13 mmHg). After multivariate analysis hNT-proBNP was independently associated with odds ratio of 4.0 (p=0.021) for elder age, 4.3 (p=0.038) for high creatinine levels, 9.6 (p<0.001) for expanded volume on end-diastole, and 4.4 (p=0.004) for elevated ventricular pressure on end-diasole. Clinically, Fontan patients with hNT-proBNP had low cardiac output (3.0 vs. 3.5 L/min/m^2, p=0.029), high pressure of central vein (13.9 vs. 12.0 mmHg, p=0.006). They also had deteriorations in liver function on blood examination: blood platelet counts (17.5 vs. 23.0 x104/ml, p=0.0012); levels of gamma-glutamyl transpeptidase (126 vs. 67 U/L, p<0.001).
Conclusion: Like in adult patients with biventricular heart, hNT-proBNP was associated with ventricular stretch, aging, and renal function in Fontan patients. Not-so-massive valve regurgitation and low driving pressure of pulmonary artery were also related to hNT-proBNP in Fontan circulation. Hepatic impairment already subsisted in this study population. We should pay much attention to venous system failure as well as ventricular functions in Fontan patients with hNT-proBNP.

P737 | BEDSIDE
Dipeptidyl peptidase IV in chronic heart failure with reduced ejection fraction

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Background: Dipeptydil peptidase-IV (DPP-IV) is an ubiquitary enzyme that plays a major role in incretin and natriuretic peptides physiology. Incretin-based therapies namely DPP-IV inhibitors in Heart Failure (HF) have been the focus of controversy and intensive investigation. Association of DPP-IV inhibitors with worse prognosis in HF was suggested. We aimed to assess the serum DPP-IV levels in chronic stable HF patients and determine their association with prognosis.
Methods: Chronic stable HF patients with optimized prognostic modifying therapy were prospectively recruited. Eligible patients were scheduled a medical visit in which clinical examination was performed and a venous blood sample was collected. Exclusion criteria: 1) ejection fraction>45%, 2) patients with dose adjustments in the previous 2 months, 3) patients hospitalized in the previous 2 months; 4) patients on renal replacement therapy, and 5) patients medicated with DPP-IV inhibitors. Patients were followed for 3 years. Primary endpoint was all-cause death and the secondary endpoint was all-cause death or HF-hospitalization. DPP-IV was measured in all patients. Patients' characteristics were compared according to DPP-IV quartiles. A Cox regression analysis was performed and multivariate models were built.
Results: We studied 264 patients. Mean age was 69 (±13) years and 70.5% were male and 33.7% were diabetic. Median (IQR) serum DPP-IV levels were 455.6 (350.0–625.5) ng/mL. DPP IV had an inverse relationship with age. Patients with higher DPP-IV levels less often had ischemic heart disease but were more often on ACE inhibitors or ARBs, and those in 3rd DPPIV quartil were in lower NYHA classes. Patients in 3rd DPPIV quartil had the lowest all-cause mortality at 3 years. Patients in the 1st DPPIV quartil had a multivariate adjusted HR of 3-year mortality of 2.62 (95% CI:1.15–5.95), p=0.02 when compared with the reference category and the HR for the 4th quartil was of 3.79 (95% CI: 1.68–8.54), p=0.001. Similar, although not so strong, results were observed for the secondary endpoint.
Conclusions: There is a U-shaped association of serum DPP-IV with mortality in chronic stable HF patients with reduced ejection fraction. Patients in the 3rd DPP-IV quartil have the best multivariate adjusted 3-year survival. A minimum DPP-IV level seems to be physiologically necessary. The DPP-IV inhibition may be of interest in a specific subgroup of HF patients.

P738 | BEDSIDE
Differential association of plasma biomarkers with myocardial fibrosis or heart failure symptoms in heart failure with preserved ejection fraction patients

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Objectives: Heart failure with preserved ejection fraction (HFPEF) is mainly characterized by myocardial interstitial fibrosis. The aims of this study were to characterize the detailed relationship between various novel biomarkers with cardiac fibrosis or heart failure symptoms in HFPEF patients.
Methods: HFPEF was diagnosed according to the consensus of European society of cardiology with evidence of diastolic dysfunction under echocardiography and elevation of plasma NT-proBNP level. A total of 77 patients with HFPEF were recruited. All HFPEF patients received echocardiographic with tissue doppler imaging (TDI), cardiac magnetic resonance imaging (CMRI) as well as measurements of plasma inflammatory, remodeling, endothelial function and heart failure biomarkers. Phenotypic expression of myocardial fibrosis were determined by CMRI extracellular volume. Forward conditional logistic regression was applied to demonstrate the determinants of myocardial fibrosis or heart failure symptoms.
Results: Patients with higher myocardial fibrosis levels have more heart failure symptoms and higher percentages of diabetes. The levels of growth differentiation factor (GDF15), Tissue inhibitors of metalloproteinase 1 (TIMP1), Galectin-3 and NT-proBNP were significantly higher in HFPEF patients with higher myocardial fibrosis (high ECV volume). Multivariate logistic regression analysis identified Matrix Metalloproteinase 2 (MMP2), Galectin-3 as the independent markers to be the determinants of ECV levels in HFPEF patients (odds ratio [OR]: 1.05, 95% confidence interval [CI]: 1.02 to 1.09, p=0.005 and OR: 2.11, 95% CI: 1.35–3.28, respectively). After adjustment for confounding factors, on the other hand, TIMP2 and NT-proBNP were the major determinants for the presence of heart failure symptoms (OR: 1.05, 95% CI: 1.01–1.06 and OR: 1.02, 95% CI: 1.01–1.04, respectively).

Comparison of serum biomarkers

	EC V<28% (N=39)	ECV ≥28% (N=38)	P
CRP, ug/ml	1.81±1.58	2.41±2.22	0.235
GDF15, pg/ml	982.43±461.14	1823.87±1516.36	0.007
Galectin-3, ng/ml	7.05±2.07	11.13±4.18	<0.001
CTGF, ng/ml	3.05±6.11	8.09±14.34	0.051
NT-proBNP, pg/ml	688.39±903.75	4156.21±8305.21	0.033

Conclusions: Plasma Galectin-3 and MMP2 levels correlated with myocardial fibrosis levels while NT-proBNP only were associated with heart failure symptoms in HFPEF patients. Specific biomarkers correlate to myocardial fibrosis might be more specific long-term prognostic factors in HFPEF patients.

P739 | BENCH
Assessing the influence of the genetic background on anthracycline induced cardiotoxicity with hiPSC derived cardiomyocytes

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Purpose: The anthracycline doxorubicin (DOX), one of the most effective chemotherapeutic drugs for the treatment of various cancers, is limited in its clinical applications due to cumulative dose-dependent cardiotoxicity. The mechanisms of anthracycline-induced cardiotoxicity (ACT) and potential risk factors are still not fully understood. However, recent studies suggest that single nucleotide polymorphisms (SNPs) in subunits of the NADPH oxidase might cause a predisposition for ACT. We aim to use human induced pluripotent stem cells (hiPSCs) as a powerful means to model the cardiac phenotype of ACT and to investigate potential genetic risk factors.
Methods and results: We generated iPSCs from five patients, which were treated with DOX during chemotherapy. Three patients with SNPs in the NADPH

oxidase subunits RAC2 and p22phox developed ACT. Two patients without these SNPs did not develop ACT and were used as controls. We directly differentiated iPSCs into a 95% pure cardiomyocyte (iPSC-CMs) culture. The iPSC-CMs expressed the cardiac marker genes cTNT, ACTN2, SCQ, a/b-MHC, and MLC2a/v without any differences between ACT patients and controls. Furthermore, we were able to show a nuclear localization of the NADPH oxidase subunits NOX2 and NOX4 and the latter was also found to be localized at the sarcomere. Two month old iPSC-CMs were exposed for 24h to different concentrations of DOX (0.1–5μM) and used for analysis. Since oxidative stress is discussed as a key pathomechanism of ACT, we analyzed the H2O2 amount in iPSC-CMs after DOX treatment using Amplex Red and found an increased H2O2 production in ACT patients compared to controls. In addition, physiological DOX concentrations of 0.1–0.5μM DOX caused a dose-dependent increase of H2O2 whereas higher concentrations (0.75 - 5μM) did not change the level of H2O2, independent of the genetic background.
In order to examine if the analyzed SNPs have an influence on gene expression of NADPH oxidase subunits, we investigated NOX2, NOX4, p22phox, RAC1 and RAC2 by real-time PCR in non-treated cells and upon exposure to DOX. We found an increased RAC1 expression in iPSC-CMs of the ACT patients 2 and 3 compared to controls. RAC2 and NOX2 were significantly higher expressed in iPSC-CMs from ACT patient 3 in comparison to controls. Furthermore, DOX treatment resulted in decreased expression of all investigated genes in ACT patients and controls. Using an automatic cell counter, we showed that the iPSC-CM cell diameter of ACT patients is smaller compared to controls (difference between means: 1.01μm). Further studies regarding apoptosis, calcium handling and proteomics are in progress.
Conclusion: Our findings show that iPSC-CMs of ACT patients with SNPs in NADPH oxidase subunits react differently to increasing concentrations of DOX compared to control cells without SNPs with regard to oxidative stress and gene expression. This indicates the importance of the genetic background for the risk to develop ACT.
Acknowledgement/Funding: Heidenreich von Siebold (KSB); SFB1002 (GH); DZHK (KSB)

P740 | BEDSIDE
Is an abnormal ECG just the tip of the ICE-berg? Examining the utility of electrocardiography in recognizing methamphetamine-induced cardiac pathology

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Background: Methamphetamine use is escalating globally, with increasing emergency department attendance, hospital admissions, and mortality. Cardiac complications play a large role in methamphetamine-related mortality, and it would be informative to assess the frequency of abnormal electrocardiograms (ECGs) amongst methamphetamine users.
Purpose: To determine the frequency and severity of ECG abnormalities amongst methamphetamine users compared to a control group.
Methods: We conducted a retrospective cohort analysis on 212 patients admitted to a tertiary hospital (106 patients with methamphetamine abuse, 106 age and gender-matched control patients). ECGs were analysed according to American College of Cardiology guidelines, and compared to echocardiographic (TTE) findings.
Results: Mean age was 33.4 years, with 73.6% male gender, with no significant differences between groups in smoking status, ECG indication, or coronary angiography rates. Methamphetamine users were more likely to have psychiatric admissions (22.6% vs 1.9%, $p<0.0001$) and undergo TTE (21.7% vs 0.9%, $p<0.0001$). Overall, ECG abnormalities were significantly more common (71.7% vs 32.1%, $p<0.0001$) in methamphetamine users, particularly tachyarrhythmias (38.7% vs 26.4%, $p<0.0001$), right axis deviation (7.5% vs 0.0%, p=0.004), left ventricular hypertrophy (26.4% vs 4.7%, $p<0.0001$), p pulmonale pattern (7.5% vs 0.9%, p=0.017), inferior Q waves (10.4% vs 0.0%, p=0.001), lateral T wave inversion (3.8% vs 0.0%, p=0.043), and longer QTc interval (436.41±31.61ms vs 407.28±24.38ms, $p<0.0001$). TTE (n=24) demonstrated left ventricular dysfunction (38%), thrombus (8%), valvular lesions (17%), infective endocarditis (17%), and pulmonary hypertension (13%). ECG was only moderately sensitive at predicting abnormal TTE.
Conclusion: ECG abnormalities are more common in methamphetamine users than age and gender- matched controls. Due to the high frequency of abnormalities, we suggest ECGs should be performed in all methamphetamine users who present to hospital. Methamphetamine users with abnormal ECGs should be considered for further cardiac investigations.

P741 | BEDSIDE
Early change in left atrial function in patients treated with anthracyclines assessed by real-time three-dimensional echocardiography

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Objective: Real-time three-dimensional echocardiography has allowed a better assessment of LA volumes and function. In this study we sought to assess the early change in left atrial size and function in patients treated with anthracyclines using three-dimensional echocardiography.
Methods: Sixty-one patients aged 44.9±11.9 years with large B-cell non-Hodgkin lymphoma treated with doxorubicin were studied. Echocardiography was performed at baseline and 1 day after completion of the chemotherapy. Maximum (LAVmax), minimum (LAVmin) and pre-atrial contraction LA volumes (LAVpre-a) were measured and reservoir, conduit and booster pump function were assessed.
Results: Despite of normal left ventricular ejection fraction (LVEF), passive emptying percent of total emptying (0.51±0.14 vs. 0.40±0.12; <0.001) and passive emptying index (0.29±0.10 vs. 0.23±0.06; $p<0.001$) were remarkably reduced compared to baseline values, while active emptying percent of total emptying (0.49±0.14 vs. 0.60±0.12; $p<0.001$) and active emptying index (0.41±0.16 vs. 0.47±0.16, p=0.048) were increased. However, filling volume, expansion index and diastolic emptying index showed no significant difference after doxorubicin exposure.
Conclusions: Early LA dysfunction occured after doxorubicin exposure in patients with preserved LVEF, which could be detected by real time-three dimensional echocardiography (RT-3DE).

P742 | BENCH
Levosimendan protects against doxorubicin induced acute cardiotoxicity by regulation of oxidative stress and by activation of antiapoptotic mechanisms

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Introduction: Doxorubicin (DXR) is a very effective chemotherapeutic agent but with a dose-dependent induction of cardiomyopathy and heart failure. Levosimendan (Levo) is an inotropic drug with vasodilator activity indicated for the treatment of advanced heart failure.
Purpose: We sought to investigate the effect of Levo on acute doxorubicin-induced cardiotoxicity and the underlying signaling mechanisms.
Methods: In vitro: PC3 cell line was treated with DXR (10–200 nM), Levo (1–50 uM) as well as with a combination of the two compounds in order to investigate the possible inhibition of DXR antitumor activity by Levo. In vivo: Male rats were randomized into the following groups: 1) Control group, 2) DXR group (DXR 20mg/kg) 3) DXR+LEVOA group (DXR 20mg/kg + LEVO 12mg/kg) 4) DXR+LEVOB group (DXR 20mg/kg + LEVO 24mg/kg). On the third day, after drug administration, echocardiography was performed and then the rats were sacrificed. The hearts were rapidly excised for histological evaluation, determination of nitroxidative stress biomarkers (MDA, PCs, Nitrotyrosine), mRNA levels of MMP2, TGF-β1 and protein expression of iNOS, phospho-Akt/Akt, phospho-ERKs, MnSOD, IL-6 and NOX-4.
Results: In vitro: Levo exhibited cytotoxic activity on PC3 cell line at concentrations 10–50 uM as well as amplified the antitumor effect of DXR. In vivo: DXR reduced the fractional shortening (FS) ($p<0.001$ vs Control), while no change was observed by the administration of Levo. Myocardium exhibited morphological changes in DXR group including extensive cytoplasmic vacuolization (CV) and infiltrations of immune cells; only a small degree of CVs was present in myocytes treated with Levo. Levo reduced oxidative stress biomarkers and IL-6 in a dose-dependent manner (DXR+LEVOB vs DXR, $p<0.05$). Moreover, at the higher dose it decreased mRNA levels of MMP2 and NOX-4; it reduced the expression of iNOS in both doses. An increase of MnSOD expression and phosphorylation of Akt was observed in LEVOB group. No changes were observed in the levels of TGF-β1 and in the phosphorylation of ERKs.
Conclusion: Levosimendan, although it did not reduce reverse the FS, exhibited structural and biochemical beneficial effects by regulation of oxidative stress and activation of antiapoptotic mechanisms. Its potential antitumor activity may provide an additional fortuitous effect, supporting its adjunctive use in DXR therapy.

P743 | BEDSIDE
Investigation of left ventricular diastolic stiffness associated with cardiac toxicity from anticancer agents

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Background: Cardiotoxic anticancer regimens result in an increase in left ventricular mass (LVM), and can result in heart failure with preserved ejection fraction (HFpEF). The pathophysiology of HFpEF is complex, but increased left ventricular (LV) diastolic stiffness plays a key role.
Purpose: This study investigated the utility of diastolic wall strain (DWS) to assess diastolic stiffness in heart failure with HFpEF in patients receiving cardiotoxic anticancer agents (CAA).
Methods: We studied 282 consecutive breast cancer patients who completed adjuvant chemotherapy with three drugs (cyclophosphamide, epirubicin, and 5-fluorouracil [5-FU] [CEF]). These patients were categorized into the following two

groups: DWS<0.759 (group A; n=142) and DWS≥0.759 (group B; n=140). Echocardiography was performed before and after four cycles of CEF, and the following parameters were calculated: left atrial diameter (LAD); LV diameter in diastole/systole (LVDd/s); LV end-diastolic volume (LVEDV); LV end-systolic volume (LVESV); interventricular septal thickness in diastole/systole (IVSTd/s); posterior wall thickness in diastole/systole (PWTd/s); LV ejection fraction (LVEF); ratio of early to late ventricular filling velocity (E/A); mitral annulus velocity (e'); E/e'; Tei index (TI); relative wall thickness (RWT); DWS [DWS=(PWTs-PWTd)/PWTs]; LVM; LVM index (LVMI); diameter of the inferior vena cava (IVC); pulmonary artery systolic pressure (PASP); LV end-diastolic pressure (LVEDP); and systolic blood pressure (BPs). We also analyzed the rate of change (%) in all indices as follows: ΔLAD, ΔLVDd/s, ΔLVEDV, ΔLVEDSV, ΔIVSTd/s, ΔPWTd/s, ΔLVEF, ΔE/A, Δe', ΔE/e', ΔT-I, ΔRWT, ΔDWS, ΔLVM, ΔLVMI, ΔIVC, ΔPASP, ΔLVEDP, and ΔBPs. Data were then compared between the two groups. We also analyzed the correlation between the total amount of CEF (∑CEF)/LVM and ΔLVM and ΔDWS.
Results: No significant changes were observed in the indices of cardiac function, including LAD, LVEF, TI, E/A, IVC, and PASP. Significant increases were observed in LVDd/s, LVEDV, LVESV, IVSTd, PWTd, E/e', RWT, LVM, LVMI, and LVEDP ($p<0.0001$). Following chemotherapy, a significant decrease was observed in IVSTs, PWTs, e', DWS, and BPs. There was a significantly greater increase in group B than in group A in ΔPWTd, ΔRWT, ΔLVM, and ΔLVMI, and a significantly greater decrement in group B in ΔPWTs and ΔDWT. No significant differences were observed in two groups in the rate of change in the other 16 indices. Moreover, ∑CEF/LVM correlated well with ΔLVM ($r=0.40$, $p<0.00001$), and an inverse correlation was observe between ∑CEF/LVM and ΔDWS ($r=-0.13$, $p<0.05$).
Conclusion: A CAA-induced increase in diastolic stiffness with an increase in LVM was related to concentric hypertrophy and HFpEF. CAA has a larger effect in patients with higher DWS than in those with lower DWS. Furthermore, the increase in diastolic stiffness is dependent on the dose of CAA.

P744 | BEDSIDE
Evaluation of cardiotoxicity in cervical cancer patients and nimotuzumab treatment

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Background: Cardiotoxicity is one of the most significant adverse effects of cancer treatment, and is responsible for considerable morbidity and mortality. Among the effects of chemotherapeutic agents on the cardiovascular system, the most frequent and serious is heart failure with ventricular systolic dysfunction. New therapeutic agents, such as the monoclonal antibody trastuzumab induce transient reversible myocyte dysfunction which is unrelated to the dose used. Nimotuzumab has shown a major security profile than the previous monoclonal antibodies, nevertheless the evidence is still limited.
Purpose: To evaluate cardiotoxicity of nimotuzumab in combination with cisplatin-vinorelbine in first-line chemotherapy for patients with persistent-recurrent cervical cancer.
Methods: This is a sub-analysis of a phase III, multicenter, randomized, double-blind, clinical controlled trial study; we included two groups of patients which were divided by it's treatment: the first one received 200 mg nimotuzumab + chemotherapy (6 cycles every 21 days of cisplatin 75 mg/m^2 day 1/vinorelbine 30 mg/m^2 day 1–day 8) for 12 weeks; the second group received placebo besides chemotherapy in a similar dosis scheme. The volumes and function of the left ventricle were evaluated by ECHO (echocardiography), MUGA (Multi Gated Acquisition Scan), and MRI (magnetic resonance imaging), at the beginning, 3rd and 6th month of treatment.
Results: 166 patients were analized with a mean age of 50±10yrs, 23% with hypertension, 5% diabetic, 28% with persistent carcinoma, the rest with recurrent cancer; 78% received chemoradiotherapy previously, without any significant difference between groups. No significant difference was observed among the initial and final left ventricle ejection fraction (LVEF) in both groups (final LVEF, placebo and nimotuzumab, by MUGA 61±11 vs 57±6%, p=0.19; by ECHO 59±8 vs 62±8%, p=0.28; by MRI 58±6 Vs 58±8%, p=0.9). When performing paired analysis, the nimotuzumab group showed a significant decrease at 6 months with MUGA (initial 62±5%, final 57±6%, p=0.005) and with MRI (initial 61±8%, final 58±8%, p=0.02) without achieving traditionial criteria of cardiotoxicity. No difference was observed in diastolic function by ECHO.
Conclusions: In patients with recurrent-persistent cervical carcinoma the combination of nimotuzumab with cisplatin-vinorelbine in a first line of chemotherapy along 6 months it's not related to cardiotoxicity, nevertheless, MRI and MUGA showed significant decrease in repeated measurements. Nowadays, the clinical impact of this early decline in ventricular function is not known.
Acknowledgement/Funding: PISA, Farmacéutica.

P745 | BEDSIDE
Comparison of two-dimensional and three-dimensional speckle tracking echocardiography in early detection of biventricular systolic function after anthracycline therapy in patients with lymphoma

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Background: Anthracycline (ATC) cardiotoxicity occurred anytime, from the early onset of therapy to decades after its completion. The aim of this study was to compare the sensibility between two-dimensional (2D) and three-dimensional (3D) speckle tracking echocardiography (STE) for early assessment of both left and right ventricular systolic function in patients with lymphoma after anthracycline (ATC) chemotherapy.
Methods: Eighty-nine patients with newly diagnosed diffuse large B-cell lymphoma treated with ATC containing chemotherapy were studied. Echocardiographic assessment included 2D and 3D left ventricular (LV) global longitudinal strain (GLS), global circumferential strain (GCS) as well as right ventricular (RV) GLS. All the parameters were analyzed at baseline, after the completion of two cures (100mg/m^2) and four cures of the regimen (200mg/m^2) respectively.
Results: None of the patients developed clinical cardiac toxicity either on left ventricle nor on right ventricle during follow-up (The reduction of ventricular ejection fraction of ≥5% detected by nuclear medicine was defined as clinical cardiotoxicity). After two cycles of therapy, 3D LVGLS (–21.82±2.90% vs. –19.30±2.71%), LVGCS (–29.90±4.40% vs. –27.59±4.57%) as well as RVGLS (–23.71±4.10% vs. –20.65±5.47%) showed significant decrease compared with those at baseline (all $p<0.01$). However, 2D LVGLS (–21.53±2.50% vs. –20.77±2.13%), LVGCS (–25.35±4.54% vs. –24.92±4.20%) and RVGLS (–22.21±7.02% vs. –21.22±7.04%) manifested no obvious alternation at the same stage (all $p>0.05$). After four cures of treatment, 2D LVGLS and LVGCS deteriorated markedly (both $p<0.05$) while 2D RVGLS still presented stable and normal ($p>0.05$).
Conclusions: 3D STE seems to be a most sensitive method to assess the early subclinical biventricular dysfunction in patients with lymphoma after ATC chemotherapy compared with 2D STE.

P746 | BEDSIDE
Late-onset cardiotoxicity in Anthracycline-based chemotherapy for breast cancer patients

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Background: Anthracycline cardiotoxicity (AC) represents a mayor limitation for the treatment of breast cancer patients (pts) and it may manifest years after treatment (late-onset cardiotoxicity). The aim of the study is to establish incidence and predictors of late-onset cardiotoxicity in a cohort of these type of pts.
Methods: 100 consecutive pts receiving Anthracycline-based chemotherapy (CHT) were included in this prospective study. All pts underwent evaluation at baseline, at the end of CHT, 3 months after the end of CHT and 1 and 4 years after the beginning of CHT. Clinical data, systolic and diastolic echo parameters and cardiac biomarkers including high-sensitivity Troponin T (TnT), NTproBNP and Heart-type fatty acid binding protein (H-FABP) were assessed.
Results: Mean doxorubicin dose was 243 mg/m^2. Mean follow-up was 51.8±8.2 months. At one year incidence of AC was 4% and at the end of follow-up was 18% (15 pts asymptomatic left ventricular systolic dysfunction, 1 pt heart failure and 2 pts a sudden cardiac death). Forty nine pts developed diastolic dysfunction (DD) during first year. In the univariate analysis DD during first year was the only parameter associated with AC (Table1). In the logistic regression model DD was independently related with the development of AC, with an odds ratio value of 7.5 (95% CI 1.59–35.3).
Conclusions: Incidence of late-onset cardiotoxicity is high but mostly subclinical. Diastolic dysfunction early after chemotherapy is a strong predictor of anthraciclyne cardiotoxicity.

	AC+ (N=18)	AC– (N=82)	P value
Age	50.4±9.2	51±9.1	0.78
DD (%)	88	41	0.005
Hypertension	33.3	28.0	0.77
Diabetes	11.1	9.8	1
Hyperlipidemia	11.1	14.6	1
Smoking status	38.9	32.9	0.84
Anthracycline dose (mg/m^2)	243±4.8	242±4.6	0.73
Radiotherapy (%)	38.9	42.7	0.79
TnT end of CHT (ng/L)	13.2±5.8	12.0±5.6	0.44
TnT 3 months after CHT (ng/L)	14.1±8.2	12.1±5.5	0.20
H-FABP end of CHT (ng/mL)	2.8±1.4	3.2±2.0	0.43
H-FABP 3 months after CHT (ng/mL)	3.5±2.2	3.3±1.8	0.65
NTproBNP end of CHT (pg/mL)	86±103	60±47	0.10
NTproBNP 3 months after CHT (pg/mL)	78±95	58±62	0.28

Abbreviations: AC+, pts developing AC; AC–, pts not developing AC; rest abstract text.

Acknowledgement/Funding: Unrestricted grants from Red Temática de Enfermedades Cardiovasculares (RECAVA) RD06/0014/002 of the Instituto de Salud Carlos III

P747 | BEDSIDE
Trastuzumab therapy: temporal trends of left ventricular dimension and function indices and incidence of cardiotoxicity in patients with breast cancer

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Purpose: Previous studies have demonstrated that trastuzumab therapy during or after chemotherapy increases survival in patients with HER2 positive breast cancer. However, this benefit is associated with higher risk of cardiotoxicity. We sought to: (1) study the temporal trends of the dimension and function indices of the left ventricle during chemotherapy and trastuzumab therapy; (2) evaluate the incidence and factors associated with trastuzumab induced cardiotoxicity (TIC).
Methods: Retrospective study of patients with first non-metastatic breast cancer treated with trastuzumab after March 2010 who underwent a comprehensive echocardiographic examination before and after chemotherapy and quarterly during trastuzumab therapy. Patients with baseline left ventricular ejection fraction (LVEF) <50%, severe valvular heart disease or prosthetic valves were excluded. TIC was defined as a decrease >10% in the LVEF or LVEF<53%.
Results: Sixty-two patients were included, all female and with 54±14 years. Fifty (80.6%) patients underwent anthracycline chemotherapy prior to trastuzumab and 58 (93.5%) were treated with taxane chemotherapy concurrently with trastuzumab. At the end of trastuzumab therapy, there was an increase of indexed left ventricle end-diastolic (42.6±9.6 vs. 47.5±11 ml/m^2, p=0.023) and end-systolic (13.4±4.7 vs. 17.6±5.8 ml/m^2, p<0.001) volumes and a reduction of LVEF (66.1±4.5 vs. 61.3±7.7%, p<0.001), global longitudinal strain (-16.8±2.2 vs. -14.7±3.2%, p=0.001) and mitral S' (8.1±1.6 vs. 7.3±1.5 cm/s, p=0.013) compared to baseline. There was no change in diastolic function parameters during therapy with trastuzumab. Thirteen (21%) patients had TIC and 5 (8.1%) had heart failure. Trastuzumab was temporarily suspended in 1 (1.6%) patient and permanently suspended in 10 (16.1%) patients. The number of trastuzumab cycles was lower in patients with CIT (10.3±4.8 vs. 17.8±2.5, p<0.001). Patients who underwent anthracycline chemotherapy had higher TIC incidence (26% vs. 0%, p=0.043). In a multivariate analysis, baseline (OR:0.826, CI 95% 0.704–0.969, p=0.019) and after anthracycline chemotherapy (OR:0.841, CI 95% 0.729–0.971, p=0.018) LVEF and GLS after anthracycline chemotherapy (OR:0.740, IC95% 0.550–0.995, p=0.046) were associated with TIC. None of cardiovascular risk factors were associated with TIC. Patients were followed during 33 (IQR 25–45) months. During follow-up, 2 (3.2%) patients had tumor progression, 7 (11.3%) had tumor relapse and 4 (6.5%) died. TIC was not associated with the composite endpoint of tumor progression, relapse or death (OR:1.784, CI 95% 0.174–18.297, p=0.626).
Conclusions: Trastuzumab therapy was associated with subclinical progressive left ventricular dilatation and systolic dysfunction. Although little symptomatic, TIC was common and caused a reduction in the number of trastuzumab cycles.

P748 | BENCH
Thioredoxin overexpression protects cardiomyocytes, but enhances cancer cell apoptosis in response to daunomycin

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Introduction/Background: Anthracyclines are potent anticancer drugs that are widely used for the treatment of a variety of cancers including leukemia. Currently 270,000 children in USA and more than 20,000 in UK are cancer survivors after anthracycline chemotherapy. Some of these children will develop clinical heart failure (CHF) or other cardiac complications in later part of their lives due to cardiotoxicity of anthracyclines. A particular limitation of anthracycline chemotherapy is the dose-dependent cardiotoxicity that can lead to CHF. Additionally, among serious cardiac complications that have been reported are: 1) arrhythmias; 2) myocardial necrosis causing dilated cardiomyopathy; 3) vasoocclusion or vasospasm resulting in angina or myocardial infarction.
Purpose: The objective of this study was to determine whether cardiomyocytes would be protected against anthracycline toxicity due to increased expression of Thioredoxin (Trx) a potent antioxidant and protein disulfide reductase, while enhancing the toxicity in cancer cells.
Methods: We utilized rat embryonic cardiomyocytes (H9C2) cells as our model system to determine differential toxicity of cancer cells and cardiomyocytes in response to daunomycin, a potent anthracycline. H9C2 or cancer cells (HCT116, A431, U937, MCF7, MDA-MB231) were exposed to daunomycin and apoptosis was determined by cleavage of PARP, cytochrome c release, p53 expression and cell viability studies. We also utilized normal cells such as breast epithelial cells (HMEC), normal human endothelial cells (HMVEC) to determine the effect of Trx on anthracycline-mediated toxicity of normal cells.
Results: We found that cancer cells from various tissue origins undergo enhanced apoptosis due to daunomycin treatment in the presence of high levels of hTrx. However, in presence of high levels of Trx cardiomyocytes or normal cells did not undergo enhanced apoptosis in response to daunomycin as determined by PARP cleavage. This apoptosis potentiation by Trx is limited to only anthracyclines, as etoposide, another topoisomerase II inhibitor did not increase apoptosis in the presence of increased hTrx. In contrast, hTrx protected against etoposide-induced apoptosis of cancer cells. Collectively, these findings indicate a specific effect of Trx in potentiating anthracycline toxicity in cancer cells, but not in cardiomyocytes.
Conclusion: We conclude that hTrx enhances the anthracycline redox cycling in cancer cells, redox cycling of daunomycin would not occur in cardiomyocytes, as they are non-cycling cells. Additionally, Trx could protect against daunomycin-mediated ROS generation due to scavenging of superoxide anion and H2O2-Fe2+ -mediated hydroxyl radicals via increased peroxiredoxins expression.
Acknowledgement/Funding: The National Heart, Lung And Blood Institute of the National Institutes of Health under Award Number R01HL107885 and R01HL109397, supports research re

P749 | BEDSIDE
Contemporary trends in pulmonary artery catheterization use in congestive heart failure: results from the United States national inpatient sample database

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Introduction: In patients with congestive heart failure (CHF), pulmonary artery (PA) catheterization is recommended in certain situations such as clinically indeterminate volume status, cardiogenic shock, worsening renal function and failure of initial therapy. However, there remains uncertainty of its impact on mortality and other clinical outcomes. This had resulted in a decrease in its use in the United States. However, contemporary trends in utilization of PA catheterization in the United States in patients admitted with CHF are unknown.
Purpose: This study was conducted with the objective of understanding the current use of PA catheterization in CHF hospitalizations and its association with in-hospital mortality.
Methods: A secondary analysis of the United States National Inpatient Sample (NIS) database from 2008–2012 was conducted. All patients age 18 years or older with the primary admission diagnosis of CHF were included. Cohort was divided based on PA catheterization use. Also, numbers of days from admission to the first PA catheterization in each hospitalization was recorded. PA catheterization codes which were used included: PA or wedge-pressure monitoring, measurement of mixed venous blood gases, or monitoring of cardiac output.
Results: Between 2008 and 2012, PA catheterization use increased from 7.02 to 10.4 per 1000 CHF admissions (48%, P<0.001 for trends). PA catheterization use was lower in women (0.6% vs. 1.1%, P<0.001). Patient who had PA catheterization were younger (62.1±14.7 years vs. 72.8±14.2 years, P<0.001).
There was an observed increased mortality associated with PA catheterization use (8.9% vs. 3.1%, P<0.001) in the whole cohort, but in patients with cardiogenic shock, use of PA catheterization was associated with lower mortality (21% vs. 28.1%, P<0.001). On the other hand, patients who died during hospitalization had higher rate of PA catheterization use (2.4% vs. 0.8%, P<0.001). Interestingly, patients who underwent PA catheterization in the first week of hospitalization had much lower mortality than those undergoing the procedure later in their hospitalization (7.6% vs. 15%, P<0.001). Length of stay and cost of hospitalization were higher in patients with PA catheterization use (13.7±16 days vs. 5.1±5.4 days, P<0.00; $166K±248K vs. $36.1K±61k, P<0.001; respectively).
Conclusion: Our study results show that for patients admitted to the hospital with CHF, the inpatient use of PA catheterization has increased significantly in recent years. The higher observed mortality in the overall group with PA catheterization use likely reflects a sicker population. However, the mortality was actually better when it was used in those with cardiogenic shock and earlier during hospitalization. This finding indicates that timely use of PA catheterization in tenuous hemodynamic conditions has a favorable effect. A causative role can not be attributed to the found associations form this retrospective database-based study.

P750 | BENCH
Load sensitivity in left bundle branch block: septal contribution to left ventricular stroke work is abolished with elevated afterload

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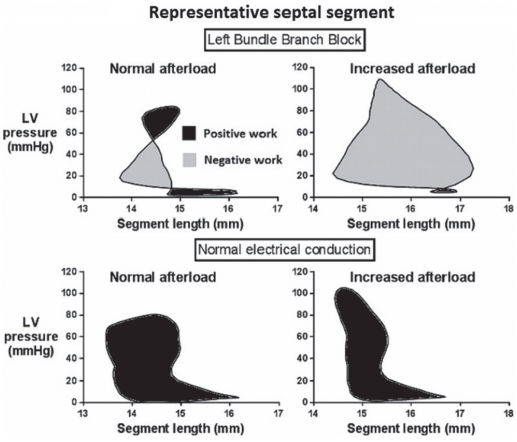
Introduction: In patients with left bundle branch block (LBBB) a dyssynchronous contraction pattern reduces septal contribution to left ventricular (LV) function. It is not known how this is affected by increased afterload.
Purpose: To assess the effect of increased afterload on regional LV function during LBBB to test the hypothesis that increased afterload further deteriorates septal performance.
Methods: In eight anaesthetized dogs, septal and LV lateral wall circumferential

segment lengths (SL) by sonomicrometry and LV pressure by micromanometer were measured during baseline and LBBB induced by radiofrequency ablation. Afterload was increased by aortic constriction. Segmental work was calculated by pressure-segment length analysis. Since segments which shorten in systole perform positive work, whereas segments which lengthen do negative work, we calculated net work as the sum of positive and negative work.
Results: During LBBB, aortic constriction increased LV pressure from 94±10 (mean±SD) to 118±16 mmHg (P<0.01). Net septal work decreased from 43±194 to -227±168 mmHg*mm (P<0.01), which means that the septum made no net contribution to LV work and instead absorbed energy from work done in the LV lateral wall (figure). In the LV lateral wall there was no significant change in net work (685±157 to 666±300 mmHg*mm). Prior to induction of LBBB, aortic constriction caused no significant change in septal net work, but a small decrease (P<0.05) in net work in the LV lateral wall.



Conclusions: Elevation of afterload during LBBB resulted in a complete loss of septal contribution to LV stroke work. Instead the septum absorbed energy from work performed by the LV lateral wall. These findings indicate that ventricles with LBBB are highly sensitive to changes in afterload. Future studies should investigate if a similar afterload dependency is present in patients with LBBB.
Acknowledgement/Funding: Norwegian Health Association

P751 | BEDSIDE
Dobutamine stress test as a predictor of left ventricular reverse remodeling in dilated cardiomyopathy

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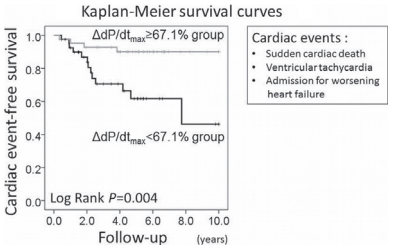
Background and purpose: Heart failure (HF) is responsible for significant morbidity and mortality. Dilated cardiomyopathy (DCM) is a major cause of HF hospitalization and sudden cardiac death due to lethal arrhythmia. Left ventricular reverse remodeling (LV-RR) induced by pharmacological therapy is important to prevent cardiac events. Cathecholamine sensitivity estimated by dobutamine stress testing is recognized as an ability of beta-adrenergic contractile reserve. However, little is known about the relationship between response of dobutamine stress test and LV-RR in patients with dilated cardiomyopathy (DCM).
Methods: Between July 2001 and February 2015, we enrolled consecutive 83 DCM patients (52.5±12.5 years) with NYHA I or II. DCM was defined as <50% left ventricular ejection fraction (LV-EF) determined by echocardiography and in the absence of secondary cardiac muscle disease. All patients underwent laboratory measurements, echocardiography and biventricular cardiac catheterization analysis. After evaluating baseline hemodynamics, a pigtail catheter with micromanometer was advanced into the LV cavity for collecting LV pressure data and measured the maximal first derivative of left ventricular pressure (LVdP/dtmax) as an index of LV contractility during baseline and infusion of dobutamine (10 μg /kg/min) and divided into two groups based on the value of ΔdP/dtmax (ΔdP/dtmax≥67.1%, N=42, ΔdP/dtmax<67.1%, N=41). LV-RR was defined as an increase in LV-EF from ≥10% to a final value of>35%, accompanied by a decreased in LV end-diastolic dimension≥10% under follow-up period.
Results: LV-EF was 32.5±9.7% and the plasma brain natriuretic peptide (BNP) level was 73.0 (48.4 - 240.1) pg/mL at baseline. During the follow-up period (4.5±2.7 years), LV R-R were recognized in 50/83 (60.2%) patients. BNP was lower (64.7 vs 118.0 pg/mL, P=0.014) and LV end-diastolic volume index (111.9 vs 131.1 mL/m^2, P=0.029), LV end-systolic volume index (75.9 vs 92.5 mL/m^2, P=0.031) and the LV pressure half-time as an index of isovolumic relaxation (39.9 vs 44.7 ms, P=0.002) were significantly smaller in the ΔdP/dtmax≥67.1% group. There were no differences in age, estimated GFR, LV-EF and cardiac index between the two groups at baseline. Multivariate logistic regression analysis revealed that ΔdP/dtmax≥67.1% was an independent predictor of LV-RR (HR:3.795, P=0.016) and in Kaplan-Meier survival analysis, cardiac events (sudden cardiac death, ventricular tachycardia and admission for worsening heart failure) were significantly lower in the ΔdP/dtmax≥67.1% group (Log Rank P=0.004) (Figure).



Conclusions: Dobutamine stress test is a useful predictor of LV-RR and lower rate of cardiac events in mildly symptomatic patients with DCM.

P752 | BEDSIDE
Left ventricular non-compaction and idiopathic dilated cardiomyopathy: the significant diagnostic value of longitudinal strain

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Background: Left ventricular non-compaction (LVNC) is characterized by abnormal trabeculations that are most frequently present at the apex. Despite diagnostic progress, the distinction between LVNC and non-specific dilated cardiomyopathies (DCMs) remains challenging. We sought to compare the longitudinal strain characteristics in LVNC versus idiopathic DCM.
Methods: 49 cases of LVNC were compared with 45 cases of DCM. Global and regional multi-layer (sub-endocardial, mid-wall, and sub-epicardial) longitudinal strain analysis was performed for these 93 patients. The results were compared to define the best tool for distinguishing LVNC from DCM. A validation cohort (41 LVNC) was then used to assess the performance of the proposed diagnostic tools.
Results: In the derivation cohort, all longitudinal strain components were higher in LVNC than in DCM patients. In LVNC, strain values were higher in the non-compacted segments than in the compacted ones (fig1). A base-apex gradient in sub-endocardial strain (AUC = 0.85) with a cut-off of -1.8% had 88% sensitivity and 69% specificity in distinguishing LVNC from DCM. Using a multivariable analysis model, two independent parameters allowed the distinction between LVNC and DCM: the base-apex sub-endocardial gradient in an apical 4-chamber view and the indexed left atrial volume (OR = 0.83, CI 95% [0.76; 0.92], p=0.0002 & OR = 0.94, CI 95% [0.91; 0.98], p=0.0026, respectively).
In the validation cohort, the base-apex sub-endocardial gradient had a sensitivity of 80.5%. The positive and negative predictive values were 57.9 and 69.2% for the diagnosis of LVNC.

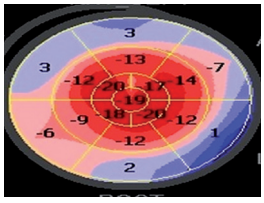

Figure 1

Conclusion: Longitudinal strain, especially the base-apex sub-endocardial longitudinal strain gradient, appears relevant for distinguishing LVNC from (Fig. 1). This functional approach might help for difficult anatomical cases.

P753 | BEDSIDE
Baseline hemodynamic characteristics of patients in the REDUCE elevated left atrial pressure in patients with heart failure trial

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Introduction: We measured the hemodynamic responses to exercise in patients

with heart failure and preserved ejection fraction (HFpEF) enrolled in a study evaluating the effects of an interatrial shunt device to lower left atrial pressure (the REDUCE LAP-HF trial).
Purpose: To determine the hemodynamic responses to exercise at baseline (pre-treatment) for HFpEF patients enrolled in the REDUCE LAP-HF trial.
Methods: Patients with HFpEF, as defined by LV ejection fraction (EF) ≥40%, New York Heart Association (NYHA) class II–IV, PAWP≥15 mmHg at rest or ≥25 during supine bike exercise, and CVP <15 mmHg at rest, were eligible for participation in this study. Pressures and cardiac outputs (CO, by thermodilution) were measured via standard right heart catheterization at rest and during symptom limited supine bike exercise. All tests were read at a central core laboratory.
Results: 64 patients qualified for the study. Mean age was 69±8.3 years and 65% were female. Patients exercised for an average of 7.3±3.1 mins to 42.5±18.3 Watts with an increase of heart rate from 69.3±14.4 to 95.8±18.4 bpm and an increase of CO from 5.5±1.6 to 8.7±2.6 L/min. CVP increased from 9.0±3.6 to 17.6±5.8 mmHg and PAWP from 17.4±5.2 to 34.3±7.4 mmHg. Consequently, the PAWP-CVP difference increased from 8.3±4.1 mmHg at rest to 16.7±6.5 mmHg at peak exercise. All differences listed above were significant at p<0.001.
Conclusions: HFpEF patients qualified for the REDUCE LAP-HF study had marked increases in PAWP and CVP during supine bicycle exercise. PAWP increased approximately twice as much as CVP so that the PAWP-CVP pressure gradient (the driving force for flow through an interatrial shunt) increased significantly. This suggests that the hemodynamic impact of such a shunt device would be significantly greater during exercise than at rest. Results of repeat hemodynamic exercise testing 6 months following shunt implant in these patients will elucidate the degree of PAWP reduction by this approach as well as its impact on exercise tolerance and morbidity.
Acknowledgement/Funding: Corvia Medical Inc.

P754 | BENCH
Septal motion in left bundle branch block: more wobbling with high afterload

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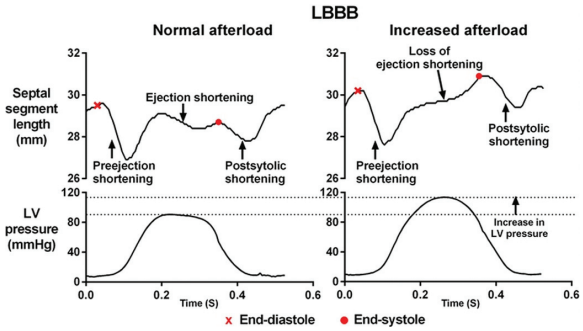
Background: In patients with left bundle branch block (LBBB) there is "wobbling" of the interventricular septum and deformation analysis shows typically three phases of contraction, (1) preejection shortening, (2) ejection shortening, and (3) postsystolic shortening (Figure).
Purpose: To investigate if increased afterload modifies septal contraction pattern in LBBB.
Methods: LBBB was induced by radiofrequency ablation in 6 anaesthetised dogs. Measurements were done at baseline and during increased afterload by aortic constriction. Septal circumferential segment length was measured by sonomicrometry and left ventricular (LV) pressure by micromanometer.
Results: Peak LV pressure increased from 91±9 to116±11 mmHg with aortic constriction (P<0.05). At baseline, septal preejection shortening was -7±4% and remained unchanged at -7±4% with aortic constriction. Shortening during LV ejection, however, was abolished and there was instead net lengthening from end-diastole to end-systole (1±2% with aortic constriction vs -4±3% without aortic constriction, P<0.05). Postsystolic shortening increased from -1±2 to -3±2% (P<0.05) with aortic constriction. The figure shows a representative experiment.



Septal response to increased afterload

Conclusions: Elevation of afterload during LBBB converted septal shortening to net lengthening during systole, indicating aggravation of septal dysfunction. This load dependency also implies that care should be exerted when using time delay between septal and LV lateral wall shortening as a marker of electrical dyssynchrony.

P755 | BENCH
Septal beaking in left bundle branch block induces right ventricular dysfunction

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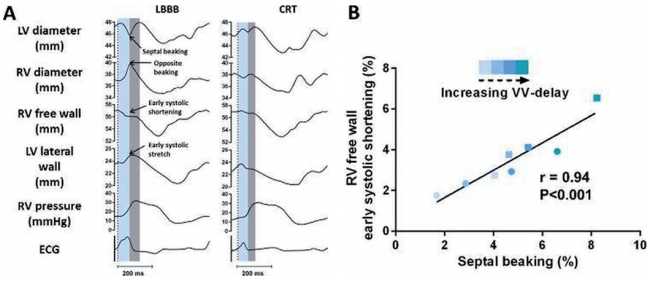
Background: We have previously demonstrated that left bundle branch block (LBBB) reduces right ventricular (RV) long axis function due to abnormal early systolic shortening in the RV free wall, and this contraction pattern is restored by cardiac resynchronisation therapy (CRT) (Figure A). We hypothesised that abnormal RV early systolic shortening in LBBB is a result of preejection leftward motion of the interventricular septum, named septal beaking or flash.
Purpose: To explore the mechanism of reduced RV work during LBBB.
Methods: Eight anaesthetised dogs with LBBB induced by RF-ablation received CRT. Pressures by micromanometer and dimensions by sonomicrometry were used to calculate myocardial shortening and work. In two additional dogs, measurements were also obtained during progressive interventricular (VV) conduction delay (4–16–32ms) and ultimately LBBB (44ms).
Results: In the eight dogs CRT improved RV function by reducing early systolic shortening in the RV free wall from 4±1 to 2±2% (P<0.01) (Figure A), however, total systolic shortening was unchanged at 8±3 vs 8±3%. Therefore, regional RV free wall work increased from 24±16 to 36±17 mmHg*mm (P<0.01). Septal work increased correspondingly from 8±60 to 91±50 mmHg*mm (P<0.01). With increasing VV-delay there was progressive increase of septal beaking and reduction of septal work (r=-0.95, P<0.001). Similarly, in the RV free wall, regional work was progressively reduced as RV early systolic shortening increased (r=-0.77, P<0.05). There was a significant correlation between the septal beaking and RV free wall early systolic shortening (Figure B). Furthermore, the magnitude of septal beaking correlated with the reduction of regional work in the RV free wall (r=-0.79, P<0.05).



Conclusion: The extent of early systolic shortening and reduced regional work in the RV free wall correlated with septal beaking in LBBB. This suggests that reduced RV free wall function in LBBB is a direct mechanical effect of septal beaking.

P756 | BEDSIDE
Temporal change of myocardial tissue character is associated with left ventricular reverse remodeling in patients with dilated cardiomyopathy: a cardiovascular magnetic resonance study

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Background: Left ventricular reverse remodeling (LVRR) related to favorable prognosis in patients with non-Ischemic dilated cardiomyopathy (DCM). However it has been difficult to predict who can achieve LVRR. Cardiac magnetic resonance (CMR) including late gadolinium enhancement (LGE) can detect myocardial damage, fibrosis, and edema.
Purpose: We investigated here the correlation between LVRR and temporal change in myocardial tissue characterization by CMR.
Methods: Sixty-eight patients with newly-diagnosed DCM who underwent CMR including LGE both at baseline and follow-up together with high-sensitive Troponin T (Hs-TnT) measurement and echocardiography. LVRR was defined as an increase in LVEF from ≥10% to a final value of ≥35% together with a decrease in LV end-diastolic diameter index (LVDDi) ≥10% at follow-up echocardiography. LGE score was defined by a signal intensity of ≥5 standard deviations above the remote reference myocardium mean. T2 ratio was defined was calculated by the ration of myocardial signal intensity and the erector spinae muscle signal intensity. Cardiac events after follow-up CMR examinations were defined as cardiac death, sudden death, implantation of ventricular assist device, readmission for HF exacerbation and major ventricular arrhythmias

Results: Follow-up LGE-CMR was performed 36±24 after discharge. 30 patients (44%) achieved LVRR during follow-up. There was not significant difference in LVEF (30±8% vs 33±8%; P=0.09) and LVDDi (38±5 mm/m^2 vs 36±6 mm/m^2; P=0.23) at baseline between patients with LVRR and those without. The change in LGE score (ΔLGE) was significantly lower in patients with LVRR than those without (-0.5%±3.4% vs. 3.0±7.4%; P=0.02). On the other hand, T2 ratio during the follow-up significantly reduced (1.95±0.48 vs 1.67±0.56; P<0.01); however, there was no significant difference in the change in T2 ratio between patients with LVRR and those without (-0.29±0.73 vs -0.27±0.66; P=0.88). Multivariate logistic analysis indicated that both of baseline LGE score (odds ratio; 0.78; 95% confidence interval (CI) 0.66 to 0.90; P<0.01) and ΔLGE (odds ratio; 0.77; 95% CI 0.61 to 0.92; P=0.01) together with QRS duration were independently associated with subsequent LVRR. Cardiac events occurred in 8 patients. Both LGE score (P<0.01) at baseline and ΔLGE (P=0.01) were significantly higher in patients with subsequent cardiac events than in those without. ΔLGE was significantly higher in patients positive for Hs-TnT than in those negative (P=0.04).
Conclusions: The temporal change in LGE-CMR score during the clinical course was significantly correlated with following LVRR, which showed an additive clinical value to the LGE score at baseline.

P757 | BEDSIDE
Excess pressure integral predicts long-term all-cause mortality in stable heart failure patients

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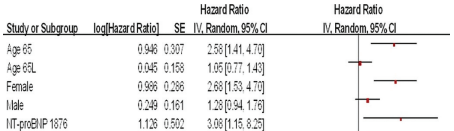
Background: Excess pressure integral (XSPI) derived from the reservoir wave analysis has been proposed as a novel indicator of cardiovascular dysfunction for predicting cardiovascular events in the treated hypertensive individuals. The present study investigated whether XSPI is useful in predicting the outcomes in stable heart failure patients.
Methods: We enrolled 168 heart failure patients (mean age 63±18 years, 111 men) with preserved (HFpEF) or reduced (HFrEF) left ventricular ejection fraction (LVEF), and 70 healthy controls. Tonometry-derived carotid pressure waveforms alone were analyzed according to the reservoir-pressure theory. XSPI was calculated by subtracting the reservoir pressure from the measured pressure waveform.
Results: XSPI in HFrEF (14.01±5.16 mmHg.sec) and HFpEF (13.90±5.05 mmHg.sec) were significantly higher than that in controls (11.01±3.67 mmHg.sec, both p<0.001). A total of 52 deaths incurred during a median follow-up of 10 years. XSPI was a significant independent predictor of total mortality after adjusting for age and sex (Hazard ratio (HR) = 2.259, 95% confident interval [CI], 1.02–5.02), and with further adjustments for LVEF, estimated glomerular filtration rate (eGFR) and NT-proBNP (HR=4.371, 95% CI, 1.24–6.10). In the subgroup analysis stratified by different baseline characteristics including age, gender, NT-proBNP, LVEF, and eGFR, a higher XSPI was consistently associated with a greater risk of total mortality.

	Hazard ratio	95% confident interval	p value
Univariate	3.053	1.48–6.31	0.003
Model 1	2.259	1.02–5.02	0.045
Model 2	2.747	1.24–6.10	0.013
Model 3	4.371	1.31–14.5	0.016

Model 1: adjust sex and age; Model 2: adjust sex, age, and left ventricular ejection fraction; Model 3: adjust sex, age, left ventricular ejection fraction, eGFR and NT-proBNP.



Subgroup analysis

Conclusions: In patients with stable heart failure, XSPI, a novel maker of cardiovascular dysfunction, was associated with the long-term risk of total mortality.

P758 | BEDSIDE
Normalisation of left ventricular systolic function following cardiac decompensation - frequency of occurrence, predictors and associated echocardiographic changes

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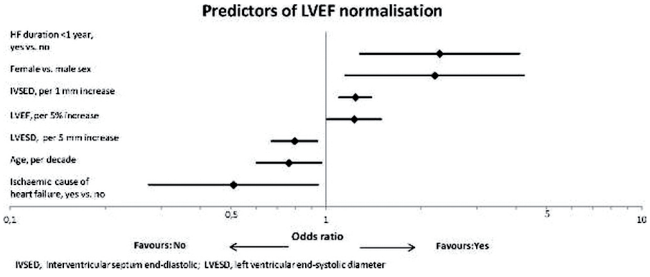
Introduction and aim: Improvement of left ventricular ejection fraction (LVEF) is associated with improved survival and reduced hospitalisation for worsening of heart failure (HF) in patients with systolic HF. However, the proportion of patients with systolic HF experiencing normalisation of LVEF (>50%) following acute cardiac decompensation (AHF), predictors of recovery and associated echocardiographic changes require further investigation.
Method and results: Out of 1022 participants in a heart failure program, 633 (66±12 years; 74.2% male; LVEF≤40% before discharge from hospital (BL)) entered the current post-hoc analysis since high quality echocardiograms were available at BL and after 6 months (FUP6), allowing unambiguous determination of LVEF (Simpson's biplane or monoplane method). Patients were grouped according to LVEF at FUP6 into "HF with normalised LVEF" (HFnEF; n=147, 23%) and "HF with persistently reduced LVEF" (HFrEF; n=486; 77%). HFnEF and HFrEF patients differed regarding the following characteristics: Age (64±14 vs. 66±12 years, p=0.02); sex (65 vs. 77% male, p=0.005); HF aetiology (arterial hypertension 19 vs. 12%, p=0.029; ischaemic HF 37 vs. 50%, p=0.011); HF duration <1 year (57 vs. 37%, p<0.001). Between BL and FUP6, LVEF increased significantly within both groups, from 32±7 to 56±5% (p<0.001) in HFnEF, and from 29±8 to 37±9% in HFrEF (p<0.001). Further differences in echocardiographic changes between HFnEF and HFrEF patients were (median [quartiles]): Left ventricular (LV) end-diastolic (ED) and end-systolic (ES) diameters (-3.0 [-9.0;1.3] vs. 0.0 [-7.0;4.0] mm, p<0.001, and -10.0 [-16.0;-2.0] vs. -3.0 [-10.0;3.0] mm, p<0.001, respectively); LVED and LVES volumes (-24.0 [-68.3;4.5] vs. -17.0 [-51.0;14.0] ml, p=0.041, and -44.5 [-62.0;-18.8] vs. -20.0 [-50.0;2.5] ml, p<0.001, respectively); A-wave (+16.0 [-0.8;39.3] vs. +7.0 [-7.8;30.8] cm/sec, p=0.006); early diastolic peak of mitral annular velocity (+1.0 [-1.0;4.0] vs. 0.0 [-4.0;2.0] cm/sec, p=0.004). The figure shows independent predictors of LVEF normalisation (multivariable regression analysis).



IVSED, Interventricular septum end-diastolic; LVESD, left ventricular end-systolic diameter

Conclusion: In 23% 6-month survivors of AHF with serial high quality echocardiograms LVEF normalised between BL and FUP6. HFnEF patients showed not only significant LV reverse remodeling, but also improved LV diastolic function. Several independent predictors were identified for HFnEF and HFrEF, respectively, thus allowing for early risk stratification and tailored, risk-adapted care after AHF.

P759 | BEDSIDE
Outcome after implantation of an ImpellaCP microaxial-flow pump in patients with cardiogenic shock

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Background: The outcome of patients in cardiogenic shock is poor. The Impella Circulatory Support System has been developed to unload the left ventricle in patients with severely reduced systolic function and to maintain basic circulation in such patients. The ImpellaCP is an active support system providing up to 4 liters per minute of haemodynamic support.
Purpose: To assess cardiovascular outcome after left-ventricular support in cardiogenic shock.
Methods: From January 2013 to December 2015 108 patients who received an ImpellaCP microaxial pump for treatment of cardiogenic shock were enrolled in our registry. Data on baseline characteristics and in-hospital treatment including cardiovascular risk factors, details on coronary angiography, hemodynamic parameters, and laboratory parameters were documented in detail.
Results: Mean age was 60±14 years, mean support time was 104±90 hours. Out-of-hospital cardiac arrest had occurred in 35% of the patients, additive right-ventricular failure (cardiac index <1.5 and CVP >18 mmHg) was present in 41%. In-hospital survival in this severely diseased cohort was 60%, with 46% having recovery and 13% receiving a permanent left-ventricular assist device. Out-of-hospital cardiac arrest (45% in non-survivors, 28% in survivors) as well as intrahospital cardiac arrest (37% in non-survivors, 15% in survivors) were associated with increased mortality rates (out-of-hospital arrest 69%, intrahospital arrest 77%, p<0.05 vs. no arrest). Mortality in shock patients without out-of-hospital cardiac arrest was 50%. In patients requiring an ImpellaCP for left-ventricular failure in the absence of right-ventricular failure, mortality was 31%. Right-ventricular failure was more often observed in non-survivors (66% in non-survivors, 13% in survivors, p<0.001). In patients with ischemic acute LV failure, implantation of the ImpellaCP before revascularization was associated with a significant mortality benefit.
Conclusion: Implantation of an ImpellaCP is performed more frequently in cardiogenic shock patients. Additive right-ventricular failure as well as out-of-hospital

or intrahospital resuscitation are factors associated with an increased mortality in this real world cohort.

P760 | BEDSIDE
The effect of the GLP-1 receptor agonist liraglutide on systolic function in patients with coronary artery disease and type 2 diabetes: a randomized double-blind placebo-controlled cross over study

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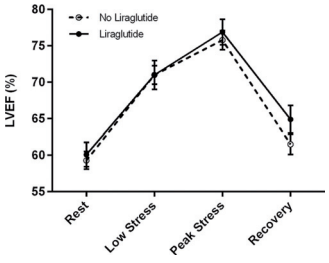
Background: Patients with type 2 diabetes have increased risk of cardiovascular mortality and cardiac dysfunction. Glucagon-like-peptide-1 (GLP-1) has shown to improve myocardial function and to protect against ischemia.
Purpose: We hypothesized that treatment with the GLP-1 receptor agonist (GLP-1 RA), liraglutide, will improve the systolic function of the left ventricle (LV) in patients with type 2 diabetes and coronary artery disease (CAD).
Methods: Forty-one subjects were randomized to receive liraglutide plus metformin or placebo plus metformin in this double-blind, placebo-controlled, cross-over 12 plus 12 week intervention study. Each subject underwent contrast-enhanced dobutamine stress echocardiography (DSE) and exercise tolerance test at the start and finish of each study-phase.
Results: Thirty subjects completed the study. Liraglutide, when compared to placebo, induced a significant weight loss (-3.2 kg; $p<0.01$) and reduction in glycated hemoglobin (-0.4%; $p<0.01$). No significant changes in LV ejection fraction during DSE at rest (0.5%; p=0.71), at low stress (0.03%; p=0.98), at peak stress (1.1%; p=0.62), or during recovery (4.1%; p=0.10) were observed. No significant changes in wall motion score index were observed: rest (0.009; p=0.49), low stress (0.007; p=0.72), peak stress (-0.04; p=0.29), recovery (0.001; p=0.96). Global longitudinal strain (0.63%; p=0.23), strain rate (0.01 sec-1; p=0.71) and maximal exercise capacity estimated by metabolic equivalents (0.29; p=0.244) were not affected by liraglutide as compared to placebo.

Liraglutide versus Placebo on LVEF

	Liraglutide	Placebo	Difference	95% CI	p-value
LVEF rest	0.7 (6.3)	0.1 (5.0)	0.5 (7.8)	-2.4 to 3.5	0.71
LVEF low stress	0.3 (6.3)	0.2 (6.5)	0.03 (8.6)	-3.3 to 3.3	0.98
LVEF peak stress	0.9 (6.9)	-0.2 (7.3)	1.1 (10.8)	-3.5 to 5.7	0.62
LVEF recovery	4.2 (7.1)	0.2 (9.0)	4.1 (12.8)	-0.8 to 8.9	0.10

LVEF, left ventricular ejection fraction.



Conclusions: In patients with CAD and newly diagnosed type 2 diabetes mellitus, the GLP-1 RA liraglutide had a neutral effect on the systolic function of the LV without any improvement in exercise capacity.
Acknowledgement/Funding: Novo Nordisk A/S, The Danish Heart Foundation, The AP Moller Foundation, Amager Hospital, Hvidovre Hospital, Bispebjerg Hospital

P761 | BEDSIDE
The ratio of the bilateral-filling pressure (RAP/PCWP) is an important prognostic factor in chronic heart failure with low cardiac index

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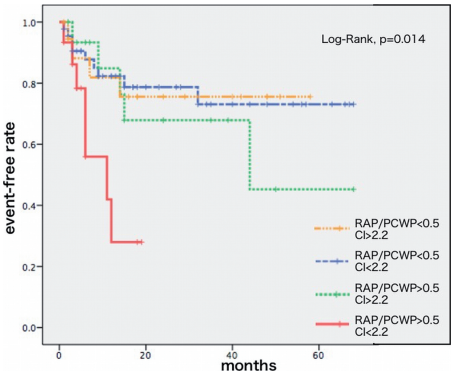
Background: The right ventricular filling pressure (i.e. right atrial pressure: RAP) usually correlates to the left ventricular filling pressure (i.e. pulmonary capillary wedge pressure: PCWP) with about 1 to 2 ratio in left-sided chronic heart failure (CHF). However many patients show discordance probably due to the presence of (i) right ventricular (RV) dysfunction, (ii) pulmonary arterial diseases, (iii) severe pulmonary diseases, and (iv) left-to-right cardiac shunt diseases. Hence, in CHF patients without (ii), (iii), or (iv), we can analyze simply (i) RV function using the parameter of right heart catheterization (RHC).
Purpose: To clarify whether the ratio of bilateral filling pressure (RAP/PCWP ratio) correlates to RV function and predicts adverse events in left-sided CHF. And, we surveyed whether the results are influenced by the cardiac index.
Methods: Among the consecutive patients who underwent RHC and met the criteria of post-capillary pulmonary hypertension: mean pulmonary arterial pressure $\geq$25 mmHg and PCWP $\geq$15 mmHg, we excluded following patients to extract simply left-sided CHF: those who were diagnosed with (ii) pulmonary arterial diseases, (iii) severe pulmonary diseases, (iv) left-to-right cardiac shunt diseases; who received RHC for preoperative study of cardiovascular surgery; or who received hemodialysis. Finally we assessed 95 patients who underwent RHC for evaluation of CHF, and analyzed parameter of RHC, laboratory datas, findings of echocardiography, and the adverse events: death, HF readmission, and left ventricular assist device (LVAD) implantation. Event-free rates were assessed with Kaplan-Meier analysis using log-rank tests for patients divided into 4 groups according to RAP/PCWP ratio (<0.5 or ≥0.5) and cardiac index (<2.2 or ≥2.2ml/min/m^2).
Results: The average patients age was 64±14, 75% of them were male. 9 patients (9.5%) died for cardiovascular disease, 15 (15.8%) readmitted for HF, and 3 (3.2%) received LVAD implantation. RAP/PCWP ratio was inversely correlated with RV stroke work index (r=-0.49). Cox proportional hazards regression analysis revealed that RAP/PCWP ratio, MR grade, and cardiac index were significant predictive factors of the adverse events. The Kaplan-Meier analysis showed that patients with high RAP/PCWP ratio and low cardiac index had the highest event-rate significantly (log-rank test, p=0.014, figure).



Kaplan-Meier event-free curve

Conclusion: RAP/PCWP ratio correlates to RV function in CHF patients. Moreover, this ratio predicts the adverse events especially in patients with low cardiac index.

P762 | BEDSIDE
Characterization of left ventricular energy loss and its gender difference in healthy adults using vector flow mapping: a preliminary results

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Background: Energy loss (EL) is a new hemodynamic index to assess the cardiac function, quantifying the friction between blood flow and wall shear flow energy due to blood viscosity by converting the kinetic energy into heat. EL may have relation to the cardiac workloads.
Purpose: We aimed to characterize EL within left ventricle (LV) of health adults and its dependence with age, gender, clinical data and echocardiographic parameters.
Methods: Sixty-three healthy adults were enrolled in the study. We analyzed EL of LV frame by frame using color Doppler images of standard apical 3-chamber dynamic view on the offline VFM workstation. The average EL during systole and diastole were calculated respectively. The correlation between EL and age,

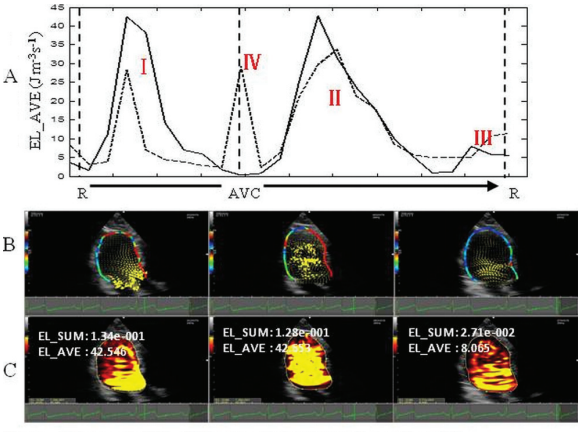

Figure. A)Two typical EL_AVE curves during one cardiac cycle and B) flow vector image and C) its corresponding EL mode image of the three major peaks

clinical data and echocardiographic parameters was calculated. Averaged EL between men and women was compared.
Results: The average EL was 11.07±5.53 (J m^{-3} s^{-1}) for systole and was 11.74±5.54 (J m^{-3} s^{-1}) for diastole, respectively. In healthy adults, EL within LV shows three peaks during one cardiac cycle including two higher peaks in rapid ejection phase and rapid filling phase, one weaker peak during the period from atrial systolic phase to iso-volumetric contraction phase. In some cases, a fourth peak appeared at the frame that the aortic valve just closed. The average EL during systole had a positive correlation with aortic velocity time integral (AVOTI, r=0.614) and A wave peak velocity, and a negative correlation with isovolumetric contraction time (IVCT). Meanwhile the average EL during diastole had positive correlation with E wave peak velocity (r=0.602) and HR, and negative correlation with height and IVCT. For female the average systolic EL was 12.27±6.52 (J m^{-3} s^{-1}) and average diastolic EL was 13.83±5.45 (J m^{-3} s^{-1}). For male the values were 8.95±4.37 (J m^{-3} s^{-1}) and 9.47±3.30 (J m^{-3} s^{-1}).
Conclusion: EL in LV changes regularly during cardiac cycle. The average EL during systole was almost equal to average EL during diastole. The average systolic EL has a high correlation with AVOTI and the average diastolic EL has a high correlation with E wave peak velocity. Women have higher average EL than men both in systole and diastole. By recognizing the EL characterization of normal adults, the variation in EL may reflect cardiac dysfunction. These were preliminary result only and may warrant further researches.

P763 | BENCH
Mutation spectrum in Russian patients with left ventricular non-compaction

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Introduction: Left ventricular non-compaction (LVNC, MIM#300183) is a cardiomyopathy characterized by prominent trabeculation of left ventricular mostly in the ventricular apex, lateral wall, and ventricular septum areas. The origin and genetic background of this cardiomyopathy is still controversial. Mutations in more than 20 genes were found in LVNC patients but all those genes were assessed as causes for other forms of cardiomyopathy. The clinical presentation varies from asymptomatic course to severe heart failure. Nowadays no genotype-phenotype correlations for LVNC were found, and specified recommendations for DNA-diagnostic are absent.
Materials and methods: We have had under the observation 50 symptomatic probands with LVNC (27 men), median age 41 y.o.; six of them have underwent the heart transplantation due to terminal heart failure. Clinical examination included echo-cardiography, cardiac MRI and 24-hours Holter monitoring of ECG. Mutation screening of the MYH7, MYBPC3, DTNA, ACTC1, TAZ, CASQ, ZASP, TAZ, MYL3, TNNT2, TNNI3, MYL2, and TPM1 genes was performed for 32 probands. All variants found by NGS (Ion Torrent PGM) were confirmed by bi-directional Sanger sequencing. Possible functional role of missense VUCS was evaluated by PolyPhen2 and SIFT resources.
Results: In our patient group autosomal-dominant inheritance trait was the most frequent, though sporadic cases were also present. In the group of 32 probands screened for mutations in 13 genes, seven pathogenic genetic variants (21% of cases) were identified. Three of 6 patients with terminal heart failure were genotype-positive. Three mutations were found in MYH7 gene; 2 mutations and 1 possibly pathogenic VUCS - in MYyBPC3 gene; and 1 mutation was detected in DTNA gene.
Conclusion: Mutations in the MYH7 and MyBPC3 genes are the most common genetic defects in the symptomatic LVNC Russian patients. Those genes are also the leading causes of HCM and some severe DCM forms. Genetic relationship of those cardiomyopathies raises the questions whether LVNC is distinct clinical entity or variant of manifestation of other cardiomyopathy.

P764 | BENCH
Abnormal left and right ventricular peak systolic strain and myocardial perfusion reserve in young patients with obstructive sleep apnea

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Introduction: Obstructive sleep apnea (OSA) is an important public health issue due to the associated high cardiovascular morbidity and mortality.
Purpose: To obtain better insight into the underlying pathophysiologic mechanisms of association between obstructive sleep apnoea and increased cardiovascular burden.
Methods: We prospectively recruited OSA patients (n=163, 20 females, age 49.6±9.6 years; BMI 29.6±4.5; Epworth Sleepiness score 10±4) undergoing first time polysomnography. The patients received a 2-D Doppler and Dipyridamol-stress myocardial contrast echocardiography, cardiac CT-scan (for calcified and non-calcified plaque), Carotid artery intima media thickness (IMT) measurement and Brachial artery vascular reactivity assessment by flow mediated dilatation (FMD).
Results: Patients were divided into groups according to the apnea-hypopnea index (AHI). Group 1 (n=30) with AHI <15 and without cardiovascular comorbidity was considered as control, group 2 (n=77, OSA healthy) with AHI >15 and without cardiovascular comorbidity and group 3 (n=56, OSA unhealthy) with AHI >15 and concomitant cardiovascular comorbidity (primarily hypertension). There were significant differences in heart rate, interventricular septum thickness, IMT, inflammatory parameters, triglyceride levels and coronary plaque burden between group 1 and patients with AHI >15 ($p<0.05$ for all). Furthermore, graded significant differences were observed for fibrinogen, HDL-cholesterol, triglyceride levels, left ventricular myocardial performance index (LVMPI), left ventricular mass index (LVMI), left atrial volume index (LAVI), E/E' ratio, global longitudinal peak systolic strain of the left (GLPSS) and right ventricles (RVLS), as well as myocardial contractile and perfusion reserve ($P<0.02$ for all). Linear regression models showed that AHI and lowest oxygen saturation were associated with increased LV mass index and abnormal myocardial strain and perfusion. After adjustment for age and BMI, multivariate analysis showed that presence of significant OSA (AHI >15) and abnormal FMD predicted coronary plaque burden ($p<0.014$), abnormal global LV and RV strain was associated with presence of any coronary plaque ($p=0.024$), abnormal FMD predicted reduced contractile reserve ($p=0.0078$) and combined significant OSA and lowest oxygen saturation predicted reduced myocardial perfusion reserve.

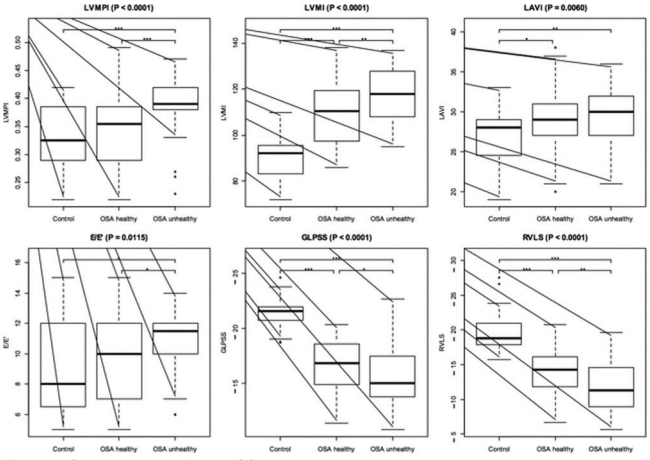

Figure 1: Graded Abnormalities in OSA

Conclusion: Young OSA patients with or without associated cardiovascular comorbidity show significant and graded subclinical alterations in cardiac structure, functional and perfusion reserve with worsening AHI. Early recognition and appropriate treatment of OSA is imperative in reducing the OSA associated cardiovascular morbidity and mortality.

P765 | BEDSIDE
Prognostic impact of antegrade diastolic pulmonary artery flow in adult cases

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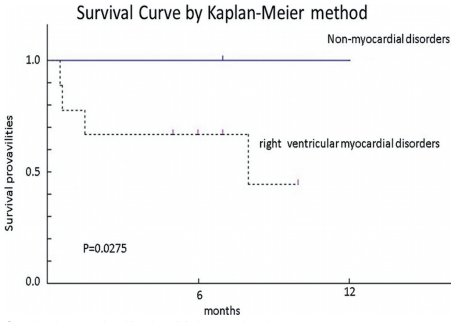
Background: It has been known that end-diastolic opening of pulmonary valve and subsequent antegrade diastolic pulmonary artery flow (ADPAF) reflect restrictive right ventricular (RV) physiology in children. However, the appearance of ADPAF is uncommon phenomenon, and the study of ADPAF has been strangely neglected in adult cases.
Purpose: The aim of this study was to clarify the underlying mechanism of ADPAF, and to estimate its prognostic value in adult cases. Specifically, we examine whether ADPAF can reflect the restrictive right ventricular physiology in adult patients with heart failure.
Methods and results: We studied 23049 consecutive adult patients who underwent echocardiography in our hospital from 2008 to 2015. ADPAF was found in 17 patients (0.07%) with right-sided heart failure. The appearance of ADPAF has less relevant to the duration of heart failure and New York Heart Association (NYHA) severity [(NYHA class I/II (n=11) and class III/IV (n=6)]. Nine patients (53%) of them had right ventricular myocardial disorders due to cardiomyopathy, myocardial infarction or congenital heart diseases, and 8 patients had non-myocardial disorders comprising constrictive pericarditis, tamponade and severe pulmonic regurgitation. On cardiac catheterization, simultaneous recording of right ventricle and pulmonary artery pressures revealed the dip-and-plateau configuration of right ventricular diastolic pressure which exceeded pulmonary artery pressure during atrial systole. Convincingly, none of them showed atrial fibrillation. These data suggest that ADPAF reflects the inversion phenomenon between right ventricle and pulmonary artery pressures under the condition of right ventricular restrictive physiology. During 19 months follow-up period, 5 patients (29%) had died or undergone implant of ventricular assist system. Notably, patients with right ventricular myocardial disorders had worse prognosis and re-

sulted in high mortality (44%) compared with patients with non-myocardial disorders (0%).



Survival curve by Kaplan-Meier method

Conclusion: ADPAF could be a sign of right ventricular restriction in adult cases, and suggest a less favorable prognosis in patients with right ventricular myocardial disorders.

P766 | BEDSIDE
Importance of acute hemodynamic effects of inhaled nitric oxide in optimization of heart failure treatment in patients with pulmonary hypertension owing to left heart disease

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Background: Pulmonary hypertension (PH) owing to left heart disease (LHD) is one of the major categories of the disorder. We have recently reported that elevated pulmonary vascular resistance (PVR) in patients with post-capillary PH (pc-PH: defined as mean pulmonary arterial pressure (mPAP)≥25mmHg and pulmonary capillary wedge pressure (PCWP)>15mmHg) is associated with poor prognosis compared with those with no PH or pc-PH without elevated PVR. Although new treatment is required for targeting pulmonary vascular disease (PVD), there is a concern about raising PCWP. In this study, we thus examined acute hemodynamic effects of inhaled nitric oxide (iNO) in patients with PH owing to LHD and addressed whether optimal heart failure (HF) treatment ameliorates pc-PH.
Methods: We examined a total of 114 consecutive pc-PH patients owing to LHD (62±14 [SD] years, M/F 72/42, NYHA≥2), who underwent acute vasoreactivity test in response to iNO (40 ppm for 10 min) during right heart catheterization at the Tohoku University Hospital from June 2011 to Dec 2015. Among them, cardiomyopathy (CM) was noted in 66 patients, including dilated cardiomyopathy in 18 and hypertrophic cardiomyopathy in 13. The remaining 48 patients had valvular heart disease (VHD), including aortic valvular disease in 20 and mitral valvular disease in 20, and 10 out of them had previous surgical repair. PVD was defined as diastolic pressure gradient ≥7mmHg and/or pulmonary vascular resistance (PVR) >3WU, as defined by the ESC/ERS guidelines. We also evaluated right ventricular systolic pressure (RVSP) by echocardiography after optimization of HF treatment such as medications and valvular surgery.
Results: At baseline, PVD was noted in 36, including CM in 19 and VHD in 17. iNO significantly decreased mPAP (-1.5±0.3 mmHg; P<0.0001) and PVR (-0.82±0.12WU, P<0.0001) without altering cardiac output (0.05±0.04 L/min; P=0.17). However, iNO also increased PCWP in both CM and VHD groups (1.2±0.4 mmHg; P=0.008, 1.6±0.7 mmHg; P=0.02, respectively). pc-PH patients with PVD were re-classified as having pc-PH without PVD in 17 and no PH in 2 by iNO and the remaining 17 patients had fixed PVD. When patients were divided into 2 groups according to the PCWP response to iNO (PCWP deteriorating and non-deteriorating groups), those in the PCWP deteriorating group tended to have higher mPAP and PVR compared with those in the non-deteriorating group (P=0.054, P=0.08, respectively). After the optimal medical treatment for 7.6 months, RVSP was significantly decreased in both CM and VHD patients (-8±3mmHg, P=0.04, -19±8mmHg, P=0.01, respectively). However, in CM, significant reduction in RVSP was noted only in pc-PH patients without PVD (-8±3mmHg, P=0.03).
Conclusions: These results indicate that elevated PVR in patients with pc-PH owing to CM could be a novel therapeutic indication for NO-related pulmonary vasodilators in the current practice of HF.

P767 | BEDSIDE
Pulmonary hemodynamics in heart failure with reduced and preserved ejection fraction: similarities and disparities

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Background: The current evidence on pulmonary hypertension (PH) due to left heart does not make any distinction between heart failure with reduced ejection fraction (HFrEF) as opposed to patients with heart failure and preserved ejection fraction (HFpEF). Specifically, the pathophysiological and prognostic role of pulmonary vascular compliance (PCa) and the diastolic pulmonary gradient (DPG) in HFrEF vs HFpEF is still under scrutiny.
Purpose: 1) To compare the pulmonary hemodynamics in the two groups of HF patients. 2) To evaluate the impact of PCa vs DPG on survival.
Methods: We retrospectively reviewed the charts of 86 patients with HFpEF and 167 with HFrEF. The independent association between PCa and DPG and prognosis was assessed by means of Cox proportional hazard model.
Results: The trans-pulmonary gradient and the DPG were significantly higher in patients with HFpEF vs HFrEF (DPG: 6.1±7.1 vs 1.8±4.5, p<0.001). PCa was significantly lower in patients with HFpEF vs HFrEF (1.7±0.7 vs 1.9±1.2, p<0.001) while pulmonary vascular resistance (PVR) tended to be higher although not statistically significant. Using different preset cutoffs in HFrEF and HFpEF, PCa was a significant predictor of survival in both HFrEF and HFpEF whereas DPG did not show any impact on survival in either groups.
Conclusions: Findings suggest that the pulmonary circulation tree in patients with HFpEF may be stiffer than in HFrEF with higher DPG and lower PCa. This hypothesis finds a solid background in the higher prevalence of comorbidities and related systemic proinflammatory state leading to endothelial inflammation and dysfunction. PCa rather than DPG is a better predictor of survival in both groups of patients.

P768 | BEDSIDE
Cardiac mechanics and circulating Nt-proBNP level in current 4-tiered classification of ventricular geometry and hypertrophy in asymptomatic population: does concentricity matter?

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Background: Left ventricular hypertrophy (LVH) as a more severe phenotype of cardiac remodeling has been proposed as a clinical risk to heart failure development. However, the mechanistic link between cardiac deformations analysis in concentric (cLVH) or eccentric form LVH (eLVH) in Asians remains largely unknown.
Methods: A total of 4,050 asymptomatic participants (age: 49.8±10.8 years, 35% female) from annual cardiovascular survey participated this study. Conventional echocardiography, deformation measures (speckle-tracking), and N-terminal Pro-brain natriuretic peptide (Nt-ProBNP) were obtained. The participants were assigned into 4 groups based on gender-specific cardiac mass index and relative wall thickness (RWT) as: Normal, Concentric Remodeling (CR), eLVH, and cLVH.
Results: A graded reduction of global longitudinal strains (GLS), rather than circumferential strains (GCS) were observed (Table 1) across 4-tiered LV geometry classifications with compensatory increase in cardiac torsion. cLVH demonstrated lowest GLS, but highest cardiac twist/torsion (all p<0.05). Compared to Normal

Abstract P768 – Table 1

	Normal geometry (n=3,192)	Concentric remodeling (CR) (n=639)	Eccentric LVH (eLVH) (n=144)	Concentric LVH (cLVH) (n=75)	p value[#]
GLS-4CH, %	–20.17±1.97	–19.82±2.14[†]	–19.21±1.54[†§]	–18.52±1.93[†§*]	<0.001
GLS-3CH, %	–20.26±2	–20.03±2.14[†]	–19.25±1.48[†§]	–18.58±1.81[†§*]	<0.001
GLS-2CH, %	–20.43±2.01	–20.09±2.12[†]	–19.51±1.55[†§]	–18.75±1.9[†§*]	<0.001
GLS-average, %	–20.28±1.85	–19.95±2.04[†]	–19.31±1.31[†§]	–18.31±2.47[†§*]	<0.001
GCS-MV, %	–18.26±2.24	–18.41±2.41	–18.24±2.43	–18.78±2.39	0.157
GCS-PM, %	–21.59±4.72	–21.89±5.02	–21.31±5.3	–22.65±5.07	0.121
GCS-apex, %	–24.01±4.69	–24.57±5.03[†]	–24.48±4.54	–25.04±5.23	0.015
GCS-average, %	–21.29±3.62	–21.61±3.85	–21.22±3.88	–22.11±4.08	0.061
Nt-ProBNP, pg/mL (median, 25th–75)	27.5 [12.9–51.9]	24.3 [9.8–48]	49.4 [28.1–81.6][†§]	77.6 [32.5–133][†§*]	<0.001
Cardiac twist, degree	13.54±5.24	14.82±5.71[†]	13.6±5.45	15.38±5.9[†]	<0.001
Cardiac torsion, degree/cm	2.16±0.88	2.39±0.99[†]	2.33±0.96	2.57±1.04[†]	<0.001

[#]Kruskal-Wallis H test with post hoc analysis, after adjusting for baseline clinical covariates, [†]p value<0.05 vs Normal geometry; [§]p value<0.05 vs Concentric remodeling (CR); *p value<0.05 vs Eccentric LVH (eLVH).

geometry, eLVH and cLVH had nearly 2% and 1% reduction in GLS. Finally, both cLVH and eLVH also showed similarly elevated Nt-ProBNP (all p<0.001).
Conclusion: In the asymptomatic Asians, concentric LVH carries worst and meaningful reduction of certain systolic function than eccentric LVH or remodeling. This finding indicates an urgent need to discriminate different phenotypic LVH in clinical practice, thus for timely therapeutic intervention.

P769 | BEDSIDE
Combining peak mitral inflow and annular velocities with left atrial strain improves estimation of left ventricular filling pressure

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Introduction: Classification of left ventricular (LV) filling pressure as normal or high using E/e' below 8 or above 15, respectively, results in a large number of unclassified patients in the intermediate range. Peak left atrial (LA) strain during left ventricular (LV) systole has been shown to correlate with LV filling pressure.
Purpose: We tested if combining E/e' and LA strain would improve estimation of LV filling pressure.
Method: In 58 patients we recorded pulmonary capillary wedge pressure, an indirect estimate of LV filling pressure, while simultaneously acquiring echocardiographic images. LA strain was assessed by speckle tracking echocardiography. Patients were first classified using E/e' alone (average of septal and lateral e') (Fig. 1a). Optimal cut-off-value for LA strain to classify normal or increased LV filling pressure, was found by ROC-analysis (Fig. 1b). Patients were subsequently classified combining E/e' and LA strain as shown in the algorithm in Fig. 2.
Results: The number of wrongly classified patients using E/e' alone, was very small (2%), but came at a price of a large proportion of unclassified patients (40%), (Fig.3.). Combining E/e' with LA strain, correctly classified 88% of the patients, reduced the number of unclassified to 3, while 9% were wrongly classified (Fig. 3).

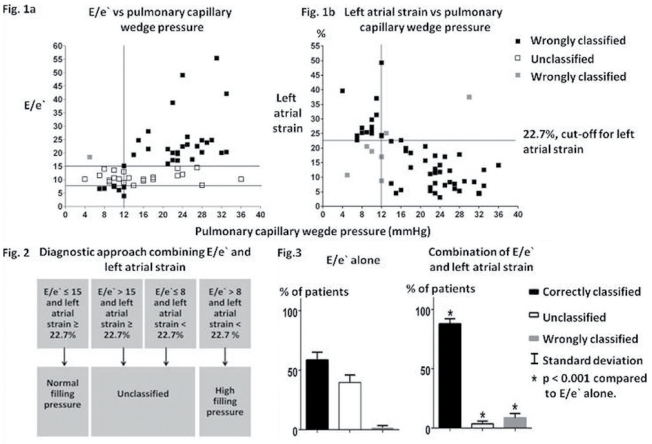

Fig.1a: Classification using E/e`: >15 ⇨ high LV filling pressure; ≤ 8 ⇨ normal LV filling pressure; 8-15 ⇨ unclassified.
Fig.1 b:Classification using left atrial strain: < 22.7% ⇨ high LV filling pressure; ≥ 22.7% ⇨ normal LV filling pressure.
Fig.2: Diagnostic approach combining E/e` and left atrial strain to estimate LV filling pressure.
Fig. 3: Ability to correctly classify patients using E/e` alone (left) compared to the combinatation of E/e` and left atrial strain (right).

Conclusion: Combining E/e' and LA strain in the evaluation of LV filling pressure, significantly improved the ability to correctly classify patients, while there was a modest increase in the number of wrongly classified patients. Our results suggest that LA strain should become part of the echocardiographic evaluation of patients with suspected heart failure.
Acknowledgement/Funding: South-Eastern Norway Regional Health Authority

P770 | BEDSIDE
Predictors of transition of preclinical diastolic dysfunction to heart failure with preserved ejection fraction in patients with metabolic syndrome

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Preclinical diastolic dysfunction (PDD) remains poorly understood and while it may progress to the heart failure with preserved ejection fraction (HFpEF) the predictors of this transition are yet to be defined.
Methods: We followed up for 3 years 228 patients (pts) with metabolic syndrome (NCEP-ATP III 2001 criteria) and PDD, mean age 67±8 years (118 female). All pts had an impaired relaxation transmitral patterns and E/e' 8–13 at rest on echocardiography (EchoCG), normal NT-proBNP values, and systolic pulmonary artery pressure (sPAP) ≤30mmHg. PDD was defined as LV impaired relaxation at stress EchoCG if E/e' ≥13, transmittal E wave deceleration time reduction >50ms, systolic pulmonary artery pressure (sPAP) increase >30mmHg, and patients remained asymptomatic. EchoCG measurements of maximal left atrial (LA) volume index (LAVi), right ventricular E/e' (E/e'RV), left ventricular global strain (LVGS), LA strain (LASt) by speckle trakcing, mean values of left atrial maximal strain rates in systole (SSr) and both phases of diastole (ESr, ASr) at the atrial septum and lateral wall, LA stiffnes index (LASi) as E/e'LV/LASt, intraatrial (INAD) and interatrial (INTAD) dyssynchronies were obtained at baseline and 3 years follow up. INAD and INTAD were assessed by strain rate imaging (SRI) as the ASr time delay of the LA septal and lateral walls (INAD) or the RA and LA lateral walls (INTAD).
Results: 84 pts (37%) developed HFpEF during follow up. Pts with HFpEF had less LVGS, SSr, ESr, and greater values of systolic BP (SBP), LAVi, ASr, E/e'RV, LASi, sPAP, INAD, and INTAD at baseline compared with pts without further HFpEF transition: (SBP 145±18mmHg vs 134±12, p<0.05; LVGS -16.2±2,1% vs -17.4±2.4, p<0.05; SSr 0.8±0.2 1/s vs 0.6±0.1, p<0.03; ESr 0.7±0.2 1/s vs 0.5±0.1, p<0.03; Asr 0.9±0.3 1/s vs 0.7±0.2, p<0.02; E/e'RV 3.9±1.3 vs 5.6±1.9, p<0.01; LASi 0.4±0.1 vs 1.0±0.4, p<0.01; sPAP 38±5 mmHg vs 43±6, p<0.01; INAD 23.8±8.4 ms vs 34±9.1, p<0.01; INTAD 27.6±8.8 ms vs 37.5±9.3, p<0.01). BMI, glucose levels and diastolic BP values did not differ between groups at baseline and follow up. Logistic regression analysis defined SSr, ESr, ASr, E/e'RV, sPAP, LASi, INAD and INTAD as an independent predictors of HFpEF.
Conclusion: PDD transition to HFpEF appears to be frequent. E/e'RV, sPAP, inter- and intraatrial dyssynchrony, LA stiffness as well as other SRI parameters predict the progression of PDD to HFpEF in pts with metabolic syndrom.

P771 | BEDSIDE
Left atrial compliance predicts limited exercise in patients with HFpEF and right ventricular dysfunction

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Background and aim: The power of left atrial (LA) and right ventricular (RV) measurements in predicting exercise capacity and clinical outcome in heart failure (HF) patients with preserved ejection fraction (HFpEF) is not fully understood. The aim of this study was to assess the predictors of exercise capacity in patients with HFpEF and RV dysfunction.
Methods: In 138 consecutive patients with HFpEF (age 62±9 years, NYHA class I–III, LV EF ≥45), a complete echocardiographic study was performed. LA compliance was calculated from the formula [LAV max – LAV min/LAV min × 100]. The exercise capacity was assessed using six-minute walk test (6MWT). TAPSE values divided patients into HFpEF with RV dysfunction (n=37) and HFpEF with normal RV function (n=101) groups.
Results: Patients with HFpEF and RV dysfunction were older (p=0.04), had higher NYHA class (p=0.003), limited 6MWT (p=0.03), increased LV mass (p=0.001), decreased septal and lateral MAPSE (p<0.001, for both), increased LA maximal (LAVI max) and minimal volume index (LAVI min) (p=0.04 and p=0.002, respectively) and impaired LA compliance (p=0.003) compared with those with normal RV function. In multivariate analysis, only LA compliance predicted limited exercise (OR = 0.982, 95% CI 0.966–0.999, p=0.037). A LA compliance <60% was 88% sensitive and 61% specific (P=0.004), having an area under the ROC of 0.76 in predicting exercise capacity.
Conclusions: HFpEF patients with RV dysfunction have impaired LA compliance, despite normal size. The LA compliance is the best predictor of limited exercise in these patients, a finding that suggests the need for routine assessment of LA for better explanation of symptoms and possibly treatment of these patients.

P772 | BEDSIDE
The potential of daily high intensity training for exercise interventions in patients with heart failure with preserved ejection fraction

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Background: Heart failure (HF) with preserved ejection fraction (EF) is a common condition with high morbidity and mortality. Still no pharmacological treatment has been identified yet. Physical activity prevents the development of HF with reduced EF and improves symptoms and quality of life (QoL) in prevalent HF irrespective of EF.
Purpose: The aim of this study was to determine the association of physical activity (amount and intensity) on phenotype including exercise performance in patients with HF with preserved EF.
Methods: 422 patients (Aldo-DHF trial) with stable HF with preserved EF were investigated (52% women, age 67±8 years). All patients underwent detailed cardiopulmonary exercise testing (CPET) and echocardiography. Daily physical activity and physical function in QoL were assessed by self-reporting questionnaires (KöBet, SF-36). Exercise performance was measured by 6-minute walk test and CPET (peak oxygen uptake, peak VO2). Patients were classified according to the amount and intensity of physical activity and the association of physical activity

and submaximal/maximal exercise capacity, diastolic function and QoL was analysed.
Results: Total physical activity (MET hours per week) was positively correlated with 6-minute walking distance ($p<0.002$) and QoL ($p<0.05$), but not with peak VO2. 6-minute-walking distance and peak VO2 values were significantly higher in patients who performed high intensity exercise >8 hours per week ($p<0.001$ and $p=0.02$, respectively). Time of high physical exercise was also positively correlated with 6-minute walking distance ($r=0.21$, $p<0.001$), with peak VO2 and QoL (both $r=0.13$, $p=0.01$), whereas low physical exercise did not show significant associations. Interestingly, type or amount of exercise was not significantly related to any measure of diastolic function.
Conclusion: The total amount of daily physical activity is related to submaximal exercise capacity and QoL, whereas only daily high intensity exercise is associated with maximal exercise capacity in patients with HF with preserved EF.

P773 | BEDSIDE
Contribution of ventilation-perfusion mismatch resulting from abnormal diastolic response to exertion to exercise limitation in HFpEF

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Introduction: "Backward" character of heart failure with preserved ejection fraction (HFpEF) with an early increase in LV filling pressure (LVFP) and premature exercise termination before the development of deficiency in peripheral perfusion and metabolic acidosis may generate in some patients controversies regarding the attainment of maximal effort during cardiopulmonary exercise testing (CPET).
Purpose: To investigate the spectrum of cardiorespiratory reserve impairment in relation to different patterns of diastolic response to exercise in HFpEF.
Methods: We recruited 207 pts (64±8 yrs) with symptomatic HFpEF (exertional dyspnea, NYHA II-III, reduced exercise capacity,LVEF>50%,diastolic dysfunction) and 60 pts with normal exercise tolerance.Echocardiographic assessment of cardiac performance including E/e' ratio approximating LVFP was performed at rest and immediately post CPET.
Results: Symptomatic pts were categorized into two groups: with and without exertional increase in E/e' >13 (AbnE/e' and NE/e', respectively), reflecting elevated and non-elevated LVFP. Pts with E/e'>13 at peak exercise demonstrated more advanced impairment of exercise capacity (lower peak VO2), lower O2 uptake efficiency (OUES), peak respiratory exchange ratio (RER), LV contractility reserve (delta EF), but higher ventilatory equivalent for carbon dioxide (VE/VCO2) and dead space to tidal volume ratio (VD/VT) as compared to both the asymptomatic and NE/e' groups (Table). Multivariable analysis revealed that exertional E/e' and VD/VT were the independent correlates of peak VO2 ($\beta=-0.24$, $p<0.001$ and $\beta=-0.27$, $p<0.001$, respectively) and a significant interaction effect ($p=0.03$) between E/e' and VD/VT was found.

Results

Parameter	Asymptomatic (n=60) (1)	NE/e' (n=63) (2)	AbnE/e' (n=144) (3)	p 1 vs 2	p 1 vs 3	p 2 vs 3
E/e' at exercise	9.0±1.9	10.0±1.6	17.0±4.4	0.20	0.0001	0.0001
Peak VO_2, ml/min/kg	22.3±4.1	17.6±4.7	14.6±4.5	0.0001	0.0001	0.0001
OUES	1.78±0.59	1.68±0.77	1.45±0.62	0.49	0.01	0.02
VE/VCO_2	26.5±5.2	26.9±4.5	29.3±6.5	0.79	0.02	0.01
RER	1.08±0.12	1.06±0.10	1.01±0.10	0.38	0.0002	0.0004
Peak VD/VT	0.17±0.05	0.17±0.06	0.20±0.07	0.77	0.003	0.001
Delta EF, %	10.4±8.1	6.9±8.8	3.6±6.7	0.03	0.0001	0.01

Delta: value at exercise minus value at rest.

Conclusions: An abnormal E/e' response to exercise in symptomatic HFpEF is associated with higher VD/VT and VE/VCO2 and lower peak RER, which distinguishes this group from pts with a non-elevated E/e' at exercise. Raised exertional VD/VT might be a marker of impaired ventilation to perfusion ratio due to pulmonary congestion resulting from increased LVFP, which leads to dyspnea and earlier cessation of exercise at lower RER in the AbnE/e' group despite maximal effort intensity.

P774 | BEDSIDE
Association between left atrial enlargement and obstructive sleep apnoea in a general male population

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Background: Left atrial enlargement (LAE) has been associated with obstructive sleep apnoea (OSA) in patients with coronary artery disease. However, this association has not been studied in the general population.
Purpose: To investigate the association between obstructive sleep apnoea and left atrial enlargement. To our knowledge, no previous study has investigated this association in a random sample from the general male population.
Methods: The study population consists of 536 male participants of the study "Men Born in 1943", a population study consisting of a random sample of men born in 1943 in the city of Gothenburg, Sweden. In 2014, in addition to a medical examination, 12-lead ECG and extensive questionnaires addressing medical history and aspects of general health, each participant was offered to be examined by both echocardiography and an overnight sleep recording in their own homes using a standard cardio-respiratory polysomnography device.
Results: Of the 411 participants who underwent both echocardiography and sleep apnoea screening, 153 were found to have LAE. Of these 153 participants, 41.2% (63/153) were diagnosed with OSA, compared to 22.5% (58/258) in the group without LAE. Participants with LAE also showed significantly higher frequencies of atrial fibrillation/flutter, systolic heart failure, hypertension, and were more often obese. Smoking was more frequent in the non-LAE group. In multivariate regression analysis, both moderate OSA (odds ratio [OR] 2.60, 95% CI 1.42–4.75) and severe OSA (OR 3.21, 95% CI 1.40–7.35) were significantly associated with LAE after adjusting for body-surface-area, atrial fibrillation, smoking and hypertension.

Table 1. Sleep apnoea screening data

	Normal left atrium, n=258	Enlarged left atrium, n=153	p-value
Apnoea-hypopnoea index	10.10±11.32	14.50±12.42	<0.001
Lowest saturation	82.22±7.08*	82.10±5.91*	0.86
Mean pulse	61.76±8.53*	59.76±9.72*	0.032
Oxygen desaturation Index	8.61±9.29*	12,27±11.30*	<0.001
Mean saturation	92.39±2.49*	92.49±2.19*	0.686
Respiratory index	12.98±11.36	17.21±12.22	0.0004
Saturation below 90%	20.83±27.65*	20.61±26.06*	0.937

Continuous variables are presented as mean ± SD (standard deviation), groups compared by Student's t test. *244 participants in the group with normal left atrium, 147 in the group with enlarged left atrium.

Conclusions: Obstructive sleep apnoea is associated with left atrial enlargement in 71 year old men from the general population. The frequency of LAE was shown to increase with the severity of the OSA.
Acknowledgement/Funding: Grants from Västra Götalandsregionen, The Skaraborg Research and Development Council, ResMed Sweden supplied the ApneaLink Plus devices.

P775 | BEDSIDE
Predictors of long-term prognosis of ambulatory patients with heart failure and preserved ejection fraction

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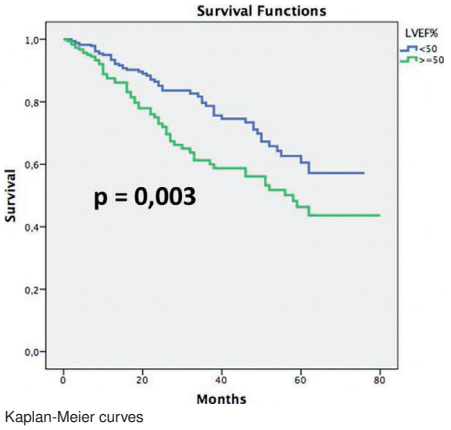
Background: Patients (pts) with heart failure and preserved ejection fraction (HFpEF) have been historically considered with better prognosis than those with reduced systolic function (HFrEF). However, actual prognosis of these patients is uncertain.
Purpose and methods: To asses the prognosis of pts with HFpEF, a cohort of 536 outpatients with HF was prospectively followed in a tertiary HF clinic during the 2010–2015 period. Clinical, ECG, echocardiographic and biochemical data were registered. Cox regression analysis was used to identify the predictors on mortality of pts with HFpEF.
Results: Mean age was 68±13 years and 67% were men. The etiology of HF was ischemic (35%), cardiomyopathy (25%), valvular (16%), hypertension (14%) and others (10%). Pts were in NYHA functional class I-II (61%) and III-IV 39%. HFrEF was found in 348 pts (65%) and the remaining 188 (35%) had HFpEF. Mean follow-up was 24±20 months. Comparing HFrEF with HFpEF, the latest group had older age (74±12 vs. 65±13 years, $p<0.001$), more frequently were females (51 vs. 33%, $p<0.001$), had higher hypertension rates (80 vs. 71%, $p=0.02$), higher incidence of atrial fibrillation (56 vs. 33%, $p<0.001$) and lower median NT-ProBNP values (1369 [642–2499] vs. 2000 [857–4416] $p=0.002$). Pts with HFpEF had higher mortality (32 vs. 16%, $p=0.001$). Kaplan-Meier curves comparing 3-year survival of the two groups, showed that pts with HFpEF had a significant worse survival (60% vs. 78%, $p=0.003$) (figure 1). Multivariate analyses identify as in-



Kaplan-Meier curves

dependent predictors of worse prognosis in HFpEF: older age (1.068 [95% CI 1.031–1.106]; p<0.001), NT-proBNP >1500 ng/L (2.837 [95% CI 1.614–4.984]; p<0.001), Na^+ <135 mmol/L (2.316 [95% CI 1.05–5.109]; p=0.03) and lower systolic pressure (0.767 [95% CI 0.655–0.899]; p=0.001). The discrimination ability of this model was 0.77 (c-statistics index), with a good internal validation after the boots trapping (0.75).
Conclusions: 1) In this cohort, pts with HFpEF had worse prognosis than HFrEF. 2) NT-proBNP >1500 ng/L may help to identify pts at higher risk of death. 3) Based on the worse prognosis of pts with HFpEF, more studies are needed to improve their survival.
Acknowledgement/Funding: This work was supported by an unrestricted Servier grant.

P776 | BENCH
Bicoronary infusion of nitroglycerin and atrial natriuretic peptide improves diastolic distensibility in healthy pigs

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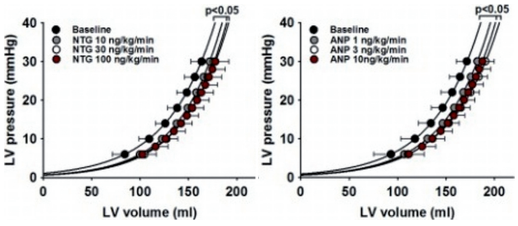
Background: Experimental data indicate that the acute post-translational modification of the myofilamental titin spring by cGMP-activated protein kinase G can increase left ventricular (LV) end-diastolic distensibility (LVed-Dist). Intracellular cGMP production can be stimulated either by nitric oxide via the soluble guanylate cyclase (sGC), or by the natriuretic peptides via the particulate guanylate cyclase (pGC). We tested the hypothesis that acute intracoronary infusion of nitroglycerin (NTG) or atrial natriuretic peptide (ANP) would exert direct myocardial effects and improve LVed-Dist in healthy myocardium.
Methods: 5 anaesthetized, closed-chest pigs (59±2kg) were acutely instrumented with a left ventricular (LV) pressure-volume catheter, a Swan-Ganz catheter and an aortic ballon catheter. Two 5F coronary catheters were positioned in the right and left coronary ostia via femoral access. Pressure-volume relationships were derived from short aortic occlusions. Following baseline measurements, NTG was infused bicoronarily at 10, 30 and 100 ng/kg/min over 20 min, respectively. After 30 min wash-out, the same protocol was repeated with ANP at 1, 3 and 10 ng/kg/min. *: p<0.05 vs baseline
Results: LV peak pressure slightly decreased at the highest dose compared to baseline (NTG: 87±3* vs 94±4, ANP: 85±4* vs 96±6) while systemic vascular resistance was not altered during NTG infusion and to a minor extent during the highest dose of ANP (11.1±0.6* vs 12.7±0.7 mmHg/l/min). The maximum rate of positive LV pressure change, LV dP/dtmax, decreased and the calculated end-systolic volume at 100 mmHg end-systolic pressure increased dose-dependently, indicating a negative inotropic effect. The end-diastolic pressure volume relationships (EDPVR, graph) before and during infusion of NTG and ANP were shifted rightwards compared to the respective baseline (see graphs).



Conclusion: The acute pharmacological stimulation of cGMP-dependent signalling improves LV end-diastolic distensibility in healthy pigs in vivo. The molecular mechanisms mediating such acute modulation of LV distensibility may represent pharmacological targets to treat a pathological loss of LV distensibility as, for instance, heart failure with preserved ejection fraction (HFpEF).

P777 | BEDSIDE
Comparing novel biomarkers associated with heart failure preserved ejection fraction (HFpEF): A matched case-control analysis

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Background: In the U.S., 5.1 million Americans >20 years have heart failure (HF) and heart failure preserved ejection fraction (HFpEF) accounts for at least 50% of all admissions for HF. HFpEF has no single guideline for diagnosis or treatment, the patient population that is heterogeneously and inconsistently described and longitudinal studies are lacking. This study was designed to detect differences in biomarkers associated with incident HFpEF when comparing matched case-control groups.
Methods: A study cohort of 310 patients, that included case (incident HFpEF patients, n=155) and matched control (patients with no prior HF, n=155) groups were retrospectively identified. Matching criteria included race, sex, age (within 3 years) and previously acquired echocardiogram biomarkers (within 1year). Physiologic and echocardiogram biomarkers were collected from previously acquired 2-D (dimensional) M-mode Doppler echocardiograms. Echo images were re-analyzed from previously obtained echo to calculate measures factored into calculating ventricular-arterial coupling. Using conditional logistic regression and controlling for covariates, models were fit to detect differences in HFpEF biomarkers between the matched case-control groups.
Results: Statistically significant differences in ventricular elastance (Ees) (p=0.0030) and left atrial diameter (LAdiam) (p=0.0002) were detected when comparing the case-controls. Conditional logistic regression demonstrated a 30% higher odds of converting to the case group with every 1 unit increase in Ees, OR 1.315 (1.097, 1.575) and a 4.57 times higher odds of being in the case group for every 1 unit increase in LAdiam, OR 4.565 (2.038, 10.223).
Discussion: The case group had significantly higher SBP, HR, BMI, Ees and LAdiam. Previous studies have demonstrated increases in LAdiam and Ees in older women, but have not been longitudinally tested.
Conclusions: Prospective studies are indicated that test Ees and LAdiam as predictors of impending HFpEF. This study demonstrates feasibility in calculating Ees and LAdiam from routinely obtained echo images without increasing cost or risk.

P778 | BEDSIDE
Abnormal right ventricular reserve capacity in patients with heart failure and preserved biventricular function is caused by ventricular stiffness, impaired relaxation and vascular stiffness

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Background: Right ventricular (RV) dysfunction has been shown to be a potent predictor for adverse outcomes in patients with Heart Failure and Preserved Ejection Fraction (HFpEF). However, little is known about RV function abnormalities during exercise which might manifest prior to RV dysfunction at rest in patients with preserved biventricular function.
Invasive tracings of pressure-volume relations provide the unique opportunity to directly assess mechanical properties of the right ventricle under different loading conditions.
Purpose: To invasively assess right ventricular stiffness and right ventricular function in HPpEF patients compared to patients without heart failure symptoms.
Methods: We performed cardiac magnetic resonance imaging to evaluate cardiac dimension and biventricular function in 18 HFpEF patients and 9 patients without heart failure symptoms. Pressure volume loops were obtained with a conductance catheter during basal conditions and handgrip exercise. Transient preload reduction was used to extrapolate the RV end systolic elastance and diastolic stiffness constant.
Results: HFpEF patients and controls showed similar left ventricular (LV) and RV dimensions and LV ejection fraction while RV ejection fraction was even higher in HFpEF patients (p=0.04) Invasively determined load-independent systolic RV function (p=0.8) was comparable between groups. In contrast, HFpEF patients demonstrated an elevated load-independent passive RV stiffness constant β (p<0.01).
While RV active relaxation, filling pressures, arterial elastance and cardiac output where similar at baseline; HFpEF patients demonstrated a blunted increase in cardiac output under exercise (p<0.01) resulting from a longer active RV relaxation (p=0.01), higher RV-filling pressures (p<0.01) with a marked rise in the enddiastolic-pressure-volume relationship (p<0.01) and increased pulmonary artery elastance (p=0.05).
Conclusion: In HFpEF patients with preserved RV function increased intrinsic RV myocardial stiffness, impairment of active RV relaxation and increased pulmonary artery stiffness lead to a blunted increase in cardiac output during exertion. These functional abnormalities can be unmasked by exercise testing and possibly precede overt RV dysfunction at rest.

EXERCISE TESTING AND TRAINING I

P779 | BEDSIDE
Telomere length a hallmark of vascular aging is altered in mild cognitive impairment and improved after an environmental enrichment program: the train the brain- mind the vessel cellular study final

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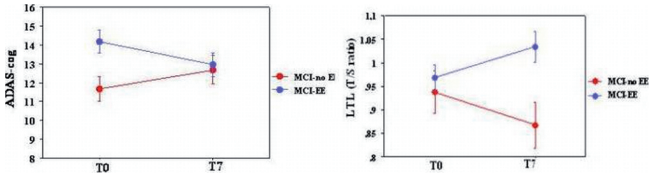
Background: Environmental Enrichment (EE) may slow cognitive decay in Mild Cognitive Impairment (MCI), an early stage of Alzheimer disease, possibly acting also through an improvement in cellular and molecular hallmark of vascular aging.
Purpose: To assess the efficacy of an EE program in slowing cognitive decay and improving leukocyte telomere length (LTL).
Methods: In a single center, parallel group study design (Train the Brain, clinical-

trials.gov. identifier NCT 01725178), 113 MCI subjects were randomized to the training group (MCI-EE, N=55) and the non-training group (MCI-no EE, N=58). Training consisted in the combination of multi-domain cognitive, social and physical exercise (9 hrs/wk for 7 months). All pts were evaluated for primary cognitive endpoint (neuropsychological testing and ADAS-cog score) and LTL as secondary molecular endpoint of vascular aging. At study entry, an age-matched control group was also studied (C). LTL was evaluated by real-time PCR.
Results: Compared to healthy controls, MCI patients had at study entry a reduced LTL (0.95±0.23 vs. 1.07±0.3, p=0.02). LTL and cognitive evaluation was available in 25 no-EE and 50 EE patients. In MCI, EE improved neuropsychological score (ADAS-cog, EE= 14.2±4.5 to 13.0±4.5, p=0.02; no-EE= 12.0±3.06 to 13.0±4.0, p=0.02) and ameliorated LTL (0.97±0.21 vs. 1.03±0.23, p=0.04). No significant difference was observed in no-EE group for LTL (see figure). In MCI individual patient analysis, there was no correlation between variations in ADAS-cog and changes in LTL (r=–0.14, p=0.23).



Conclusions: MCI subjects show impaired molecular hallmark of cellular and vascular aging versus healthy controls. In MCI, a long-term EE program slows cognitive decay with a beneficial effect of modest size, accompanied by lengthening of telomeres, but in the absence of correlation between cognitive and cellular-molecular changes at individual patient analysis.

P780 | BEDSIDE
Exaggerated exercise blood pressure response is related to increased arterial stiffness, asymmetric dimethylarginine and osteoprotegerin in essential hypertension

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Background/Introduction: A hypertensive response to exercise (HRE) is associated with high cardiovascular risk, while elevated levels of asymmetric dimethylarginine (ADMA) and osteoprotegerin (OPG) are related to atherosclerosis progression.
Purpose: In this study we sought to determine the relationships of HRE with ADMA, OPG and arterial stiffness in essential hypertension.
Methods: Our population of 240 newly diagnosed never treated non-diabetics with stage I to II essential hypertension [155 men, mean age=51 years, office blood pressure (BP)=150/96 mmHg] with a negative treadmill exercise test (Bruce protocol) was divided into those with HRE (n=70) (peak exercise systolic BP $\geq$210mmHg in men and $\geq$190 mmHg in women) and those without HRE (n=170). Arterial stiffness was evaluated on the basis of carotid to femoral pulse wave velocity (PWV) values.
Results: Patients with HRE compared to those without HRE had greater 24-h systolic BP (143±9 vs 131±8 mmHg, $p<0.05$), while did not differ regarding metabolic profile and left ventricular mass index (p=NS). Patients with HRE as compared to those without HRE exhibited greater levels of ADMA (0.63±0.04 vs 0.52±0.05 μmol/l, $p<0.0001$), OPG (5.4±0.1 vs 4.1±0.5 pmol/l, $p<0.0001$) and PWV (8.9±1.7 vs 7.5±0.9 m/sec, $p<0.0001$), independently of confounders. In the total population, peak exercise systolic BP was related to 24-h systolic BP (r=0.249, $p<0.05$), PWV (r=0.278, p=0.003), ADMA (r=0.260, p=0.007) and OPG (r=0.214, $p<0.05$). Regarding OPG, it was associated with 24-h systolic BP (r=0.285, $p<0.0001$), ADMA (r=0.284, $p<0.05$) and PWV (r=0.424, $p<0.0001$). Multiple regression analysis showed that 24-h systolic BP (b=0.216, p=0.003), male sex (b=0.270, $p<0.05$), ADMA (b=0.225, p=0.006) and OPG (b=0.188, $p<0.05$) were independent predictors of peak exercise systolic BP.
Conclusions: In essential hypertension, a HRE is accompanied by a state of increased arterial stiffening, endothelial dysregulation and progressive atherosclerosis. The interrelationships of ADMA and OPG with exercise BP response support that diffuse vascular dysfunction contributes to HRE-related risk in hypertension.

P781 | BEDSIDE
Significance of change in heart rate recovery from test to test

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Background: Heart rate recovery (HRRec) is a powerful predictor of mortality in many cardiovascular (CV) diseases. If so a change in HRRec should signal a change in mortality risk.
Purpose: We analyzed a large cohort of patients who underwent 2 stress tests to determine the significance of a test-to-test change in HRRec.
Methods: Non-imaging exercise tests performed on patients from Minnesota ages 30–89 years from 1994 through 2010 were reviewed. Patients with 2 tests performed a minimum of 6 months apart were included. Patients were assigned to 4 groups according to their HRRec change: NN = HRRec normal (<13 bpm) both tests; NA = normal becomes abnormal; AN = abnormal becomes normal; and AA = abnormal both tests. Mortality was determined from Minnesota and National Death Indices. Mortality risk according to HRRec change was assessed using Cox regression with adjustment for age, sex, presence of CV disease, hypertension, diabetes, current smoking, and use of a HR-lowering drug.
Results: A total of 6,512 qualifying patients (76% men) were included in the analysis. Mean age was 53±13 years. CV disease was established in 2540 patients (39%), hypertension in 1757 (27%), diabetes in 475 (7.3%), current smoking in 523 (8.6%), and use of HR-lowering drug in 2120 (33%). HRRec overall was similar between the first and second tests (17±9 vs 17±10) performed an average of 4.0±3.2 years apart. Number of patients by HRRec change was 3797 for NN (58%), 756 for NA (12%), 775 for AN (12%), and 1184 for AA (18%). There were 913 deaths (14%) over a mean follow-up of 10.2±4.7 years after the second test. Using NN with 232 deaths (6.1%) during follow-up as the referent, the age-sex-risk factor-adjust hazard ratio [95% confidence interval] for total mortality was 2.01 [1.62–2.49] for NA, 1.50 [1.18–1.90] for AN, and 2.83 [2.38–3.36] for AA.
Conclusions: HRRec change on consecutive exercise tests has a significant independent impact on all-cause mortality. The best outcomes were seen in patients with NN HRRec. Compared to patients with AA HRRec, improved HRRec (AN) patients showed reduced risk. Similarly, worsening HRRec (NA) patients had increased risk versus NN HRRec patients.

P782 | BEDSIDE
Long term prognostic value of heart rate recovery in patients with pre-test probability for coronary artery disease of 15-65% and negative exercise testing

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Background: Herat rate recovery (HRR) has been shown to predict cardiovascular and all-cause morbidity and mortality. However there are insufficient data on prognostic significance of HRR in patients with pre-test probability for coronary artery disease (CAD) of 15–65%.
The aim of our study was to determine the long term prognostic value of HRR in patients with chest pain and pre-test probability of CAD of 15–65%.
Material and methods: We included in the study 627 patients (60±24 years, 58% females, 12.2% with diabetes) without known CAD and pretest probability of 15–65% who were referred to exercise testing (stress echocardiography or stress electrocardiography) for the evaluation of chest pain. HRR was calculated as the difference between heart rate at the peak stress and heart rate in the first minute of rest. Slow HRR was defined as $\leq$18 beats/min. Patients were followed for mean of 94±2 months for the occurrence of cardiovascular death, myocardial infarction and clinically indicated revascularization.
Results: Out of 627 patients 54 patients (8.6%) had positive test and were excluded from further analysis. Of the remaining 573 patients with negative finding, 35 (6.1%) had slow HRR. There was no difference in the baseline characteristics between the groups except for the age of patients (slow HRR group 68±8 vs normal HRR group 58±26, $p<0.001$). During the follow up period 38 patients (6.8%) had an adverse event (6 cardiovascular deaths, 11 myocardial infarction, 21 clinically indicated revascularization). There was significant difference in events between groups (6/35, 17.1%) in slow HRR and (32/538, 6.1%) in normal HRR group (p=0.012). The modality of exercise testing (stress echo or stress ECG) was not related to the outcome (p=0.689). Other univariate predictors of adverse events were presence of diabetes and male gender ($p<0.001$, for both). Slow HRR (OR 0.36 [95% CI 0.13–0.98], p=0.046) along with the presence of diabetes (OR 0.27 [95% CI 0.13–0.57], p=0.001) and male gender (OR 3.1 [95% CI 1.5–6.3], p=0.002) were also independent predictors for the occurrence of adverse events.
Conclusion: Slow HRR is an independent long term predictor of adverse cardiovascular events in patients with pre-test probability for CAD of 15–65% and negative exercise test. Male patients and patients with diabetes also have more pronounced risk for the occurrence of adverse events.

P783 | BEDSIDE
Impact of physiological aging beyond chronological aging on exercise time: lessons from a 25 year observational cohort

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Introduction: Treadmill exercise time is a reflection of exercise capacity and a major predictor of subsequent cardiovascular morbidity and mortality.
Purpose: Evaluate the change, by age category and time period, in exercise time in patients referred for exercise stress testing over a 25 year period.
Methods: All patients who underwent exercise stress testing: exercise ECG and

exercise imaging (echo and nuclear) at our institution, from 1990 to 2014, were included. Patients' age, exercise testing date and exercise time in seconds (sec) were documented. Patients were divided into 4 groups based on their age: Group 1: <45 years; Group 2: 45–54 years; Group 3: 55–64 years and Group 4: >65 years. The 25 year study period was split into 5 time intervals: Interval #1: 1990–1994; Interval #2: 1995–1999; Interval #3: 2000–2004; Interval #4: 2005–2009 and Interval #5: 2010–2014. Median exercise time (median, 25–75 percentile) for each age group, at each interval, was measured. Trend permutation tests were used to detect significant changes in exercise times over the years. Two-sample Wilcoxon tests were used to compare exercise times among different groups.

Results: A total of 167,754 patients were included. Exercise times for the different age groups and time intervals are presented in table 1 (all exercise times are expressed in sec). For the same age group, there has been a significant decline (by trend permutation tests) in exercise time over the study period (figure 1). Two-sample Wilcoxon tests showed that the median exercise time [median (25–75 percentile) = 540 sec (430–600)] for age >65 in the 1990–1994 interval was statistically equivalent to that [540 sec (435–600)] for age 55–64 in the 1995–1999 interval, and to those (see table 1) for age 45–55 for the subsequent time intervals (2000–2014). Also, in every time interval, trend permutation tests showed a significant decrease in exercise time with increasing age group (figure 1).

Exercise times in seconds

Time period	Age <45yrs (N=39209)	Age 45–54 yrs (N=47573)	Age 55–64 yrs (N=44258)	Age >64 yrs (N=36714)
1990–1994	614 (530–270)*	600 (540–660)	553 (480–630)	540 (430 (600)
1995–1999	600 (520–701)	560 (480–630)	540 (435–600)	480 (390–585)
2000–2004	600 (495–690)	540 (450–617)	480 (394–597)	425 (345–540)
2005–2009	600 (495–720)	540 (446–630)	482 (388–588)	410 (313–520)
2010–2014	588 (480–688)	540 (430–630)	480 (369–579)	406 (314–525)

*All exercise times are expressed as median (25–75 percentile); yrs = years.

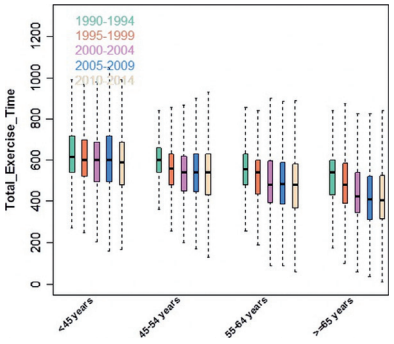

Figure 1. Exercise times by age and time period

Conclusion(s): As a proof of "physiological aging" beyond "chronological" aging, in a large population of patients referred for exercise stress testing over a 25 year period, there has been a significant decline in exercise time in all age groups (figure 1).

P784 | BEDSIDE
Cardiorespiratory fitness in women with previous preeclampsia

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Background: Preeclampsia (PE) increases the risk of future cardiovascular disease (CVD) in premenopausal age of women. Poor cardiorespiratory fitness (CRF) is a prognostic factor for development of CVD.

Variables at rest and exercise

Variables	PE group (n=60)	Control group (n=25)	p-value
Body mass index, kg/m^2	25.5±5.5	22.8±2.9	0.03
Functional vital capacity, L	3.74±0.47	4.08±0.44	0.04
Forced expiratory volume in 1 sec, L	3.11±0.40	3.16±0.72	ns
Resting systolic BP, mmHg	133±17	114±12	<0.01
Resting diastolic BP, mmHg	87±11	73±10	<0.01
Max. oxygen uptake (VO2max), mL kg^{-1} min^{-1}	34.3±7.7	37.7±7.4	0.01
Maximal heart rate (HRmax), beat min^{-1}	178±11	184±11	0.04
Oxygen pulse, mL beat^{-1}	13.1±2	13.5±1.9	ns
Max systolic BP, mmHg	185±21	165±19	<0.01
Max diastolic BP, mmHg	87±17	74±11	<0.01
Minute ventilation (VE), L min^{-1}	89.4±11.9	91.1±14.4	ns
SpO2max, %	92±4	94±4	ns
VECO2slope	25.1±3.9	24.4±1.6	ns
VEO2slope	24.6±8.3	22.0±5.0	ns
Blood lactate, mmol L^{-1}	10.1±3.0	9.9±2.5	ns

Data presented as mean (± SD).

Purpose: To investigate CRF on long-term follow-up of women after severe PE.
Method: Sixty women, age 41±4 (mean±SD) with previous severe PE and 25 healthy controls (age 38±4) performed a cardiopulmonary exercise test on a treadmill to exhaustion for measurement of maximal oxygen uptake (VO2max). In addition, pulmonary function, and blood pressure were measured.
Results (Table 1): Sixty women fulfilled test criteria for VO2max (respiratory exchange ratio ≥1.15 or a Borg score ≥17). VO2max was 9% lower in the PE-group compared to the controls (p<0.01). Systolic and diastolic blood pressure at rest and at maximal exercise were significantly higher in the PE-group compared to controls. There were no differences in pulmonary function and ventilatory efficiency (VE/VCO2)between the groups.
Conclusion: Our study demonstrates that women with previous severe preeclampsia have a clinically lower cardiorespiratory fitness compared to healthy controls. This important finding indicates a poorer health status and increased CVD risk. Women with a history of preeclampsia need a proper CVD risk assessment and counselling.
Acknowledgement/Funding: Oslo University Hospital, no conflict of interest

P785 | BEDSIDE
Outpatient cardiac rehabilitation after myocardial infarction: predictors of improved exercise capacity

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Background: Cardiac rehabilitation decreases cardiovascular and all-cause mortality in patients after a myocardial infarction (MI); additionally, exercise-based programs aim to improve quality of life through improved exercise capacity.
Aim: To assess predictors of improved exercise performance after cardiac rehabilitation post-MI.
Methods: Consecutive patients undergoing outpatient cardiac rehabilitation at a university medical center following a MI were included. Risk factors and NT-proBNP levels were systematically collected and exercise testing was performed at inclusion and after completion of a cardiac rehabilitation program (3-times per week for 3 months).
Results: A total of 407 patients were included: 86 (21%) were women, mean age was 58±10 years. Before and after cardiac rehabilitation, exercise capacity significantly improved (from 6.8 to 9.6 METs, p<0.001). On multivariable analysis, younger age (adjusted odds ratio [OR] per 1 year of age 1.08, 95% confidence interval [CI] 1.03–1.13, p<0.001), male gender (OR 2.54, 95% CI 1.00–6.45, p=0.050), baseline exercise capacity (OR for 1 MET 1.44, 95% CI 1.15–1.80, p=0.002), lower body mass index (OR for 1 kg/m^2 1.11, 95% CI, p=0.017), but not risk factors or baseline NT-proBNP levels emerged as independent predictors of improved exercise capacity (>3 METs increase from baseline). Additionally, number of attended rehabilitation sessions showed a trend towards statistical significance (OR per session 1.02, 95% CI 0.99–1.05, p=0.087).
Conclusion: Cardiac rehabilitation significantly improves exercise capacity after MI; however, such improvement is strongly predicted by younger age and and male gender. Our findings suggest that specific needs of women and ageing post-MI patients should be better addressed.

P786 | BEDSIDE
Exercise cardiac power and the risk of subclinical atherosclerosis in men

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Background: Low exercise cardiac power (ECP), defined as a ratio of peak oxygen consumption with peak systolic blood pressure during exercise, is associated with adverse cardiovascular events, but the underlying mechanisms remain unclear. Coronary artery calcification (CAC) and carotid intima media thickness (CIMT) as surrogate markers of subclinical atherosclerosis are associated with an increased risk of cardiovascular outcomes. We tested the hypothesis that lower levels of ECP may be associated with the prevalence of subclinical atherosclerosis, independent of conventional risk factors, in a cross-sectional study of 2165 (age 53±6 yrs, range 40–78 yrs) men.
Methods: We measured CAC using multidetector computed tomography using the Agatston coronary artery calcium score and CIMT using B-mode ultrasound. The prevalence of subclinical atherosclerosis was defined as dichotomous variables of CAC score >10 and CIMT >75th percentile. ECP was calculated by a ratio of peak oxygen consumption with peak systolic blood pressure and classified into quartiles.
Results: The presence of CAC and CIMT was inversely associated with ECP quartiles (both, P<0.001 for trend). After adjusting for age, BMI, SBP, TC, HDL-C, TG, hsCRP, glucose, heart rate, smoking, hypertension and diabetes, men in the lowest quartile of ECP had a significantly elevated odds ratios for having CAC (odds ratio (OR)1.41, 95% CI 1.04–1.91) and CIMT (OR 1.98, 95% CI 1.44–2.74), respectively, compared with men in the highest quartile of ECP. Each ECP unit increment as a continuous variable was associated with 4% (OR 0.96, 95% CI 0.93–0.99) lower prevalence of CAC after adjusting for established risk factors.

Conclusion: Our findings demonstrate that lower levels of ECP are associated with the prevalence of subclinical atherosclerosis, which could contribute to increased risk of cardiovascular events.

P787 | BEDSIDE
Heart rate recovery is impaired in patients with beta-thalassemia major

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Objective: Abnormal heart rate recovery (HRR) is predictive of mortality. Autonomic abnormalities in beta-thalassemia major (TM) patients were reported in previous studies. However, the importance of low heart rate recovery in exercise stress test is not known in thalassemia patients.
Purpose: In present study, we aimed to investigate exercise properties of TM patients and the relationship between HRR and cardiac involvement by comparing T2 scores.
Methods: Exercise stress test was performed in 56 TM patients, who were being treated in the Thalassemia Center of our hospital, along with 46 control patients with anemia without TM. HRR values were recorded at 1, 2, 3, 4 and 5 min. HRR was calculated by the difference of heart rate at peak exercise and at a specific time interval following the onset of recovery.
Results: All HRR values were found lower in thalassemia major patients compared to those in the control group (figure 1). Exercise capacity (METs) was also found low in these patients ($p<0.001$) (table 1). Total exercise time was low in thalassemia major patients ($p<0.001$). Mean T2* value was 28.3±13.7 ms in TM patients on magnetic resonance imaging (MRI). In addition, there are 18 TM patients with T2* value was <20 ms.

Table 1

Characteristics	Control group (n=46)	Thalassemia group (n=56)	P
HR Stage 1, bpm	107 (±11)	121 (±14)	0.0001
HR Stage 2, bpm	121 (±14)	138 (±16)	0.0001
HR Stage 3, bpm	142 (±16)	159 (±16)	0.0001
Chronotropic index	84 (±11)	76 (±11)	0.001
Exercise capacity (METs)	13.1 (±1.8)	10.1 (±1.8)	0.0001

Values are expressed as mean ± standard deviation or median 25th-75th%. $P<0.05$ value is significant. HR: heart rate, METs: metabolic equivalents, RPP: rate pressure product, SD: standard deviation (Rate pressure product = heart rate × systolic blood pressure). One way analysis of variance, Independent samples t-test, Mann-Whitney U-test.

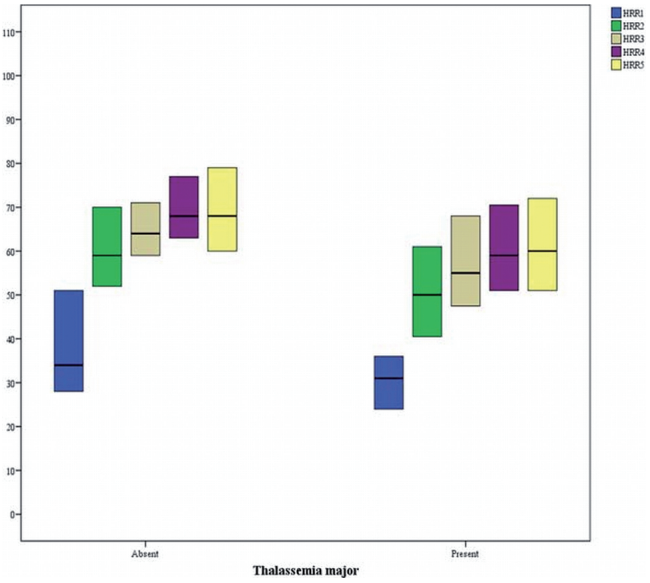

Figure 1

Conclusion: TM was independently associated with low HRR. This condition is an indicator of autonomic dysfunction in TM patients, since abnormal HRR is related with impaired autonomic response. In addition, impaired HRR may be a marker of early cardiac involvement in patients, whose T2* value is high on magnetic resonance imaging (MRI). Modifying HRR with a cardiac rehabilitation program in TM patients with impaired HRR is a field open for further investigation.

P788 | BEDSIDE
Respiratory muscle weakness increases dead-space ventilation ratio aggravating ventilation-perfusion mismatch during exercise in patients with chronic heart failure

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Background: Increased ventilation-perfusion mismatch during exercise is reportedly associated with poor prognosis in patients with chronic heart failure (CHF); in particular, those who have minute ventilation versus carbon dioxide production (VE/VCO2) slope of >34 show low event-free survival rate. Several studies have shown that elevated dead-space ventilation ratio aggravates a ventilation-perfusion mismatch. On the other hand, respiratory muscle weakness has been reported as an independent predictor for high mortality in CHF patients. However, it is still unclear whether respiratory muscle weakness aggravates a ventilation-perfusion mismatch during exercise via the elevated dead-space ventilation ratio. This study aimed to investigate the correlations of respiratory muscle weakness with elevated dead-space ventilation ratio and ventilation-perfusion mismatch during exercise and to clarify the determinants for VE/VCO2 slope of >34 in CHF patients.
Methods: We studied 256 patients with compensated CHF (60.3±12.0 years, 204 males) who performed a cardiac rehabilitation during hospitalization and after hospital discharge. The patients who received thoracic surgery within 6 months or had chronic respiratory disease were excluded from this study. Maximal inspiratory pressure (PImax) was measured as respiratory muscle strength using a pressure transducer connected to spirometer two months after hospital discharge. We monitored minute dead-space ventilation (VD), VE and VCO2 during a cardiopulmonary exercise test, and assessed VD/VE ratio as dead-space ventilation ratio and VE/VCO2 slope as ventilation-perfusion mismatch. Patients were divided into three groups based on the tertile of PImax: low PImax group (PImax ≤58.7 cmH2O), moderate PImax group (58.7< PImax ≤83.6 cmH2O) and high PImax group (PImax >83.6 cmH2O). We compared those parameters among the three groups using multiple comparison analysis. Pearson's correlation coefficient was used to assess the relationships among PImax, VD/VE ratio and VE/VCO2 slope. We performed multivariate logistic regression analysis to identify the determinants for VE/VCO2 slope of >34.
Results: Dead-space ventilation ratios during exercise are shown in Figure. The low PImax group showed significantly higher VD/VE ratios at rest, 50% of peak exercise and peak exercise, and higher VE/VCO2 slope as compared with the other two groups ($P<0.001$, respectively). PImax was negatively correlated with VD/VE ratio at the peak exercise ($r=-0.513$, $P<0.001$) and VE/VCO2 slope ($r=-0.494$, $P<0.001$). There was a positive correlation between VD/VE ratio at the peak exercise and VE/VCO2 slope ($r=0.376$, $P<0.001$). Multivariate logistic regression analysis detected the PImax as a significant independent determinant for VE/VCO2 slope of >34 (OR=0.59, 95% CI: 0.49–0.73, $P<0.001$).

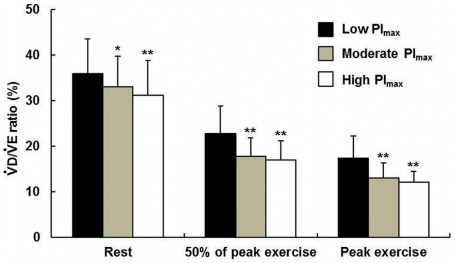

Figure Comparison of dead-space ventilation ratio during exercise among the three groups
PI_{max}: maximal inspiratory pressure, V̇D: minute dead-space ventilation, V̇E: minute ventilation, *P<0.05 and **P<0.01 vs low PI_{max} group.

Conclusion: Respiratory muscle weakness increased dead-space ventilation ratio aggravating ventilation-perfusion mismatch during exercise in patients with CHF.

P789 | BEDSIDE
A randomized controlled trial of inspiratory muscle training program in heart failure with reduced ejection fraction

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Background: Inspiratory muscle weakness is prevalent and contributes to exercise intolerance in patients with heart failure.
Objective: To study the effect of moderate-intensity inspiratory muscle training (IMT) program on functional capacity, pulmonary function, inspiratory muscle

Abstract P789 – Table 1

	Inspiratory muscle training (IMT), n=20			Control (SHAM), n=20			Treatment affect
	Before Mean ± SD	After Mean ± SD	(Within) group difference P value	Before Mean ± SD	After Mean ± SD	(Within) group difference P value	P value
Dyspnea score (MMRC)	2.3±0.4	1.7±0.5	0.001*	2.1±0.2	1.9±0.3	0.333	0.002*
6-minute walk test (m)	471±116	516±77	0.015*	476±77	495±89	0.529	0.157
Peak oxygen consumption (ml/kg/min)	17.3±4.9	19.2±4.6	0.018*	18.7±4.5	18.9±5.2	0.817	0.049*
FEV1 (%)	78±13	79±13	0.481	77±15	78±17	0.428	0.326
FVC (%)	71±10	72±10	0.553	73±11	75±14	0.316	0.929
Maximal Inspiratory Pressure (MIP), cmH2O	88±16	103±21	0.001*	88±20	97±26	0.506	0.046*
Quality of life score	24±19	15±13	0.045*	23±17	21±17	0.669	0.057

strength, and the quality of life (QOL) in patients with chronic heart failure with reduced ejection fraction (HFrEF).
Methods: We conducted a prospective randomized controlled, double-blinded study. Fourty patients with HFrEF (53±12 years, 83% male, LVEF of 26±8%, NYHA II-III) were randomly 1:1 assigned to a 6-week daily program of IMT using the Threshold® IMT device at 40% of maximal inspiratory pressure (MIP) (IMT group, n=20) or to a placebo-IMT using loading at 15% of MIP (SHAM group, n=20). Dyspnea score, 6-minute walk test, maximal oxygen consumption, pulmonary function, inspiratory muscle strength (determined by MIP), and the QOL were assessed before and after the IMT.
Results: A 6-week daily program of IMT significantly improved MIP, dyspnea, and peak oxygen consumption (Table). There was also a trend towards improvement in QOL score in the IMT group.
Conclusions: (1) Moderate-intensity inspiratory muscle training program in patients with HFrEF results in significant improvement in dyspnea, inspiratory muscle strength, and peak oxygen consumption as well as trend towards improvement in QOL. (2) Moderate-intensity IMT using threshold loading at 40% of MIP was practically feasible to apply in NYHA II-III heart failure patients. (3) These findings suggest that IMT should be considered as a complimentary therapy in those patients with heart failure.
Acknowledgement/Funding: The Royal College of Physician of Thailand

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Long duration, low frequency compared to short duration, high frequency high intensity exercise improved heart rate variability, both exercise protocols improved cardiac function in type 2 diabetes

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Background: Type 2 diabetes (T2D) is associated with cardiac autonomic neuropathy, an independent risk factor for cardiovascular disease, overall mortality and coincides with left ventricular dysfunction.
Purpose: To compare the effect of 2 isocaloric high intensity exercise training (HIT) protocols on heart rate variability (HRV), cardiac function, glycemic control and cardiorespiratory fitness.
Methods: 40 individuals with T2D (56.1±9.0 years; 25% female) were randomized to low frequency HIT (LFT) (n=18) or high frequency HIT (HFT) (n=22). The LFT group performed 4 exercise sessions/week: 3 HIT sessions containing 3 times 4 minutes work bouts (90% of max HR, 30 min/bout) and 1 bout of moderate intensity training (MIT) (70% of max HR, 30 min/bout). The HFT group performed 12 exercise sessions/week: Nine 4 minutes HIT bouts (90% of max HR, 10 min/bout) and 3 MIT bouts (70% of max HR, 10 min/bout). Both groups exercised for 12 weeks. Echocardiography including tissue Doppler, measures of HRV (5-days continuous ECG using Firstbeat Bodyguard), glycosylated hemoglobin (HbA1c) and cardiorespiratory fitness (VO2peak) test were carried out before and after intervention.
Results: The LFT group significantly improved HRV (by root-mean square differences of successive R-R intervals) and the average nocturnal heart rate significant decreased (Table 1). Systolic and diastolic function improved both after HFT and LFT (Table 1). There was a significant mean difference between the groups in stroke volume (p=0.05). Both LFT and HFT groups improved HbA1c ($p<0.0001$ and $p<0.01$, respectively) and VO2peak ($p<0.001$ and $p<0.01$, respectively).

Low and high frequency training

	Low frequency HIT		High frequency HIT	
	Pre intervention	Post intervention	Pre intervention	Post intervention
Resting heart rate, beats/min	69.2±14.4	64.1±14.5°	65.3±8.5	60.8±11.2°
Nocturnal heart rate, beats/min	69±11	64±10°°	61±10	61±7
Heart rate variability (nocturnal RMSSD), ms	27±13	32±17°	29±13	35±17
Stroke volume, ml	102.0±41.6	109.0±39.0	100.1±55.1	119.8±70.7°°
Peak systolic tissue Doppler velocity S', cm/s	7.2±0.8	7.5±1.1°	7.6±1.4	7.8±1.0
Early diastolic tissue Doppler velocity e', cm/s	–8.4±1.7	–9.1±1.7°	–8.7±3.2	–8.8±2.7
Deceleration time, ms	173.0±17.5	174.2±13.6	191.8±10.2	170.4±15.8°

RMSSD, root-mean square differences of successive R-R intervals.

Conclusions: In patients with T2D, long duration, low frequency compared to short duration, high frequency HIT improved HRV, whereas both exercise protocols improved cardiac function, cardiorespiratory fitness and glycemic control.

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Usefulness of cardiopulmonary exercise test in identification of potential non-responders to cardiac resynchronization therapy

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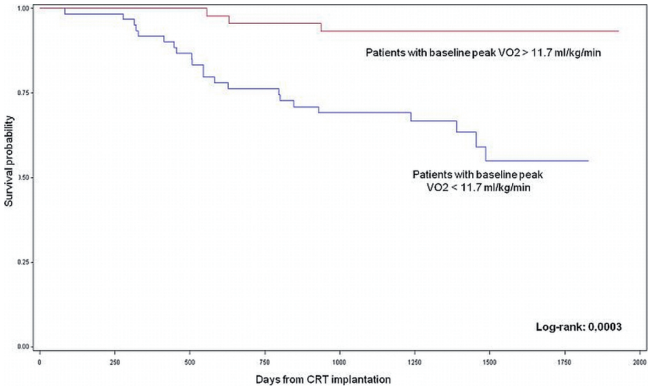
Background: The amount of non-responders to cardiac resynchronization therapy (CRT) is still high. We investigated, if any any baseline clinical settings may help in selection of potential responders to CRT.
Methods: The study comprised 117 patients (102 men, 65±9 yrs) with heart failure (HF) of ischemic (50 men/7 women) or non-ischemic (52 men/8 women) aetiology, in NYHA class II-IV, EF≤35%, QRS≥120ms. All the patients had CRT implanted. Clinical evaluation, cardiopulmonary exercise test (CPX) and NT-proBNP levels measurement were performed before CRT implantation and after 3–6 months. Positive response to CRT was defined as the improvement of NYHA class ≥1 after CRT.
Results: We identified 80 responders (68.4%) and 37 nonresponders (31.6%). Their baseline characteristics are listed in the table. In multivariate analysis, only baseline peak VO2 was the predictor of 2-year survival and response to CRT. The cut-off of peak VO2>11.7 ml/kg/min may be proposed to improve the selection of potential responders to CRT (see graphics).

Baseline characteristics of both groups

Parameters	Responders n=80 (68.4%)	Non-responders n=37 (31.6%)	Comparison R/NR (p)
Age [years]	64.3±9.3	67.7±8.4	0.0596
BMI [kg/m^2]	28.1±5.0	28.9±4.9	0.4384
Men	72 (90.0%)	30 (81.1%)	0.2346
DCM	47 (59.5%)	10 (27.1%)	0.0011
Arterial hypertension	78.2%	95.0%	0.164
Paroxysmal AF	18.5%	10.0%	0.494
Permanent AF	22.2%	35.0%	0.264
CABG	19.4%	20.0%	0.945
Myocardial infarct	43.8%	63.2%	0.152
QRS [ms]	167.1±27.1	166.8±26.8	0.967
EF [%]	24.0±7.5	24.7±8.8	0.734
LVEsV [ml]	139±54	137±98	0.969
LVEdV [ml]	202±51	218±61.5	0.693
NT-proBNP [pg/ml]	1578 [752–2682]	1415 [832–4184]	0.5184
Peak VO_2 [ml/kg/min]	12.0±3.7	10.5±3.5	0.042

R/NR, responders/non-responders; DCM, dilative cardiomyopathy; LVEsV, LV end-systolic volume; LVeDV, LV end-diastolic volume; peak VO2, peak oxygen consumption.



Kaplan-Meier survival analysis

Conclusions: 1. Baseline Peak VO2 (cut-off >11.7 ml/kg/min) is a good predictor of response to CRT and the survival after CRT.
2. No clinical nor echocardiographic baseline parameters predict the response to CRT.
Acknowledgement/Funding: Internal Grant of Institute of Cardiology

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Aerobic exercise training prevents autonomic impairment, oxidative stress and systemic inflammation in a model of aging, menopause e metabolic syndrome

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Background: Menopause aging and fructose consumption may lead to sympathetic activation, which may interact with oxidative stress, promoting cardiac dysfunction. Objective of this study was to investigate the effects of aging, menopause and metabolic syndrome (MS) on, cardiovascular, inflammatory and oxidative stress parameters in female rats submitted to ovarian hormone deprivation (OVX), as well as the role of exercise training (ET) in this condition.
Methods: Old rats with 22 month of age (n=8) were divided into: aged ovariectomized sedentary (IOS), aged ovariectomized fructose (IOF), aged ovariectomized trained (IOT) and aged ovariectomized trained fructose (IOTF). Ovariectomy was performed by bilateral ovaries removal. Fructose-fed rats received D-fructose (100g/L) for 10 weeks to develop MS. The ET was performed on a treadmill for 1 h a day, 5 days/wk for 8 wks. Arterial pressure (AP) and heart rate (HR) were directly recording by a data acquisition system (Windaq/2Hz). Hearts were processed for oxidative stress; inflammatory profile was measure in plasma.
Results: The ET decreased the adipose tissue and insulin resistance and increased physical capacity (IOT: 19.99±0.89, IOTF: 17.55±1.05 vs. IOS: 10.52±0.87; IOSF: 10.34±0.59 Min). Hemodynamic results demonstrated that the ET attenuated the increase in MBP induced by ovariectomy and/or overload of fructose (IOT: 103.3±1.0; IOTF: 107±1.1 vs.: IOS: 119.1±1.86; IOSF: 119.1±2.7 mmHg) and reduced the basal HR (IOT: 302.1±13.20; IOTF: 306.40±8.2 vs: IOS: 389.53±20.10, IOSF: 348.93±17.55 bpm). The sympathetic tonus was lower in ET groups (IOT: 62. 2±3.1; IOTF: 51.2±7.1) compared to OVX and fructose overload groups (IOS: 102.6±12.3; IOSF: 85.39±3.75 beats/min). Vagal tonus was increased only in the trained group without fructose (IOT: 44.76±5.87 vs IOFT: 22.87±3.38; IOS: 17.14±4.21; IOSF: 9.21±2.82 beats/min). Regard to inflammatory profile IL-1b, IL-10 and TNFa (pg/ml) were decreased in IOT compared all others groups. Oxidative stress SOD, CAT and GPx activities were significant differences between trained and sedentary groups. The redox status, indicated by GSH/GSSG, was increased in the trained group (IOS 4.08±0.56; IOSF 2.67±0.15; IOT 5.41±0.40; IOTF 5.33±0.24). Finally IOT and IOTF showed better diastolic function with lower isovolumetric relaxation time (IOS: 3.08±0.21; IOSF: 2.9±0.24; IOT: 1.98±0.15; IOTF: 2.72±0.2 ms), E/A ratio (IOS: 1.60±0.06; IOSF: 1.62±0.05; IOT: 1.41±0.17; IOTF: 1.66±0.08 ms), and cardiac global function by the myocardial performance index (IOS:0.40±0.06; IOSF:0.46±0.10; IOT: 0.14±0.03; IOTF: 0.29±0.04).
Conclusion: Our findings demonstrated that exercise training after ovarian hormone deprivation, with or without fructose overload, was able to positively modulate the autonomic function, reducing inflammatory and oxidative stress markers, consequently inducing improvement on cardiac function and physical capacity.
Acknowledgement/Funding: Capes 360/11

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Heated water-based exercise improves physical capacity, blood pressure and neurohormonal response but not endothelial function in resistant hypertensive patients

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Background: The control of blood pressure (BP) in resistant hypertensive (RH) patients is a recognized clinical challenge. Heated water-based exercise training (HEx) reduces blood pressure in RH patients, but some mechanisms involved in the pathophysiology of hypertension have not been studied in this population. This study examines the effects of HEx on peak VO2, ambulatory BP (ABP), neurohormonal response and endothelial function of RH patients.
Design and methods: This is a parallel-randomized controlled trial. Forty for patients age 53±6 years with RH (antihypertensive drugs 4–6) were allocated in two groups (HEx n=28 and control n=16). We analyzed the changes on peak VO2, ABP, circulating concentrations of catecholamine, renin, aldosterone, endothelin-1, nitric oxide, and endothelial function (reactive hyperemia) from baseline. The training was performed for 60-minutes sessions in a heated pool (32°C), three times a week for 12 weeks. The HEx protocol consisted of callisthenic exercises and walking inside the pool. The control group was asked to maintain habitual activities.
Results: HEx and control groups had similar peak VO2, ABPs, neurohormones values and endothelial function at baseline. Peak VO2 increased from 23.9±4.6 to 26.7±4.1 ml.kg.min-1, $p<0.0001$ in HEx group. Systolic and diastolic ABPs reduced significantly after heated water exercise (24-h: from 144.8/83.7 to 126.3/74.7 mmHg, $p<0.0001$). HEx decreased catecholamine (from 720±280 to 306±184 ng/ml, $p<0.0001$), renin (from 35±14 to 3.4±3.4 pg/ml, $p<0.0001$), aldosterone (from 101±52 to 76±18 pg/ml, p=0.01), endothelin-1 (from 41±15 to 26±9 pg/ml, p=0.03) and increased nitric oxide (from 25±8 to 75±24 pg/ml, $p<0.0001$). However, endothelial function did not change after HEx. No variable was changed in the control group after the intervention. All patients completed the protocol and there were no clinically relevant adverse events during the intervention.
Conclusion: HEx improves peak VO2, ABPs and neurohormonal response with neutral effects on measures endothelial function in RH patients. These results may help to explain the mechanisms underlying the reduction of BPs with heated water exercise. Thus, we could consider that HEx may be a tool counteracts RH in this high-risk population.

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Virtual group motivation in exercise stress testing increases patients' performance, comfort and potentially the predictive power

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Introduction: Exercise stress testing is a widely applied clinical tool to assess coronary artery disease. Patients should perform at least at 85% of their age-predicted maximum exercise capacity or should show an increase of the rate-pressure product (RPP) above 2.4 to ensure a sufficient validity of the test results. The aim of this study was to examine the effects of a "motivational video" of an exercising peer group on the exercise capacity and the comfort of patients during treadmill exercise testing.
Methods: 109 hospitalised patients and outpatients of a Swiss Teaching Hospital with a clinical indication for treadmill exercise stress testing were randomised 1:1 in an open label study to either treadmill exercise testing while watching a motivational video (group A, n=55) or treadmill exercise stress testing while watching a static colour image of a lavender flower (group B, n=54). Patients were matched for age, body weight and height, expected metabolic equivalents (METs) and expected maximum heart rate. The video consisted of an 18 min. video showing five middle aged amateur runners, running along woods and fields, giving the patient the idea of running with the group as shown in figure 1. The speed of the running group in the video correlated with the running speed of the treadmill. The exercise test was performed according to the standard ramp protocol. After the exercise test, patients rated a) their personal level of comfort, b) their perception of physical capacity limits achieved and c) how the video/picture enhanced their motivation on a 10-point scale.
Results: The patients of group A showed a significantly longer exercise duration (two-sample t-test, p=0.003), significantly higher rates of RPP increase >2.4 (chi-square-test, p=0.032) and a borderline significance to higher percentage of METs achieved (two-sample t-test, p=0.078). A sub analysis showed significantly higher percentage of METs achieved in group A in the patients with exercise stress test interruption due to exhaustion (two-sample t-test, p=0.036). The questionnaire revealed significantly higher rated levels of comfort (Mann-Whitney-test, p=0.022), significantly higher achievements of physical limits in group A (Mann-Whitney-test, p=0.010) and a significantly higher motivational effect of the video than the picture (Mann-Whitney-test, $p<0.001$).

A scene of the motivational video.

Conclusions: A motivational video, simulating the feeling of exercising in a group 1) increases the exercise duration and performance of patients, 2) enhances the patients comfort during exercise stress testing and 3) may improve the validity of the test results.
Acknowledgement/Funding: The study was funded by research funds of the Cantonal Hospital of Baden.

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Influence of O2 consumption upon cerebral function during operational memory task in red wine drinkers and abstainers subjected to exercise training: a study by functional magnetic resonance

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Introduction: Red wine (RW) and exercise (Ex) reduce cardiovascular risk and may protect cognitive function.
Purpose: We assessed the correlation between O2 consumption (peak VO2)

and cerebral response during operational memory task (two-back) in voluntary abstainers (ABS) and regular RW drinkers (VT).
Methods: 31 men without cognitive deficit, mean age 59.7±6,1 years, of whom 15 were ABS and 16 VT users were studied. Average ethanol consumption was 19.8±10.3 grams of ethanol/day during 21.1±15.2 years. Cerebral response, accuracy and time to response were studied by cerebral functional magnetic resonance imaging (RMf-3T). Cardiopulmonary exercise testing was performed in a cicloergometer. All individuals underwent supervised physical training 3 times/week/1 hour for 3 months.
Results: There were no demographics differences among groups, neither regarding accuracy and response time. VO2 peak increased in both groups with Ex (VT: 24.9±2.6 pre vs 27.1±3.5 ml/kg.min pos; $P<0.008$; ABS: 27.6±4.9 pre vs 29.9±4.1 vs ml./kg.min pos; $P<0.002$). Among ABS, before training, there was a negative correlation between VO2 peak and cerebral response (the greater VO2, smaller cerebral response) in superior frontal gyrus and right medial frontal; this was not found after physical training (statistic limiar of Z-score >2.3; $p<0.05$, corrected). However, no correlation between VO2 peak and cerebral response occurred, either before or after training, in VT group.

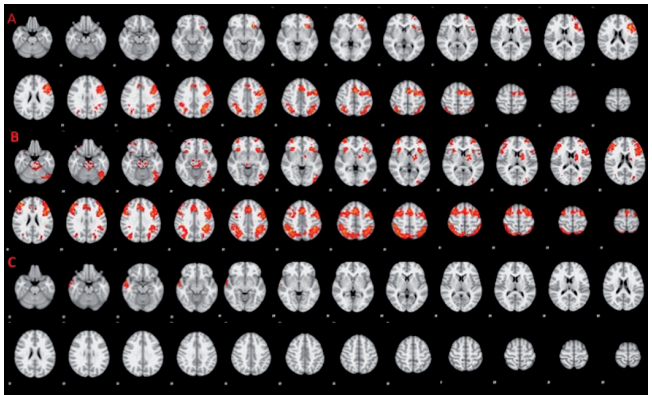

Figure 1: Two-back task fMRI results. A: ABS group map pre (active>neutral conditions contrast with BOLD effect showed in red color; B: VT group maps pre (same conditions contrast with BOLD effect showed in same color; C: negative correlation (VO_2 and BOLD effect) in ABS group in the following brain regions: superior frontal gyrus and right medial frontal (z-score>2.3; p<0.05, corrected).

Conclusions: The negative correlation between VO2 and cerebral response in right temporal area among ABS may indicate lower efficiency of the neural pathway associated with operational memory among those with worst physical conditioning. In contrast, among VT users such correlation was not observed even after training and VO2 increments. Therefore the absence of such negative correlation among RW drinkers may suggest a certain protective effect of previous long-term RW consumption. Furthermore, supervised exercise although improving physical performance in comparable degrees in both groups, seems to elicit different cognitive responses in RW drinkers and abstainers.
Acknowledgement/Funding: FAPESP

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Reduced diaphragm muscle thickness is associated with exercise intolerance in patient with heart failure

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Background: Sarcopenia is frequently accompanied by heart failure (HF), and it causes loss of limb muscle mass and strength. It is also likely to affect respiratory muscle such as diaphragm, and contribute to impaired respiratory muscle function and physical frailty. However, the relationship between diaphragm muscle, sarcopenia, and exercise intolerance in patients with HF remains undefined.
Purpose: The present study is aimed to investigate clinical characteristics and exercise tolerance in patients with HF and reduced diaphragm muscle thickness as assessed by the ultrasound.
Methods: The present study enrolled 77 patients hospitalized with HF. Diaphragm muscle thickness was assessed by ultrasound measurement, and reduced diaphragm muscle thickening was defined as less than the median value of 4 mm at end-inspiration.
Results: Compared with patients without reduced diaphragm muscle thickness, those with reduced diaphragm muscle thickness had significantly lower inspiratory muscle strength as assessed by maxim inspiratory pressure, and reduced 6-minute walk distance (6MWD) ($P<0.05$). Diaphragm muscle thickness was also positively correlated with the indicators of sarcopenia including arm grip strength, gate speed, and skeletal muscle index (all $p<0.05$). Even after adjustment for covariate, impaired diaphragm muscle thickness was independently associated with reduced 6MWD.
Conclusion: Impaired diaphragm muscle thickness was accompanied by sarcopenia, and was independently associated with exercise intolerance in patients with HF.

Acknowledgement/Funding: This study was supported by JSPS KAKENHI Grants (nos. 26350566)

P797 | BEDSIDE
Efficacy of aerobic exercise training with vascular occlusion in patients with chronic heart failure

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Background: Aerobic exercise training is an important adjunct to medical therapy in patients with chronic heart failure (CHF), but the effect that aerobic exercise training with vascular occlusion in patients with CHF improves exercise capacity is unknown.
Purpose: The aim of this study was to evaluate the impact of aerobic exercise training with vascular occlusion in patients with CHF.
Methods: Forty patients with CHF due to Ischemic cardiomyopathy were randomized to an interventional exercise group (IG, n=20) or a control exercise group (CG, n=20). Exercise was perfomed at an intensity of 40 to 60% of maximum Peak VO2/W (PVO2) for 15 min three times per week for 6 months. In IG, patients remained seated on the cycle ergometer saddle with their feet on the pedals, and the proximal end of thighs were applied by pneumatic tourniquets (width: 90mm, length 700mm) with appropriate pressure which was added 50–80 mmHg to the systolic pressure (209.5±7.6mmHg). We evaluated safety and effect of the intervention on exercise capacity, serum levels of brain natriuretic peptide (BNP) and thigh circumference (15cm above the patella).
Results: There were no differences between two groups at study entry (Age:61.7±11.2 vs 61.7±10.3 years; Height:166.7±7.4 vs 167.1±5.8 cm; Weight:68.8±10.1 vs 69.8±11.3 kg; Ejection Fraction:48.6±16.1 vs 52.9±16.2%; PVO2:17.1±3.8 vs 15.9±3.5 ml/kg/min; BNP:128.5±112.8 vs 142.6±183.3 pg/ml; Circumference of right thigh:47.7±6.0 vs 47.9±4.9 cm; Circumference of left thigh:48.2±6.1 vs 47.8±4.9 cm). Change of PVO2 was significantly larger in IG than in CG (30.4% vs 16.5%, $p<0.05$). Change of serum levels of BNP was significantly larger in IG than in CG (-58.9±7.5 vs 7.7±7.0 pg/ml, $p<0.05$). Change of circumference of right thigh was significantly larger in IG than in CG (1.9±1.7 vs -0.2±1.2 cm, $p<0.05$). Change of circumference of left thigh was significantly larger in IG than in CG (2.0±1.6 vs -0.1±1.3 cm, $p<0.05$).
Conclusion: These results suggest that aerobic exercise training with vascular occlusion can improve, without serious adverse events, exercise capacity, BNP and thigh circumference in patients with CHF.

P798 | BEDSIDE
Discriminating circulatory problems from deconditioning - Combined echo and cardio-pulmonary stress analysis

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Background: Distinguishing circulatory problems with reduced stroke volume from deconditioning in which the muscles cannot consume O2 normally based on gas exchange parameters is difficult.
Methods: We performed combined stress echo and cardio-pulmonary (CPET) tests in 115 consecutive patients to assess cardiac output, stroke volume, multiple hemodynamic parameters and oxygen content difference (A-VO2 Difference) in four predefined activity levels. We aimed to assess which of the gas exchange measures may distinguish between attenuated stroke volume response from muscular impairment.
Results: We defined attenuated stroke volume response as maximal stroke volume index $<50cc/m^2$ (based on patients with normal exam). Patients with abnormal stroke volume response (N=56) had attenuated changes in end diastolic volume, longitudinal contraction, and heart rate ($p<0.05$ for all group*time interactions), but patients with normal increase in stroke volume and low exercise capacity had lower A- VO2 Diff ($p=0.05$). Reduced anaerobic threshold (AT), low unchanging peak O2 pulse, periodic breathing, shallow delta VO2/delta work rate (WR) ratio, and high VE/VCO2 slope were all associated with abnormal stroke volume response ($p<0.05$ for all). The best single discriminator between patients with attenuated stroke volume response and muscular problems was VE/VCO2 slope corrected for peak O2/kg (VE/VCO2/peak $O2\geq2.7$; AUC 0.79: $p<0.0001$). Combined stress echo and CPET analysis showed that high VE/VCO2/peak O2 reflects an impaired cardiac condition, whose main determinants are reduced stroke volume, elevated left atrial pressure, and impaired right ventricular-pulmonary vascular function. In multivariate analysis the optimal gas exchange model included delta VO2/delta work rate<8.6, VE/VCO2/peak $O2\geq2.7$, and periodic breathing (AUC of 0.84, $p<0.0001$; sensitivity 63%, specificity 96%). Addition of rest stroke volume to VE/VCO2/peak O2 performed even better (AUC 0.87, $p<0.0001$).
Conclusion: The best gas exchange parameter to discriminate between circulatory problems to deconditioning is VE/VCO2/peak O2. Combining it to delta VO2/delta work rate and periodic breathing or to rest echo parameters improves the discriminative ability. Nonetheless, gas exchange parameters lack sensitivity, thus in borderline cases addition of stress echo is recommended.

BIOMARKERS IN CVD

P799 | BEDSIDE
Relationship of high-sensitivity cardiac troponin T and I with cardiac ischaemia in a population-based cohort - The Maastricht Study

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Introduction: Interest in high-sensitivity cardiac troponin (hs-cTn) is currently expanding from acute cardiac care to prognostic medicine and risk stratification. Basal hs-cTnT and hs-cTnI levels are associated with morbidity and mortality in various patient groups and even in apparently healthy subjects. Cardiac ischaemia is a plausible mechanism that may underlie the association between basal troponin levels and cardiovascular mortality. However, a direct comparison between the relationship of hs-cTnT and hs-cTnI with cardiac ischaemia has never been performed.
Purpose: To assess and compare the associations of hs-cTnT and hs-cTnI with cardiac ischaemia on electrocardiography (ECG), in the general population.
Methods: The relationship between the cardiac biomarkers (hs-cTnT, Roche; hs-cTnI, Abbott) and ischaemia on ECG was examined in The Maastricht Study, an ongoing prospective population-based cohort study that is enriched with individuals having type 2 diabetes mellitus. Ischaemia on ECG was classified into "probable" (Minnesota Coding (MC): 1.1, 1.2 and 1.7), "possible" (MC: 1.1, or 4.1–4.3 accompanied by 5.1–5.3) and "unlikely" (remaining MC). Multivariable logistic regression analyses with adjustment for Framingham Risk Score factors, estimated Glomerular Filtration Rate, waist-to-hip-ratio, alcohol use and educational level were conducted. For the analysis the categories "possible" and "unlikely" of ischaemia on ECG were combined as reference category. In addition, we tested for interaction with sex.
Results: A total of 3016 out of 3451 individuals were eligible for the analyses (men, n=1526, 50.6%: women, n=1490, 49.4%). For hs-cTnT and hs-cTnI the median (IQR) was 5.3 (3.8–7.7)ng/L and 1.9 (1.2–3.0)ng/L, respectively. The prevalence of ischaemia on ECG was 3.1% of the total study population. In the third tertile category of both hs-cTn assays (hs-cTnT>6.42ng/L: hs-cTnI>2.41ng/L) the prevalence of ischaemia on ECG was almost twice as high amongst women than men (hs-cTnT: men 4.3% vs women 7.8%; hs-cTnI: men 4.1% vs women 8.6%). After adjustment, the association with ischaemia on ECG was similar for both hs-cTn assays (hs-cTnT, 1-SD increase: OR 1.50, 95% CI 1.20–1.88, P<0.001; hs-cTnI, 1-SD increase: OR 1.56, 95% CI 1.32–1.83, P<0.001). The interaction between hs-cTnI and sex in the unadjusted model was significant (hs-cTnT, Pinteraction=0.738; hs-cTnI, Pinteraction=0.042). The sex-specific odds ratios for the association between hs-cTnT and ischaemia on ECG were 1.49 (95% CI 1.08–2.06, P=0.015) for men and 1.48 (95% CI 1.08–2.05, P=0.016) for women. For hs-cTnI the sex-specific odds ratios were 1.43 (95% CI 1.13–1.80, P=0.003) and 1.81 (95% CI 1.42–2.32, P<0.001) for men and women, respectively (hs-cTnI,Pinteraction=0.126).
Conclusions: The present study shows a comparable association of hs-cTnT and hs-cTnI with cardiac ischaemia in a population-based cohort. Hs-cTnI, may be stronger related to cardiac ischaemia in women than in men.
Acknowledgement/Funding: This study was supported by sources as stated in Schram MT, et al. Eur J Epidemiol. 2014 Jun;29(6):439-51. doi: 10.1007/s10654-014-9889-0

P800 | BEDSIDE
Prognostic value of high-sensitivity troponin-T in adults with congenital heart disease

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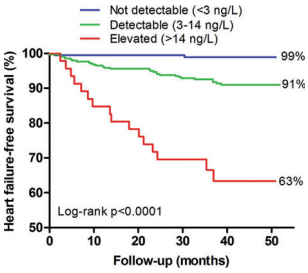
Background: Cardiac troponins are associated with adverse outcome in chronic cardiovascular conditions. In adults with congenital heart disease (CHD), high-sensitivity Troponin-T (hs-TnT) has been related to surrogate prognostic markers such as ventricular function. To our knowledge, longitudinal data are not available yet.
Purpose: The objective of this study was to investigate the association between hs-TnT and adverse outcomes in adults with CHD.
Methods: This is a prospective cohort study. Consecutive adults with stable CHD who visited the outpatient clinic between April 2011 and April 2013 underwent hs-TNT serum level measurement and extensive echocardiography at the same day. Multivariable Cox proportional hazards regression was performed to determine associations with clinical outcome events, independently of age, sex and systemic ventricular function.
Results: A total of 602 patients were included (median age 32 [IQR 25–41] years, 58% male, 90% New York Heart Association class I). Patients had a diagnosis of congenital aortic stenosis (n=138), aortic coarctation (n=112), arterial switch operation (n=24), tetralogy of Fallot (n=179), Mustard operation (n=65), congenitally corrected transposition of the great arteries (n=21), Fontan (n=36) or other (n=27). Hs-TnT was detectable (3–14 ng/L) in 346 (57%) and elevated (>14 ng/L) in 47 (8%) patients. Median follow-up was 3.5 [IQR 3.0–3.8] years. The increased risk for all primary outcome events per two-fold increase in hs-TnT is tabulated. In the figure, a Kaplan-Meier curve is presented which demonstrates the heart failure-free survival in patients with undetectable, detectable but normal and elevated levels of hs-TnT.

2log hs-TnT and events

Outcome	No. of events	Multivariable hazard ratio (95% CI)*	p-value
Death	12	2.90 (1.66–5.06)	<0.001
Hospitalization for cardiac reasons	125	1.36 (1.17–1.57)	<0.001
Heart failure	46	1.67 (1.32–2.11)	<0.001
Arrhythmia	90	1.31 (1.11–1.56)	0.002
Thromboembolic complication	20	0.99 (0.67–1.48)	0.971
Re-intervention	89	1.20 (1.00–1.43)	0.049
Death + heart failure	50	1.64 (1.31–2.06)	<0.001
Any adverse event	165	1.24 (1.09–1.41)	0.001

*Adjusted for age, sex and systemic ventricular function.



hs-TnT and HF-free survival

Conclusions: In adults with CHD, serum Hs-TnT level is independently associated with all-cause mortality, hospitalization for cardiac reasons, heart failure and arrhythmia. Hs-TnT therefore seems to be a very promising novel biomarker in this patient group.
Acknowledgement/Funding: This study was supported by the Dutch Heart foundation (grant number 2015-T-029)

P801 | BEDSIDE
Preoperative NT-proBNP levels, but not hs-TnT levels, provide independent prognostic information after cardiac surgery

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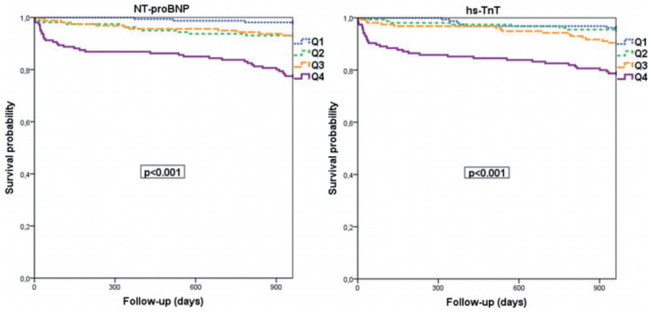
Background: N-terminal pro-B-type natriuretic peptide (NT-proBNP) and high-sensitivity troponin T (hs-TnT) are established cardiac biomarkers, but whether preoperative NT-proBNP or hs-TnT levels individually or in combination improve risk prediction in cardiac surgical patients is not known.
Methods: We included 640 consecutive patients from FINNAKI-Heart Study that were hospitalised for cardiac surgery and had preoperative blood samples available. Maximum follow-up was 961 days.
Results: In total, 61 patients (9.5%) died during follow-up with no perioperative deaths. Median preoperative levels of both NT-proBNP and hs-TnT were higher in non-survivors compared to survivors (2032 [Q1–3 476–5389] vs. 374 [136–1352] ng/L; and 39 [16–191] vs. 13 [8–32] ng/L, respectively, p<0.001 for both). Stratifying patients according to preoperative biomarker levels demonstrated highest risk in the patients with NT-proBNP and hs-TnT levels in the 4th quartile (Figure). The area under the curve (AUC) by receiver-operating statistics for preoperative NT-proBNP levels to predict time to death was 0.73 (95% CI 0.67–0.80) and the



Kaplan-Meier plot

AUC for preoperative hs-TnT to predict time to death was 0.70 (0.63–0.77). A significant correlation between preoperative levels of NT-proBNP and hs-TnT existed (r=0.58; p<0.001). In univariate Cox regression models, both NT-proBNP and hs-TnT were associated with mortality (p<0.001). In a multivariate Cox regression model that included clinical risk factors and both cardiac biomarkers, preoperative NT-proBNP levels, but not preoperative hs-TnT levels, were associated with mortality during follow-up: HR (per 1 SD in lnNT-proBNP) 1.43 (95% CI 1.18–1.74); p<0.001. Moreover, in separate multivariate Cox regression models for NT-proBNP and hs-TnT levels, only preoperative NT-proBNP levels were associated with mortality when adjusting for clinical risk factors: HR 1.44 (1.18–1.75); p<0.001.

Conclusion: Preoperative NT-proBNP levels, but not preoperative hs-TnT levels, provided incremental prognostic information to established risk indices in patients hospitalised for cardiac surgery.

P802 | BEDSIDE

New markers for cardiovascular evaluation: genetic profile, Hs-CRP, Homocysteinemia, Lipoprotein (a) and Pulse Wave Velocity

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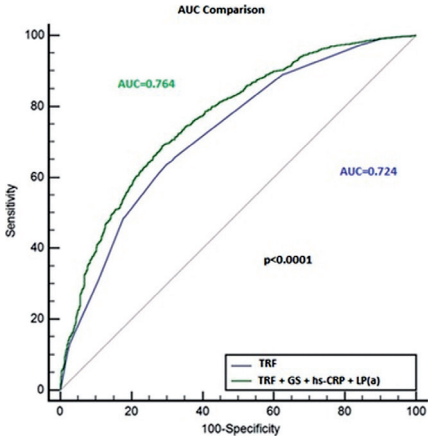
New cardiovascular markers to be included in clinical assessment have to prove to have an additional predictive value on cardiovascular risk stratification over traditional risk factors (TRF). So far, their predictive value remains unclear.

Methods: A case-control study included 2469 subjects, 1321 CAD patients and 1148 controls adjusted for age and gender. 29 genetic variants associated with CAD were evaluated and the individual genetic risk score (GRS) was calculated by multiplicative method. Additionally, the TRF as well as the pulse wave velocity (PWV), high sensitivity C-reactive protein (hs-PCR), homocysteine (Hcy) and lipoprotein (a) were determined in both populations. ROC curves and AUC were calculated for the total population, comprising the TRF before and after the inclusion of new risk markers. The comparison of ROC curves was performed by the DeLong test. A multivariate analysis was performed including TRF and all new markers.

Results: Significant differences (p<0.0001) were observed in all studied variables. After multivariate analysis, the variables that were independently associated with CAD were: GRS (OR=1.820; CI: (1.486; 2.228); p<0.0001), Lp(a) (OR=1.009; CI: (1.007; 1.012); p<0.0001) and hs-CRP (OR= 0.887; CI: (0.883; 0.943); p<0.0001). Significant increases in the ROC curve of 0.724 to 0.750 were observed when the GRS was included (p<0.0001). Similarly, the AUC increased from 0.724 to 0.742 with the addition of Lp(a) (p<0.0001) and from 0.724 to 0.734 after hs-CRP addition (p=0.0004). The inclusion of 3 simultaneously markers allowed the ROC curve to increment from 0.724 to 0.764 (p<0.0001).

Multivariate with TRF and new markers

Variables	B	S.E.	Wald	df	Odds ratio (CI 95%)	P-value
Hypertension	0.669	0.094	50.354	1	1.952 (1.622 - 2.347)	<0.0001
Diabetes	1.136	0.110	106.384	1	3.113 (2.509 - 3.863)	<0.0001
Dyslipidemia	0.930	0.138	45.769	1	2.535 (1.936 - 3.319)	<0.0001
Smoking	1.226	0.096	163.528	1	3.408 (2.824 - 4.112)	<0.0001
Genetic Score	0.599	0.103	33.598	1	1.820 (1.486 - 2.228)	<0.0001
Hs-CRP	-0.120	0.032	14.488	1	0.887 (0.833 - 0.943)	<0.0001
Lp(a)	0.009	0.001	49.003	1	1.009 (1.007 - 1.012)	<0.0001
Constante	-2.292	0.157	213.163	1	0.101	<0.0001



Conclusion: These results if confirmed in other populations, highlight the need to monitor the GRS, lipoprotein(a) and hs-C-reactive protein to be included in more accurate prediction of cardiovascular risk and as targets for future development of new therapies.

P803 | BENCH

Prognostic value of basal high-sensitive cardiac troponin levels on mortality in the general population: a systematic review and meta-analysis

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Background: The interest in the use of cardiac troponins has been expanded from diagnosis of acute myocardial infarction to risk assessment for morbidity and mortality. However, the prognostic value of cardiac troponin for all-cause mortality in the general population has not been systematically assessed. In addition, potential differences in the prognostic performance between cardiac troponin T and I are unexplored.

Purpose: The aim of this study was to quantify the relationship between basal levels of high-sensitive cardiac troponin T and I and all-cause mortality in the general population.

Methods and results: Medline, Embase and the Cochrane Library were searched (from inception through October 2015) for prospective observational cohort studies reporting on the prognostic value of basal high-sensitive cardiac troponin T and/or I levels on all-cause mortality in the general population. On a total of 2638 reviewed citations, 39 articles were retrieved, and nine articles, with data on 43988 participants, were included in the meta-analysis. Statistical pooling showed a significant association between increased basal cardiac troponin levels and an elevated hazard ratio for all-cause mortality during follow-up (HR per 1-SD 1.18, [95% CI, 1.09 to 1.27]). Meta-regression analysis showed a trend (p=0.053) towards better prognostic value for cardiac troponin T compared to troponin I (1.31 [CI, 1.13 to 1.53] and 1.11 [CI, 1.02 to 1.20], respectively).

Conclusion: Elevated, basal cardiac troponin T and I levels were significantly associated with increased risk of all-cause mortality during follow-up in the general population. Basal cardiac troponin T may better predict all-cause mortality than troponin I.

Acknowledgement/Funding: Grant support: This study was supported by a research grant from Stichting De Weijerhorst

P804 | BEDSIDE

High-sensitivity troponin-I independently correlated with angiographic severity of coronary artery disease in patients with no history of cardiovascular events: baseline data from the ANOX study

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Background: Biomarkers predicting the presence and severity of coronary artery disease (CAD) in patients with suspected CAD, but no previous history of any cardiovascular events (CVE), are unclear.

Methods: The ANOX study is a multicenter, prospective cohort study to determine the predictive value of possible novel biomarkers related to angiogenesis or oxidative stress for major adverse cardiovascular events among patients undergoing elective angiography. Between January 1, 2010 and November 1, 2013, a total of 2,513 patients were enrolled. After excluding 93 patients who were subsequently found ineligible or withdrew consent, and 1,099 patients with previous history of CVE, the baseline data of 1,321 patients (49% with CAD, 24% with multivessel disease [MVD]) were analyzed. Blood samples were collected from the arterial catheter sheath at the beginning of coronary angiography. The presence of angiographic CAD (≥50% stenosis in ≥1 coronary artery) and its severity were assessed using the Gensini score. Serum levels of vascular endothelial growth factor (VEGF), VEGF-C, soluble VEGF receptor-2, and two oxidatively modified LDLs (the α1-antitrypsin/LDL complex [AT-LDL] and serum-amyloid-A/LDL complex [SAA-LDL]), as well as N-terminal pro-brain natriuretic peptide (NT-proBNP), high-sensitivity troponin-I (hsTrop-I), and high-sensitivity C-reactive protein, were measured. We performed stepwise regression analyses including data on age, sex, systolic blood pressure (SBP), LDL-C, HDL-C, presence of diabetes (DM), history of smoking habit, and these biomarkers.

Results: The presence of CAD was significantly correlated with age (OR, 1.5 per 10 year; 95% CI, 1.3–1.6), sex (OR, 1.9 for men; 95% CI, 1.4–2.4), SBP

(OR, 1.09 per 10 mmHg; 95% CI, 1.02–1.16), HDL-C (OR, 0.81 per 10 mg/dL increase; 95% CI, 0.75–0.88), DM (OR, 2.3; 95% CI, 1.8–2.9), and natural log-transformed hsTrop-I (Ln-hsTrop-I) (OR, 1.8 per 1-SD increase; 95% CI, 1.3–2.8). The presence of MVD was also significantly correlated with age (OR, 1.3 per 10 year; 95% CI, 1.1–1.5), sex (OR, 2.2 for men; 95% CI, 1.6–3.0), SBP (OR, 1.10 per 10 mmHg; 95% CI, 1.02–1.18), HDL-C (OR, 0.82 per 10 mg/dL increase; 95% CI, 0.74–0.90), DM (OR, 2.1; 95% CI, 1.6–2.8), and Ln-hsTrop-I (OR, 1.2 per 1-SD increase; 95% CI, 1.1–1.4), as well as LDL-C, SAA-LDL, and AT-LDL. After excluding 353 patients with normal coronary (Gensini score, 0) to attain normal distribution, independent determinants of Ln-Gensini score were sex, HDL-C, DM, Ln-hsTrop-I, and Ln-NT-proBNP.

Conclusions: A high hsTrop-I value seems to serve as an independent predictor of the presence and severity of CAD in patients with suspected CAD but no history of CVE.

Acknowledgement/Funding: Grant-in-Aid for Clinical Research from the National Hospital Organization

P805 | BEDSIDE
Soluble klotho plasma levels influence the predictive value of fibroblast growth factor-23 and phosphate levels in patients with coronary artery disease

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Purpose: Low levels of 25 OH vitamin D and high levels of Phosphate (P), Parathormone (PTH), and Fibroblast Growth Factor-23 (FGF23) have been related with cardiovascular (CV) damage and adverse prognosis. The soluble form of klotho, the receptor for FGF23, has been said to have a protective effect on the CV system. However, the prognostic role of this protein in the outcome of patients (pts) with CV disease has not been studied.

Methods: We studied 704 pts with coronary artery disease (CAD). Calcidiol (vitamin D metabolite), FGF23, klotho, P, and PTH plasma levels were assessed at baseline. The outcome was the development of an acute ischemic event (any acute coronary syndrome, stroke or transient ischemic attack), heart failure, or death.

Results: During follow-up (2.15±0.99 years), 77 pts developed the outcome. Pts developing the outcome were older and were more frequently women. They had lower levels of klotho (518.6 [424.3–628.0] vs 565.7 [463.4–697.5] pg/ml; p=0.022) and calcidiol (16.5 [10.6–23.4] vs 19.1 [14.1–24.7] ng/ml; p=0.003) and higher levels of FGF23 (87.3 [62.2–148.4] vs 72.6 [55.5–98.4] RU/ml; p=0.002) and PTH (65.1 [48.1–93.0] vs 59.4 [44.4–75.9] pg/ml; p=0.025) than those remaining stable, without differences in P levels (3.35±0.61 vs 3.23±1.38 mg/dl; p=0.489). They had more often diabetes, hypertension, coronary artery by-pass graft, atrial fibrillation, ejection fraction<40%, they used more often acenocumarol, insulin, diltiazem and diuretics, and less frequently aspirin. Glomerular filtration rate was lower in these patients. There were no differences in other characteristics.

FGF23 (HR=1.109 95% CI [1.015–1.212]; p=0.022), calcidiol (HR=0.964 95% CI [0.929–1.000]; p=0.049) and P (HR=1.787 95% CI [1.168–2.736]; p=0.007) plasma levels were independent predictors of the outcome along with age and hypertension (Cox regression analysis).

The population was divided in 2 groups according to the median of klotho plasma levels (559.3 pg/ml). Pts with klotho levels < median developed the outcome more often than those with klotho ≥ median (13.5 vs 8.3%; p=0.029). In patients with klotho levels < median, FGF23 (HR=1.142 95% CI [1.039–1.255]; p=0.006) and P (HR=2.366 95% CI [1.307–4.280]; p=0.004) levels were independent predictors of the outcome, along with age and previous surgical coronary revascularization. However, in patients with klotho levels ≥ median, FGF23 and P levels were not independent predictors of the outcome, and hypertension (HR=3.809 95% CI [1.117–12.985]; p=0.033) and glomerular filtration rate (HR=0.969 95% CI [0.946–0.993]; p=0.011) emerged as predictors of outcome along with treatment with diltiazem.

Conclusions: In CAD pts with low klotho plasma levels, FGF23 and P levels are associated with adverse outcomes. This association was not present in pts with high klotho levels. These data support the hypothesis of a protective role of soluble klotho on the CV system. Further studies are needed to confirm this hypothesis.

P806 | BEDSIDE
The possible role of cystatin-C in subclinical organ damage in white coat hypertension

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Purpose: The clinical significance and pathophysiology of white-coat hypertension (WCH) have not been fully elucidated. We therefore, investigated its relation with subclinical organ damage as well as potential clinically relevant mechanisms, such as blood pressure (BP) and heart rate (HR) variability as indexes of sympathetic tone, inflammatory response and cystatin-C.

Methods: The study included 386 untreated subjects who underwent 24-hour ambulatory blood pressure monitoring. The population was divided into 204 WCH subjects and 183 normotensive controls. HR and BP variability indexes were obtained for the assessment of autonomic modulation. In all participants, flow mediated dilation (FMD), pulse wave velocity (PWV) and intima-media thickness (IMT) were evaluated, while left ventricular mass index (LVMI), the presence of hypertrophy (LVH) and mitral Doppler E/A ratio were also assessed by echocardiography. Moreover, several inflammatory biomarkers including interleukin-6 (IL-6) and C-reactive protein (CRP) as well as cystatin-C levels were also measured in both groups.

Results: WCH group compared to controls exhibited higher values of LVMI (80.0±1.3 vs 73.6±1.1 g/m^2, p<0.0001), decreased E/A ratio (1.06±0.02 vs 1.19±0.03, p=0.001) and increased prevalence for LVH [OR] = 2.3, p<0001. Also, this group had increased PWV (8.6±0.10 vs 7.6±0.09 m/sec, p<0.001) and decreased FMD values (5.2±0.3 vs 6.8±0.3, p<0.001) but showed not significant differences in IMT (p=0.399). HR and BP variability indexes did not differ between the two groups (p=NS for all). Interestingly, WCH group exhibited similar values for IL-6 (p=0.083) and CRP (p=296) but significantly elevated cystatin-C values (784±17 vs 737±14 ng/mL, p=0.035), compared to controls. Of note, using linear regression analysis, cystatin-C levels were positively correlated with LVMI (r=+0.19, p=0.036) and PWV (r=+0.38, p<0.001).

Conclusions: According to this study, the presence of WCH is accompanied by more pronounced subclinical organ damage compared to controls. Among other proposed mechanisms, cystatin-C may play significant role as an early biomarker of renal function or potentially, as a direct contributor to cardiac and vascular abnormalities.

P807 | BENCH
Novel urinary biomarkers for early detection of experimental diabetic nephropathy

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Background: Prevention of diabetic nephropathy (DN) could lead to a decrease in concomitant adverse cardiovascular outcomes. Experimental studies in animals with early stages of diabetic kidney dysfunction are necessarily to develop a new preventive approaches. Kidney injury molecule-1 (KIM-1), neutrophil gelatinase-associated lipocalin (NGAL), and fatty acid binding proteins (FABP) are considered promising urinary biomarkers for early detection of DN in clinical practice. However, their diagnostic role for early detection of experimental DN is obscure.

Purpose: In this study, we tested the hypothesis that increased urinary KIM-1, NGAL, and heart-type FABP (H-FABP) are present prior to the onset of albuminuria in uninephrectomized rats with type 2 diabetes.

Methods: All procedures were in compliance with the "Principles of laboratory animal care" (NIH Publication no. 85–23 revised 1985) and according to the national law. In three weeks after unilateral nephrectomy 18 male Wistar rats were subsequently divided into two study groups: 1) diabetic group fed high-fat diet for 5 weeks and then successively received nicotinamide (230 mg/kg) and streptozotocin (65 mg/kg) intraperitoneally; 2) non-diabetic group fed with normal diet and received citrate buffer without streptozotocin. After 10, 20 weeks, and at the end of the experiment (at week 30), urine and blood samples were collected. Histological examination (PAS and Masson's trichrome staining) and electronic microscopy were also performed.

Results: At week 10, routine blood biochemical markers of kidney dysfunction did not statistically differ between groups with tendency to hyperfiltration, and albuminuria was only slightly but not significantly different between groups indicating early stage of DN (10,0±2,1 mg/l in diabetic groups; 6,1±0,8 mg/l in control rats, p=0,052). In contrast, KIM-1 and NGAL were highly increased in diabetic animals (205,6±18 ng/ml and 565,1±50,4 pg/ml, respectively) compared to non-diabetic control rats (108, 2±10,2 ng/ml and 197,4±30,6 pg/ml, respectively) with p-value = 0,038 and 0,018, respectively. Indicating early stage of DN confirmed by early electronic glomerular and tubular changes. At the end of the study urinary KIM-1 and NGAL levels were four and three times higher compared to control animals, respectively (p<0,01 each) and positively correlated with albuminuria and serum creatinine. H-FABP didn't show significant correlation with routine renal function markers.

In conclusion, urinary KIM-1 and NGAL might offer an advantage with respect to early detection of experimental DN in type 2 diabetic rats.

Acknowledgement/Funding: The research was supported by research resource center "Molecular and cell technologies" of St. Petersburg State University

P808 | BENCH
Circulating miR-106a and miR-424 predict future fatal myocardial infarction in healthy individuals

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Background: Coronary heart disease (CHD) is currently the most common cause of death globally, and the number of individuals at risk is increasing. To manage this pandemic, improved tool for risk prediction, including more sensitive biomarkers is needed. Circulating microRNAs (miRs) have emerged as promising biomarkers for diagnosis of cardiovascular diseases in health and disease.
Objectives: To explore the potential of circulating miRs to predict future fatal myocardial infarction (MI) in healthy participants.
Methods: We performed a prospective nested case-control study with a 10-year observation period with fatal MI as endpoint. In total, 179 circulating miRs were quantified by real-time quantitative polymerase chain reaction in serum of 112 healthy men and women (40–70 years) from the HUNT2 study that either (1) suffered from fatal MI within 10 years [n=56], or (2) remained healthy [n=56, risk factor-matched controls]. Candidate miRs were validated in a separate cohort of healthy individuals (n=100, 44% women). Conditional logistic regression was used to determine the combination of miRs with the best potential for risk prediction.
Results: We found 12 miRs significantly regulated between cases and controls in the exploration cohort. Among these, 10 miRs were also regulated between cases and controls in the validation cohort ($p<0.05$). Using a more conserved p-value of 0.01, the circulating levels of miR-106a-5p, miR-151a-5p, let-7g-5p and miR-26a-5p were lower in cases compared to controls. In addition, miR-424–5p was significantly higher in male cases versus controls. The best miR-based risk-prediction model for future MI consisted of a combination of miR-424–5p and miR-106a-5p providing an overall 68% correct classification for both genders, and a 66% and 73% and overall correct classification for women and men, respectively.
Conclusion: miR-424–5p and miR-106a-5p represent promising new risk markers of MI, especially in men.
Acknowledgement/Funding: Norwegian Health Association

P809 | BEDSIDE
Cyr61, a novel soluble biomarker of acute myocardial ischaemia characterised by rapid release kinetics

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Background: Cystein-rich angiogenic inducer 61 (Cyr61) is a member of the matricellular CCN family. Cyr61 is characterised by hypoxia-induced activation and can be secreted. Increased expression of Cyr61 was described in atherosclerotic plaques and cardiomyocytes in patients with ischaemic congestive heart failure. Currently, no data exist on the release kinetics of Cyr61 during myocardial ischaemia. Transcoronary ablation of septal hypertrophy (TASH) as a therapeutic approach in patients with hypertrophic obstructive cardiomyopathy (HOCM) and represents a unique method to define precisely the onset of myocardial ischaemia. In the present study we analysed the release kinetics of Cyr61.
Material and methods: A total of 10 consecutive patients with HOCM who underwent TASH were included in the study. The TASH procedure was performed according to the current interventional standard. Venous serum samples were collected before TASH and at 15 min, 30 min, 45 min, 60 min, 75 min, 90 min, 105 min, 2 hours, 4 hours, 8 hours, and 24 hours after induction of myocardial infarction and were stored at -80°C until measurement. Concentrations of Cyr61 were measured in serum from 10 patients in duplicates using an enzyme-linked immunosorbent assay (EIA-5108, DRG Instruments, Marburg, Germany). High-sensitivity cardiac troponin I (hs-cTnI, Abbott Diagnostics, USA) was used as a reference biomarker.
Results: The median concentration of Cyr61 before TASH was 381 ng/L [IQR 294–418 ng/L] in 7 patients with HOCM. Release of Cyr61 occurred during a very short period (0 - 105 min) after induction of myocardial infarction and the kinetics showed two peaks. The maximum concentration of Cyr61 was 643 ng/L [IQR 469–646 ng/L] and occurred 15 min after induction of myocardial infarction. This represents a significant rise of 49.5% [IQR 41.9–66.7%] compared with the Cyr61 concentration before TASH (p=0.028; Wilcoxon–Test). The median concentration of hs-cTnI before TASH was 12 ng/L [IQR 6–74]. A significant rise in hs-cTnI levels was noted 15 min after induction of myocardial infarction compared with the concentration before TASH (16 ng/L [IQR 9–83 ng/L]; p=0.01; Wilcoxon–Test). The maximum concentration of hs-cTnI was measured 24 hours after TASH (17,911 ng/L [IQR 12,654–49,942 ng/L]).
Conclusion: Cyr61 is characterised by rapid release kinetics during acute myocardial ischaemia and may represent a promising novel biomarker for use in the diagnosis of patients with acute chest pain.

P810 | BEDSIDE
Long-term impact of iron deficiency on cardiovascular outcome in a male general population sample during 21-years follow-up

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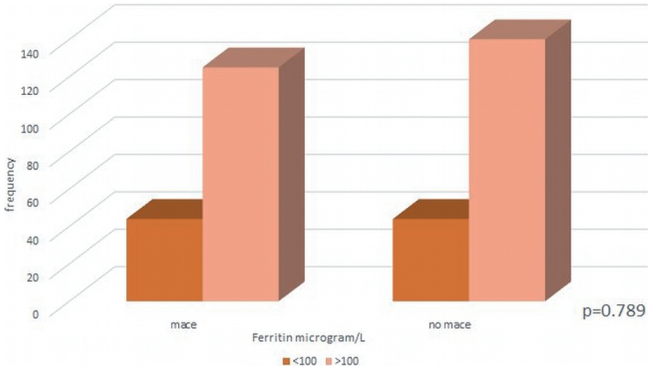
Background: Iron deficiency has been assumed to be related to the development of cardiovascular (CV) diseases. However, results from epidemiological studies have been conflicting. Moreover, the data about long-term impact of iron deficiency on CV outcome in the general population is still lacking.
Purpose: The aim of this study was to explore the relationship between iron deficiency and the CV outcome in terms of major adverse CV events (MACE) including death, stroke, TIA, heart failure requiring hospital care, myocardial infarction, unstable angina pectoris and pulmonary embolism in a general population during 21-years follow-up.
Population and methods: This investigation is part of "The study of men born in 1943", a longitudinal prospective study of men born in 1943 and living in the city of Gothenburg, Sweden. This random population sample were first examined in 1993 (at 50 years of age) and underwent a re-examination including echocardiography in 2014 (at 71 years of age). Questionnaires were used to evaluate medical history, concomitant diseases, general health, socioeconomic status, and quality of life. A panel of biomarkers for iron deficiency [serum ferritin, soluble transferrin receptor (S-TfR) and S-TfR/log ferritin] were analyzed from blood samples at the 1st visit of 1993. Endpoints were collected from 1993–2014. Hazard ratio was estimated by logistic regression.
Results: MACE occurred in 164 (46%) of 355 participants. For distribution of iron deficiency, a cut-off of S-ferritin <100 microgram/L and S-TfR/log ferritin >1.5 were used. In total, 88 participants (24.7%) had S-ferritin <100 microgram/L, 108 had S-TfR/log ferritin >1.5, 88 hade either S-ferritin <100 microgram/L or S-TfR/log ferritin >1.5 and 51 hade both S-ferritin <100 microgram/L and S-TfR/log ferritin >1.5. In those with S-ferritin <100 microgram/L MACE incidence was 50% compared with 48% in those with ferritin >100 microgram/L. Moreover, in those with both S-ferritin <100 microgram/L and S-TfR/log ferritin >1.5, the MACE incidence was 45% compared with 41% in those with both S-ferritin >100 microgram/L and S-TfR/log ferritin <1.5. After adjustment of increased inflammation (increased interleukin-6), no statistiscally significant association was found between iron deficiency and MACE (HR; 1.0; 95% CI 0.7–1.5; p 0.789).



Conclusions: Iron deficiency is not associated with adverse cardiovascular outcome in a middle-aged male population during 20 years of follow-up.

P811 | BEDSIDE
Prediction of cardiovascular events with plasma proprotein convertase subtilisin/kexin type 9 levels: a systematic review and meta-analysis

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Background/Introduction: Proprotein convertase subtilisin/kexin type 9 (PCSK9) is a protein that enhances degradation of the LDL receptor and agents that inhibit PCSK9 significantly reduce atherogenic lipoproteins that could lead to cardiovascular event reduction. However, it is unknown whether plasma PCSK9 levels predict future cardiovascular events.
Purpose: We performed a meta-analysis of all longitudinal studies for determining the ability of PCSK9 levels to predict risk of future CV events and dissected factors influencing this predictive ability.
Methods: The MEDLINE, Cochrane and EMBASE databases, and reviewing reference lists from retrieved articles and abstracts from large international cardiovascular conventions were searched until January 2016. Longitudinal studies that reported events or relative risk (RR) estimates with 95% confidence intervals were included. Two reviewers extracted data independently and summary estimates of association were obtained using a random-effects model.
Results: Of the 7 studies included (7,273 participants, mean follow-up 6.23 years), all reported results on total CV events. Four studies with significant heterogeneity (I2=73.3%) provided data on the risk according to strata of PCSK9

and allowed estimation of the shape of the association between PCSK9 and the risk of events. Analysis of the 4 studies reporting tertiles for cardiovascular events showed that the pooled relative risk (RR) did not increase from the first (reference group) to the third tertile [RR for the 2nd tertile=1.00 (95% confidence interval (CI): 0.73 to 1.37), p=1.00 and RR for the 3rd tertile=1.12 (95% CI: 0.87 to 1.43, p=0.38). The pooled RR for an increase of PCSK9 levels by 1 standard deviation was 1.08 (95% CI: 0.99 to 1.16, p=0.0502 and I2=0%). We observed no publication bias.
Conclusions: PCSK9 levels, although marginally, are not significantly associated with increased risk of total CV events. Further studies are warranted for a better understanding of the predictive role of PCSK9 levels on cardiovascular health.

P812 | BEDSIDE
Increased levels of copeptin, a surrogate marker of AVP, are associated with an increased risk of CKD in a healthy population

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Background: Our aim was to test if plasma copeptin, a stable surrogate marker of arginine vasopressin (AVP), predicts decline of glomerular filtration rate (GFR) and risk of new onset chronic kidney disease (CKD).
Methods: We measured copeptin and renal function during baseline exam and reassessed renal function after a follow-up time of 16.6±1.5 years (n=3186) in a population-based longitudinal study (mean age 56.4±5.7 years, 39.8% males). Furthermore, we defined CKD based on an estimated GFR (eGFR) calculated by the Modification of Diet in Renal Disease (MDRD) <60 ml/min (CKD_60MDRD), <45 ml/min (CKD_45MDRD) and <30 ml/min (CKD_30MDRD).
Results: After multivariate adjustment (gender, age, baseline eGFR, smoking status, systolic blood pressure, antihypertensive treatment, and follow-up time) copeptin (beta-coefficient per one SD increment of copeptin) was independently associated with significantly greater annual decline of eGFR (mL/min) according to the MDRD formula [0.057 (0.022–0.093); p=0.001] as well as according to the Cockroft-Gault (CG) formula [0.037 (0.014–0.060); p=0.002]. Each SD increment of copeptin independently predicted incident CKD_60MDRD (odds ratio, OR, 95% confidence interval) (OR 1.19, 95% CI: 1.04–1.36; p=0.010), CKD_45MDRD (OR 1.33, 95% CI: 1.04–1.71; p=0.026) and CKD_30MDRD (OR 3.69, 95% CI: 1.41–9.66; p=0.008). The relationship between copeptin and CKD defined by CG gave similar results.
Conclusion: Our data suggest that increased levels of copeptin independently predict decline in eGFR and greater risk of new-onset CKD. Furthermore, our data suggest that copeptin can be used to identify high-risk individuals for CKD development in order to offer early preventive strategies.

P813 | BEDSIDE
Endothelial nitric oxide synthase Glu298Asp gene polymorphism is an independent risk factor for inducible myocardial ischemia in patients with suspected coronary artery disease

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Background: Inducible myocardial ischemia may occur in the presence or absence of obstructive coronary artery disease (CAD). Genetically determined coronary endothelial dysfunction may predispose to functional coronary abnormalities contributing to myocardial ischemia in patients with or without obstructive CAD. The most studied eNOS gene polymorphism (Glu298Asp, G894T), able to reduce eNOS activity, has been associated with CAD while the association with myocardial ischemia was not established.
Purpose: To investigate the potential association of Glu298Asp polymorphism with inducible myocardial ischemia in patients with suspected CAD.
Methods: Six cardiology units enrolled a total of 269 consecutive patients (158 males; mean age 61.8±9.8 years) referred for suspected CAD within the BIOGENCARE Tuscan Region Italian Study. All patients underwent stress cardiac imaging and were referred to coronary computed tomography angiography (CCTA) or invasive coronary angiography following the referring physicians' choice. Blood samples were collected for genotyping and clinical bio-humoral characterization.
Results: In the study group, 49.4% of patients were homozygous for the G894allele, 40.5% heterozygotes, and 10.0% homozygous for T894. Inducible myocardial ischemia was documented in 99 patients (36.8%) and obstructive CAD in 80 (29.7%). At logistic regression analysis, the T allele was significantly associated with inducible myocardial ischemia (HR 2.03, 95% CI 1.23–3.37, P=0.006) even after adjustment for coronary risk factors or the presence of obstructive CAD. Stratifying the population by the presence/absence of ischemia and obstructive CAD, the T allele was an independent predictor of the most significant disease (CAD+Ischemia) (HR 2.27, 95% CI 1.01–5.06, P=0.046).
Conclusions: In patients with suspected CAD the eNOS Glu298Asp gene polymorphism is an independent risk factor for inducible myocardial ischemia.

P814 | BEDSIDE
Iron deficiency independently predicts cardiovascular death and myocardial infarction in patients with acute coronary syndrome: first report on the prospective relevance of iron deficiency in ACS

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Introduction: While iron deficient heart failure patients are at increased risk of future cardiovascular events and see improvement with intravenous supplementation, the clinical relevance of iron deficiency in Acute Coronary Syndrome (ACS) remains unclear. Therefore, for the very first time, we aimed to evaluate the prognostic value of iron deficiency in ACS.
Methods: Within the prospective AtheroGene study, levels of ferritin, iron and transferrin were measured at baseline in 533 patients with ACS. Iron deficiency was defined as ferritin levels <100 mg/L or between 100 and 299 mg/L, if the transferrin saturation was <20%. Main outcome measures were cardiovascular mortality and nonfatal myocardial infarction (MI).
Results: During a median follow-up of 4.0 years, 12.2% of all subjects suffered an endpoint. A total of 29.3% of our population was categorized as iron deficient. Prevalence of iron deficiency was significantly higher in women, in patients with anaemia, and in patients with multi-vessel disease. In multivariate cox regression analyses, adjusted for sex, age, body-mass-index, smoking status, hypertension, diabetes, dyslipidemia, haemoglobin, (log)NT-proBNP, and (log)Troponin I, iron deficiency strongly predicted cardiovascular death and nonfatal MI [HR 1.68 (95% CI 1.02–2.77), p=0.042]. Kaplan-Meier analyses also evidenced the prognostic relevance of iron deficiency.
Conclusions: Iron deficiency is strongly associated with adverse outcome in ACS. If validated in independent cohorts, this finding might pave the way to new therapies.

P815 | BEDSIDE
Evaluation of the creatinine uromodulin ratio as new serum marker for cardiovascular events

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Background: Uromodulin, a protein exclusively produced by the kidney, has recently been demonstrated to be lower in subjects with declined renal function and the ratio creatinine/uromodulin has been proposed as a novel and superior kidney biomarker in serum of healthy subjects.
Purpose: The purpose of this study was to investigate the prospective value of that new biomarker since it is thought to be of high clinical relevance given the link between kidney function and cardiovascular disease.
Methods: We thus evaluated the association between serum levels of uromodulin with the presence of CAD and the cardiovascular risk in 529 angiographically characterized patients. Cardiovascular events have been recorded up to 8 years.
Results: Serum uromodulin concentration did not significantly differ between patients with and without angiographically determined CAD (165.4±78.9 vs. 164.2±75.3ng/ml ng/ml vs. p=0.934) but in patients with CAD, it correlated significantly and inversely with the extent of stenoses (r=-0.191, p=0.001). Apart from that, in the total population, there was a significant and inverse correlation with proBNP (r=-0.164, p=0.002). With respect to the full follow-up time of up to 8 years (6.6±1.8 years, mean±SD), first vascular events occurred in 27% of the study population. Applying the ratio creatinine/uromodulin in serum, we observed an adjusted HR of 1.27 [95% CI 1.10–1.47] and a p=0.001 with with age, sex, bmi, LDL- and HDL cholesterol, triglycerides, presence of CAD and hypertension, T2DM, and smoking status as well as statin treatment as covariates.
Conclusion: We conclude, that serum uromodulin in combination with serum creatinine is a novel predictive tool for cardiovascular event risk.

P816 | BEDSIDE
Plasma levels of endothelin-1 and renal function among young and healthy adults

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Introduction: Endothelin 1 (ET-1), a vasoconstrictive peptide, is associated with several cardiovascular risk factors.
Purpose: The aim of this study was to investigate the association of plasma ET-1 and renal function among young and healthy adults from the general population.
Methods: Individuals aged 25–41 years were invited to participate in a prospec-

Abstract P816 – Table 1. Relationship ET1 and renal function

	Continues (n=2104)	Quartile 1 (n=527)	Quartile 2 (n=528)	Quartile 3 (n=526)	Quartile 4 (n=523)	P for trend
Creatinine						
Multivariable adjusted model	2.24 (0.94; 3.54), p<0.001	Reference	0.36 (–0.86; 1.59)	1.07 (–0.15; 2.29)	2.12 (0.88; 3.36)	0.0003
Estimated glomerular filtration rate						
Multivariable adjusted model	–2.14 (–3.57; –0.72), p=0.003	Reference	–0.29 (–1.63; 1.04)	–0.96 (–2.30; 0.37)	–2.16 (–3.52; –0.80)	0.0008
Cystatin C						
Multivariable adjusted model	0.03 (0.01; 0.04), p<0.001	Reference	0.003 (–0.01; 0.02)	0.02 (0.003; 0.03)	0.03 (0.01; 0.04)	<0.0001

Data are β coefficients (95% confidence intervals), with log-transformed endothelin-1 as outcome variable. Multivariable models were adjusted for sex, age, body mass index, current smoking status, low density lipoprotein cholesterol, hemoglobin A1c, systolic blood pressure, high-sensitive CRP, pro-brain natriuretic peptide, estimated muscle mass, estimated total body water, physical activity.

tive population-based cohort study (GAPP) in the Principality of Liechtenstein. Main exclusion criteria were established cardiovascular diseases, known renal failure and diabetes mellitus. Fasting venous plasma samples were used to measure creatinine, cystatin C and ET-1. The estimated glomerular filtration rate (eGFR) was calculated using the creatinine based chronic kidney disease epidemiology collaboration (CKD-EPI) formula. Multivariable regression models were constructed to assess interrelationships of plasma ET-1 with parameters of renal function.

Results: We included 2160 participants in this analysis. The median age was 37 years and 47% were men. The median (interquartile range) level of eGFR in our population was 112 ml/min/1.73m^2 (103; 118 ml/min/1.73m^2). Significant linear relationships were found between renal function and increasing quartiles of ET-1. Using quartile 1 as the reference group, the β-coefficients (95% confidence interval) for eGFR were -0.29 (-1.63; 1.04), -0.96 (-2.30; 0.37) and -2.16 (-3.52; -0.80) for quartiles 2–4, respectively. Results of the analyses using ET-1 as a continuous variable were similar and are shown in the Table.

Conclusion: ET-1 levels are strongly associated with parameters of renal function among young and healthy adults, suggesting an important role of ET-1 in the regulation of kidney function.

Acknowledgement/Funding: Swiss National Science Foundation, Swiss Heart Foundation, Swiss Society of Hypertension, University of Basel

P817 | BEDSIDE
Transient and rapid increase in the levels of cardiovascular stress biomarkers in amateur middle-aged male after marathon run

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Background: Cardiovascular safety of marathon running in the middle-aged amateurs remains unclear. We set up this study to evaluate the effects of a marathon run on the profile of the cardiovascular stress biomarkers.

Methods: Thirty there healthy men, aged ≥50 years (mean age 57±7), who were amateur runners were enrolled in the study. Venous blood samples were obtained at baseline (before the marathon), just after the race, 2–4 and 7 days after the marathon. Using novel single molecule counting technology we measured: plasma concentrations of high-sensitive cardiac troponin I (hs-cTnI), and endothelin-1 (ET-1). N-terminal pro B-type natriuretic peptide (NT-proBNP) was measured using electrochemiluminescence method (clinically validated assay).

Results: We observed sharp rise in the levels of all biomarkers after the race (all p<0.01), which subsequently rapidly normalized after 2–4 days and stayed in the normal range after 7 days post-race (table). Increases of the biomarkers levels were not interrelated. Neither finishing time nor any index of heart rate achieved during marathon run correlated with biomarkers levels. Interestingly, those with more intensive training program had lower leak of hs-cTnI after marathon (16.64±9.94 vs 37.99±33.53 pg/mL, p<0.05, those with ≥169 km/week run vs <169 km/week, respectively).

Table 1. Venous blood concentrations of selected biomarkers

Biomarker	Baseline	After marathon		
		0 h	2–4 days	7 days
hs-cTnI (pg/ml)	3.67 (1.88–5.38)	22 (9.58–34.56)	4.94 (1.81–9.09)	2.51 (1.44–4.03)
NT-proBNP (pg/ml)	50 (33–73)	169 (112–365)	67 (26–114)	53 (31–76)
ET-1 (pg/ml)	3.03 (2.5–3.4)	5.22 (4.4–5.89)	3.03 (2.53–4.12)	2.76 (2.31–3.42)

All data presented as median with interquartile range. hs-cTnI, high-sensitive cardiac troponin I; NT-proBNP, N-terminal pro B-type natriuretic peptide; ET-1, endothelin-1; h, hours.

Conclusions: Marathon run is associated with sharp and significant rise in the biomarkers of cardiovascular stress. However, profile of these changes resembles dynamics observed in the conditions not related with cardiovascular damage. The pathophysiology and clinical importance of these findings need further research.

FAMILIAL HYPERCHOLESTEROLEMIA AND DYSLIPIDAEMIA

P818 | BEDSIDE
Screening for familial hypercholesterolemia in brazil: data from the study of cardiovascular risk in adolescents (ERICA study)

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Introduction: Cardiovascular diseases are the main cause of mortality in Brazil and worldwide, and hypercholesterolemia in as an important risk factor. Familial Hypercholesterolemia (FH) is an autosomal dominant genetic disorder with a worldwide estimated prevalence of 1:200 to 1:500 individuals in its heterozygous form. Individuals with FH are exposed to high LDL-cholesterol (LDLc) from birth, what leads to premature cardiovascular events. Diagnosing FH in young individuals is important not only for early treatment, but also because cascade screening in relatives is recommended. In Brazil, like most countries, FH is considered a problem of public health, but it is still underdiagnosed and undertreated.

Purpose: To evaluate the prevalence of Brazilian adolescents with LDLc or non-HDL cholesterol (non-HDLc) levels that suggests FH.

Methods: The ERICA study was a national cross-sectional study, school-based, that assessed the prevalence of most cardiovascular risk factors in 75,000 adolescents between 12 and 17 years old, living in cities with over 100,000 inhabitants in Brazil (including all 27 state capitals). All the evaluations were performed at the schools, in a regular weekday. Since fasting was necessary for blood drawing, in this analysis only students from the morning period were included. Data were analyzed by sex, age, type of school (public or private) and geographic regions of Brazil. In accordance to international guidelines, FH was considered suspected in adolescents with untreated fasting LDLc ≥160mg/dl or non-HDLc ≥190mg/dl. Moreover, we evaluated the prevalence of adolescents with LDLc ≥190 mg/dl, what highly suggests the diagnosis of FH at this age.

Results: A total of 38,069 adolescents were evaluated, 48% females and 52% from public schools. The prevalence of adolescents with LDLc ≥160 mg/dl or non-HDLc ≥190 mg/dl was 0.49% (95% CI 0.34 to 0.71 – n=209). Most of these adolescents were in the age group of 12–14 years old (57% - 95% CI 40.6 to 72.1), in public schools (82.4% - CI 72.5 to 89.3) and living in the southeast region of the country. Still, 0.12% of the adolescents (95% CI 0.04 to 0.34 – n=44) presented LDLc ≥190 mg/dl. Considering the current Brazilian population, we estimate that approximately 100,000 (1:200) Brazilian adolescents aged 12 to 17 are suspected to have FH based solely on their LDLc/ non-HDLc levels and need further evaluation.

Conclusion: This study found a high prevalence of Brazilian adolescents with lipid changes suggestive of FH and in need of further analysis to confirm the diagnosis. Our results reinforce the importance of universal screening as a crucial tool for early diagnosis and treatment.

Acknowledgement/Funding: Brazilian Ministry of Health (Department of Science and Technology) and Brazilian Ministry of Science, Technology and Innovation

P819 | BEDSIDE
Prognosis of patients with clinical familial hypercholesterolemia after acute coronary syndrome

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Background: Patients with heterozygous familial hypercholesterolemia (FH) may be at particular risk of recurrence after acute coronary syndrome (ACS). However, data are limited on these patients' current prognosis in an era of intensive statin therapy, as well as of the impact of the strategy used in defining FH.

Methods: We studied 4,534 men and women from a prospective cohort of patients hospitalized with ACS in Switzerland between 2009 and 2014, in whom we applied three algorithms for FH diagnosis based on clinical criteria only, using LDL-cholesterol levels and personal or family history of premature coronary disease: (1) the latest American Heart Association (AHA) algorithm, (2) the Simon

Broome Register algorithm, and (3) the Dutch Lipid Clinic Network algorithm to assess probable/definite FH (>5 points). For each algorithm, we used multivariable adjusted Cox proportional models to assess the risk of first major adverse cardiovascular events defined as cardiovascular death, myocardial infarction, or ischemic stroke. Restricted analyses were conducted in 1,369 patients with premature coronary heart disease, defined as below 55 years for men, and below 60 years for women.
Findings: Over the year following ACS, 275 (6.1%) patients had a cardiovascular event, 217 (4.8%) had a fatal or non-fatal myocardial infarction, and a total of 153 (3.4%) died. Prevalence of clinical FH was 2.5% (95% confidence interval (CI) 2.1–3.0) using the AHA algorithm, 5.5% (95% CI 4.9–6.2) using the Simon Broome algorithm, and 1.6% (95% CI 1.3–2.0) using the Dutch Lipid Clinic algorithm. After multivariable adjustment for age, sex, body mass index, current smoking, hypertension, pre-existing cardiovascular disease and diabetes mellitus, the risk of a recurrent cardiovascular event was higher in patients with FH, as compared to patients without FH, with multivariable adjusted hazard ratio (HR) of 2.06 (95% CI 1.01–4.21, p=0.047) for the AHA algorithm, 2.34 (95% CI 1.38–3.97, p=0.002) for the Simon Broome algorithm, and 2.31 (95% CI 0.84–6.34, p=0.1) for the Dutch Lipid Clinic algorithm. Further adjustment for high-intensity statins at discharge, attendance to cardiac rehabilitation, and the 6-month GRACE prognosis score yielded HRs of 2.08 (95% CI 0.97–4.48, p=0.06) for the AHA algorithm, 2.49 (95% CI 1.43–4.33, p=0.001) for the Simon Broome algorithm, and 2.49 (95% CI 0.90–6.90, p=0.08) for the Dutch Lipid Clinic algorithm. Similar associations were found when restricting the analyses to patients with premature ACS only.
Interpretation: Patients with FH identified at the time of hospitalization for ACS using clinical criteria have more than a two-fold risk of recurrence of cardiovascular events within the first year after discharge than patients without FH.
Acknowledgement/Funding: Swiss National Science Foundation (SNSF 33CM30-124112)

P820 | BEDSIDE
Heterozygous familial hypercholesterolaemia: a common entity with unfavorable long-term prognosis in patients with very early ST-segment elevation myocardial infarction

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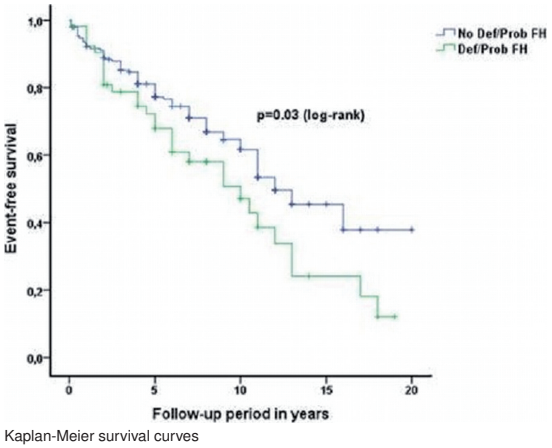
Background and aims: Familial hypercholesterolaemia (FH) is an important cause of early onset coronary artery disease. We assessed the prevalence of heterozygous (He) FH among patients with very early ST-segment elevation myocardial infarction (STEMI), and its long-term prognosis in the era of widespread utilization of statins.
Methods: We recruited prospectively 320 consecutive patients who had survived their first STEMI ≤35 years of age. Using Dutch Lipid Clinic Network [DLCN] algorithm patients having HeFH (possible, probable or definite) were identified.
Results: Sixty-five patients (20.3%) had definite/probable HeFH (DLCN algorithm). Two years after discharge among 51 patients with definite/probable HeFH and available lipid levels, 43 (84.3%) were taking statins of whom 10 (23.3%) were on high-intensity statin therapy but only 1 (2.3%) had LDL cholesterol levels <1.8 mmol/L (70 mg/dL). After a median follow-up of 9.1 years, major adverse coronary events (MACE) occurred in 99 (38.8%) of 255 patients with available follow-up information. Definite/probable HeFH was associated with an excess risk for occurrence of MACE independently of statin use, continuation of smoking after the STEMI, hypertension, diabetes mellitus, and sex (hazard ratio=1.615, 95% confidence interval, 1.038 to 2.512, p=0.03). Figure shows the event-free Kaplan–Meier survival curves in patients with probable/definite HeFH versus patients with no probable/definite HeFH.



Kaplan-Meier survival curves

Conclusions: One out of five patients who develop STEMI ≤35 years of age has definite/probable HeFH and despite the use of statins there is a therapeutic gap and a high recurrence rate of cardiac events during a long-term follow-up.

P821 | BEDSIDE
Clinical Impact of Heterozygous Carrier of ABCG5 Gene on Asymptomatic Normolipidemic Patients: Evidence from Familial Gene Analysis

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Background: Sitosterolemia is a rare recessive form of inherited disease characterized by increased levels of plant sterols such as sitosterol, the cause of which is ATP-binding cassette (ABC) sub-family G member 5 (ABCG5) or ABCG8 gene mutations. However, few data exist regarding the clinical features and significance of heterozygous sitosterolemic carrier due to the rarity of this disease. The aim of our study was to determine the clinical impact of heterozygous mutation carriers of ABCG5 or ABCG8 gene.
Methods and results: We performed genetic analyses of ABCG5 and ABCG8 genes for the 15 family members of patients with homozygous sitosterolemia from different 3 families, and investigated their serum sitosterol levels as well as their lipid levels. We identified 12 heterozygous carriers (male=6, mean age=40) which exhibit single mutation in ABCG5 gene among these families (c.130C>T, c.1306G>A, c.1813_1817delCTTTT) as well as 3 normal family members (male=1, mean age=48). Although there were no significant differences in TC, TG, HDL-C, and LDL-C levels between heterozygous carriers and normal family members, serum sitosterol level of heterozygous carriers was significantly higher than that of normal family members (10.8±4.3 vs 2.7±0.5 μg/ml, p<0.05). Interestingly, heterozygous carriers showed neither xanthomas nor any coronary artery diseases.
Conclusions: These results demonstrate that heterozygous ABCG5 gene mutation carriers which are somewhat difficult to be identified by the conventional methods may exist among the common normolipidemic patients without significant clinical manifestations. We suggest that the functional analysis of ABCG5 or ABCG8 may facilitate identifying hyper-sitosterolemic carriers.

P822 | BEDSIDE
The prevalence and prognostic importance of possible familial hypercholesterolemia in patients with myocardial infarction

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Background and purpose: Familial hypercholesterolemia (FH) is a common genetic disorder causing accelerated atherosclerosis and premature cardiovascular disease. The aim of this study was to examine the prevalence and prognostic significance of possible FH in patients with myocardial infarction (MI).
Methods and results: By individual-level linkage of data from the Eastern Danish Heart Registry and national administrative registries, a study population of patients referred for coronary angiography due to MI was selected. The study population was divided into "unlikely FH" and "possible FH" based on the Dutch Lipid Clinic Network (DLCN) criteria which included a plasma Low Density Lipoprotein cholesterol and age for onset of cardiac disease. A score of ≥3 points was used as the cutpoint between the two groups.
Among the study population of 13,174 MI patients, 1,147 (8.7%) had possible FH. These patients were younger (58.2 vs. 65.6 years, p<0.0001), had similar levels of comorbidities, and were treated more aggressively with cholesterol-lowering drugs compared to patients with unlikely FH. During a median of 3.3 years of follow-up, differences in adjusted all-cause mortality were insignificant (17% vs. 23%, adjusted Hazard Ratio (HR) 0.90, 95% CI 0.76–1.06, p=0.2). The unadjusted and adjusted event rate of recurrent MI was higher in patients with higher compared to lower LDL-C (17% vs. 11%, adjusted HR 1.29, 95% CI 1.09–1.54), p=0.003).
Conclusion: This large observational study showed that MI patients with possible FH have similar risk of mortality but higher risk of recurrent MI. Further studies on secondary prevention are warranted.

P823 | BEDSIDE
Contemporary trends in the management and outcomes of patients with familial hypercholesterolemia in Canada

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Background: Heterozygeous Familial Hypercholesterolemia (HeFH) is one of the most common genetic diseases in the world and an important cause of premature cardiovascular disease. While our knowledge of the molecular causes of HeFH has advanced dramatically and has led to the development of novel therapies for hypercholesterolemia in these patients, there are still important gaps in our knowledge. In particular, data on current patterns of treatment and cardiovascular (CV) risk of HeFH are needed.

Purpose: The purpose of this study was to characterize the HeFH population, their current treatment patterns and CV outcomes in British Columbia, Canada.
Methods: We conducted a longitudinal observational study of patients with physician diagnosed "probable" or "definite" HeFH, based on Dutch Lipid Clinic Network Criteria (DLCNC). Data were collected at baseline (the time of initial patient recruitment) and at each subsequent clinic visit. We collected data on laboratory values, medication use and CV events. CV events were defined as: myocardial infarction, stable/unstable angina, percutaneous coronary intervention, coronary artery bypass grafts, and stroke/transient ischemic attacks.
Results: As of December 2015, the BC HeFH Registry consists of 339 patients, of whom 106 have probable and 233 have definite HeFH, with a total of 3,700 person-years of follow-up. The median length of follow-up was 8.7 years. The mean age of patients was 43.9 years, and median DLCNC score was 9.0 (with scores >8 indicating definite HeFH). The mean LDL cholesterol at baseline was 5.9 mmol/L, and at last follow-up was 3.7 mmol/L. Use of lipid-lowering therapies increased from 35.7% at baseline to 84.7% at last follow-up. At last follow-up, 31% of patients were on low/moderate potency statins, 46.9% on high potency statins, and 37.2% on combination statins plus ezetimibe. At last follow up, a ≥50% reduction in LDL was achieved in 34.5% of patients, an LDL ≤2 mmol/L in 8.3% and an LDL ≤1.8 mmol/L in 5.9%. The overall CV event rate in this cohort was 33.5/1000 person-years. Among patients with a prior CV event, 59% experienced a recurrent event within 5 years.
Conclusions: These data contribute to our understanding of contemporary trends in the management of patients with HeFH in Canada, the lipid levels achieved, and the natural history of the disease. This represents the first Canadian study of HeFH to determine annualized risk of CV disease. Despite a majority of patients receiving lipid-lowering therapy, only few patients reached high risk lipid targets, and the burden of recurrent disease was substantial. These results point to ongoing challenges in the care of patients with HeFH and opportunities to improve outcomes in this patient population.
Acknowledgement/Funding: Sanofi-aventis Canada Inc.

P824 | BEDSIDE
A nation-wide survey of patients with homozygous familial hypercholesterolemia undergoing lipoprotein-apheresis in Turkey (A-HIT Registry)

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Familial hypercholesterolemia (FH) is a genetic disease characterized by extremely high levels of cholesterol leading to cholesterol deposition in skin and tissues, and premature atherosclerosis. In homozygous individuals (HoFH) lethal cardiovascular events can occur at very early ages. Where available, lipoprotein-apheresis (LA) is the mainstay of treatment to improve survival in patients with HoFH This survey was conducted to provide insight to clinical status of HoFH patients undergoing LA in Turkey.
Methods: The survey included 63 HoFH patients (29 women, 34 men) undergoing regular LA in 15 specialized centers. The principal managing physicians from each center were interviewed, and each completed a questionnaire about local LA procedures. Also, for each patient, a further questionnaire was completed to collect data on clinical characteristics, LA details, lipid levels over the last 4 apheresis sessions, co-medication, cardiovascular events, and complications etc.
Results: Mean patient age was 26±9 years. Age at first symptoms of disease was 9±10 years, and at diagnosis 11±10 years. At the time of diagnosis, mean LDL-cholesterol level was 667±201 mg/dL. Symptoms at presentation were xanthoma (41%) and ischemic symptoms (41%). Only 2 patients (3.2%) were diagnosed during family screening. Parental consanguineous marriage was present in 57% of cases. Overall, xanthomas were present in 76.2%, aortic valve pathology in 44% and coronary artery disease was documented in 54% of cases. Age at first LA was 20±11 years. Only 9 patients were undergoing LA weekly, 21% were receiving LA every 10 days, 40% every 15 days, 13% every 20 days, and 13% monthly; mean frequency of apheresis sessions was 16±7 days. For the last 4 LA sessions, LDL-cholesterol levels post apheresis reached target only in 12.5% of patients. None of the centers had a standardized approach for LA in HoFH.
Conclusions: 1. In Turkey, HoFH diagnosis is delayed with a long interval between diagnosis and the initiation of LA. These delays result in progression of atherosclerosis and aortic stenosis. Increased awareness of HoFH is needed among physicians and the public.
2. Though LA is a lifesaving therapy for patients with HoFH, in real clinical practice, most patients experience ineffective LA and fail to reach targets. A structured approach and new treatments are urgently needed for these patients.

P825 | BEDSIDE
Lp(a) levels predict cardiovascular events in patients with Familial Hypercholesterolemia with and without previous cardiovascular disease. Insights from the SAFEHEART registry

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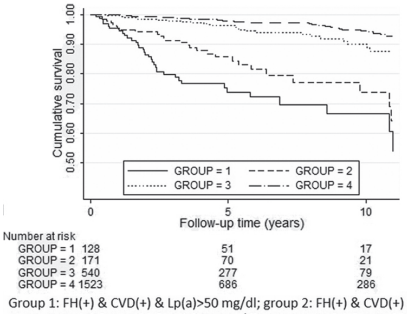
Background: Heterozygous familial hypercholesterolemia (FH) increases the risk of cardiovascular disease. Lp(a) is a predictor of cardiovascular events in patients with FH. Nevertheless, it is not well known its prognostic accuracy depending on the presence of previous atherosclerotic cardiovascular disease (ASCVD).
Aim: To determine the relationship between Lp(a) levels and the development of cardiovascular events in a large cohort of FH patients with or without previous ASCVD.
Methods: Data from the study, which recruited individuals aged 18 and older between January 2004 and October 2015 were analysed. Out of them, 2362 were genetically diagnosed of FH and followed-up. The end-point consisted of fatal or non-fatal new onset myocardial infarction, fatal or non-fatal new onset ischemic stroke, coronary revascularization, aortic valve replacement, peripheral artery revascularization and cardiovascular death. Lp(a) level cut-off point was 50 mg/dl.
Results: Mean age of FH individuals was 45.5±15.4 years; 1087 (45.2%) were male; 307 (12.8%) had previous ASCVD. Mean follow-up time was 5.4±3.2 years. Figure below shows the survival curves for the combined end-point. Log rank p value was 0.045 and 0.001 for FH patients with and without previous ASCVD respectively.



Group 1: FH(+) & CVD(+) & Lp(a)>50 mg/dl; group 2: FH(+) & CVD(+) & Lp(a)≤50 mg/dl; Group 3: FH(+) & CVD (-) & Lp(a)>50 mg/dl; group 4: FH(+) & CVD (-) & Lp(a)≤50 mg/dl
Survival curves

Conclusions: Increased Lp(a) levels are related to the development of cardiovascular events in patients with as well as in patients without previous CVD. This finding reinforces the role of Lp(a) levels in the prognosis assessment of FH patients.
Acknowledgement/Funding: Grant G03/181 and FIS PI12/01289 from Instituto de Salud Carlos III (ISCIII), Grant 08-2008 Centro Nacional de Investigación Cardiovascular (CNIC).

P826 | BEDSIDE
Higher arterial wall inflammation in familial combined hyperlipidemia (FCH) compared to familial hypercholesterolemia (hFH), independently of LDL levels

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Background: Adults with familial hyperlipidemias (FH), either heterozygous (hFH) or combined (FCH), are characterized by high levels of LDL, systemic inflammatory activation and experience higher risk for premature atherosclerosis than the general population. However, it is unknown whether these two dyslipidemias have similar effects on the arterial wall.
Purpose: The aim of this pilot study was to investigate possible differences in arterial wall's inflammation between a) patients with FH vs. controls, and b) patients with heterozygous familial hypercholesterolemia (hFH) vs. combined hyperlipidemia (FCH) using 18F fluorodeoxyglycose Positron Emission Tomography

(FDG-PET), a validated imaging technique used for the quantification of vascular inflammation.
Methods: We included 18 patients with FH, (9 with hFH and 9 with FCH), free of statin therapy for at least 6 months and 24 normolipidemic controls. In all FH patients and controls, FDG uptake was evaluated in the wall of the ascending (AA) and descending thoracic (DA) aorta as well as the aortic arch (AR), and was quantified as target-to blood ratio (TBR) in axial slices every 5mm. In the FH groups, aortic wall inflammation was further assessed using FDG-PET imaging in the wall of carotid arteries. Lipid profile was obtained in all familial hyperlipidemia subjects.
Results: In total, 36 carotids and 42 aortas were analyzed. In FH patients the arterial TBR was higher in AA, AR and DA compared with controls (2.05 vs 1.78, p<0.001, 1.99 vs 1.8, p=0.006, 1.91 vs 1.69, p=0.001, respectively). Although total cholesterol and low density lipoprotein (LDL) values were higher in hFH patients (353±112 vs 272±28 mg/dL, p=0.008, and 273±104 vs 175±31 mg/dL, p<0.001), arterial wall's inflammation was higher in FCH subjects. FCH exhibited higher TBR values in carotid and throughout aortic wall compared with hFH (2.36±0.18 vs. 1.95±0.26, p=0.001 and 2.08±0.18 vs. 1.84±0.22, p=0.03), respectively.
Conclusions: Increased vascular inflammation was observed in all FH patients. FCH patients were characterized by higher arterial wall inflammation compared with hFH. This was observed despite the higher blood's lipids levels in hFH patients.

P827 | BEDSIDE
Independent link between levels of PCSK9 and FABP4 in a general population without medication

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Purpose: Proprotein convertase subtilisin/kexin type 9 (PCSK9), a serine protease synthesized primarily in the liver, binds to and degrades the low-density lipoprotein (LDL) receptor, leading to hypercholesterolemia and cardiovascular risk. Fatty acid-binding protein 4 (FABP4/A-FABP/aP2) is secreted from adipocytes in association with lipolysis, and circulating FABP4 has been reported to act as an adipokine for the development of insulin resistance. Elevated serum FABP4 level is associated with obesity, insulin resistance, dyslipidemia and atherosclerosis. In this study, we examined if there is the association between circulating levels of FABP4 and PCSK9 in a general population.
Methods: A total of 265 subjects who were not on medication were recruited from subjects of a population-based cohort study, and serum concentrations of FABP4 and PCSK9 were measured.
Results: The level of FABP4, but not that of PCSK9, showed a gender difference, being higher in females than in males. FABP4 level was independently associated with gender, adiposity, renal dysfunction and levels of cholesterol and PCSK9. Interestingly, there was a significant and gender-different correlation between PCSK9 level and age: negative correlation in males (r = -0.250, P=0.013) and positive correlation in females (r = 0.183, P=0.018). After adjustment of age, gender and LDL cholesterol level, PCSK9 level was positively and independently correlated with FABP4 concentration.
Conclusions: PCSK9 level is differentially regulated by gender during aging. Circulating FABP4 is independently correlated with PCSK9 level, suggesting that elevation of FABP4 level as an adipokine leads to dyslipidemia through increased PCSK9 level and subsequent degradation of the LDL receptor.

P828 | BEDSIDE
Prognostic value of PCSK9 levels in patients with acute coronary syndromes

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Aims: Proprotein convertase subtilisin kexin 9 (PCSK9) is an emerging target for the treatment o fhypercholesterolaemia, but the clinical utility of PCSK9 levels to guide treatment is unknown. We aimed to prospectively assess the prognostic value of plasma PCSK9 levels in patients with acute coronary syndromes (ACS).
Methods: Plasma PCSK9 levels were measured in 2030 ACS patients undergoing coronary angiography in a Swiss prospective cohort. At 1 year, the association between PCSK9 tertiles and all-cause death was assessed adjusting for the Global Registry of Acute Coronary Events (GRACE) variables, as well as the achievement of LDL cholesterol targets of 1.8 mmol/L.
Results: Patients with higher PCSK9 levels at angiography were more likely to have clinical familial hypercholesterolaemia (rate ratio, RR 1.21, 95% confidenceinterval, CI: 1.09–1.53), be treatedwithlipid-lowering therapy (RR 1.46, 95% CI: 1.30–1.63), present with longer time interval of chest pain (RR 1.29, 95% CI: 1.09–1.53) and higher C-reactive protein levels (RR 1.22, 95% CI: 1.16–1.30). PCSK9 increased 12–24 h after ACS (374±149 vs. 323±134 ng/mL, P=0.001). At 1 year follow-up, HRs for upper vs. lower PCSK9-level tertiles were 1.13 (95% CI: 0.69–1.85) for all-cause death and remained similar after adjustment for the GRACE score. Patients with higher PCSK9 levels were less likely to reach the recommended LDL cholesterol targets (RR 0.81, 95% CI: 0.66–0.99).
Conclusion: In ACS patients, high initial PCSK9 plasma levels were associated with inflammation in the acute phase and hypercholesterolaemia, but did not predict mortality at 1 year.

P829 | BEDSIDE
Are low LDL-c levels associated with higher fasting blood glucose levels? The IPC cohort

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Background and aim: Higher doses of statins are associated with increased risk of diabetes. Whether this unexpected effect is related to HMGCoA reductase inhibition or whether lower LDL-c levels per se may cause dysglycaemia is unknown. With the recent introduction of PCSK9 inhibitors, the question of the safety of very low levels of LDL-c is raised.
Methods: We used data from the IPC cohort, a large cohort of presumably healthy individuals having a general medical work-up reimbursed by the French National Health Insurance, to assess the relationship between blood levels of LDL-c and fasting blood glucose.
The population studied comprised 30,197 individuals with no known atherosclerotic disease, no known diabetes, no cancer, and not on lipid-lowering, antidiabetic agents or hormone therapy. Of those, 97 (0.3%) had LDL-c ≤50 mg/dl, 662 (2.2%) LDL-c 51–70 mg/dl, 4,792 (16%) LDL-c 71–100 mg/dl, 9,539 (32%) LDLc >101–130 mg/dl, and 15,107 (50%) LDL-c >130 mg/dl. Fasting glycaemia levels were adjusted on age, sex, deprivation score, weight and triglycerides levels.
Results: See table.

Patient characteristics and non-adjusted and adjusted glycaemia according to LDL-c levels

	LDL-c (mg/dl)					P for trend
	≤50 N=97	51–70 N=662	71–100 N=4,792	>101–130 N=9,539	>130 N=15,107	
Age (yrs)	35±13	32±12	36±13	43±14	49±13	<0.001
Female sex (%)	30	44	45	41	34	<0.001
BMI (kg/m^2)	25±6	24±5	24±5	25±5	26±4	<0.001
Deprivation score	40±24	42±25	38±26	33±26	30±26	<0.001
Total cholesterol (mg/dl)	121±36	129±18	157±17	187±16	234±29	<0.001
LDL-c (mg/dl)	40±9	63±5	88±8	116±9	159±24	<0.001
Glycaemia (mg/dl)	96±14	92±11	93±12	95±13	98±13	<0.001
Glycaemia (ml/dl) (adjusted)	96±12	96±12	96±13	96±12	96±13	NS

Individuals with LDL-c above 100 mg/dl were older, with a higher BMI and higher total cholesterol; the % of women and deprivation index were lower in people with LDL-c levels >100 mg/dl.
Unadjusted blood glucose levels were lower in individuals with moderately low LDL-c levels compared with those with LDL-c ≤50 or >100 mg/dl. However, after adjustment, glycaemia was uniformly distributed among LDL-c level classes.
Conclusion: Low LDL-cholesterol levels per se are not associated with increased blood glucose levels in a large population of presumably healthy individuals.

P830 | BEDSIDE
In patients surviving an ACS event, concomitant diabetes mellitus does not influence lipid lowering treatment - results from the dyslipidemia international study (DYSIS) II ACS

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Background: Patients suffering an acute coronary syndrome (ACS) event with concomitant diabetes mellitus (DM) remain at very high risk for future cardiovascular complications. Current ESC guidelines recommend a low density lipoprotein (LDL-C) target of <70 mg/dl for very high risk patients.
Purpose: We aimed to determine whether the diagnosis of concomitant diabetes mellitus would influence the lipid lowering treatment after an ACS.
Methods: DYSIS IIACS, a multi country cross sectional study, enrolled ACS patients from May 2013-October 2014 in 18 countries in Asia, Europe, and the Middle East. Adult patients were hospitalized for an ACS event and had a full lipid profile available within 24 hours of hospital admission, on lipid lowering therapy (LLT) ≥3 months or not at all, alive at discharge, and not participating in clinical trials involving medication. Patient follow-up interviews were conducted 4 months after ACS hospital admission date. Diabetes mellitus was documented upon diagnosis.

Results: 3855 ACS patients were enrolled: mean age 62.3±12.1 years; 76.4% male, 36.9% had DM- 23.8% of DM patients had an LDL-C <70 mg/dl versus 16.0% of patients without DM (p value <0.0001). Median distance to LDL-C target at enrollment was 38.0 (16.0, 66.0) mg/dl among DM patients and 48.0 (24.0, 77.0) mg/dl among patients without DM (p value <0.0001). Approximately ninety-one percent of ACS patients (n=3496) had 4 month follow-up data available, with 37.5% having DM. Lipid results available for 1040 patients at follow-up showed that 38.8% of DM patients versus 28.1% of patients without DM (p value <0.001) achieved an LDL-C <70 mg/dl. Median distance to LDL-C target was 21.5 (9.0, 42.0) mg/dl for DM patients and 21.0 (6.0, 37.0) mg/dl for patients without DM (p=0.16). There was no relevant difference in LLT 4 months after an ACS event (table 1).

Table 1. LLT 4 months post ACS

	DM patients (n=1231)	Patients without DM (n=2071)
Atorvastatin equivalent dose (mg/day)[a]	33±20	32±22
Statin monotherapy[b]	85.5%	87.2%
Statin + ezetimibe[b]	5.0%	5.0%
Statin + other non-statin[b]	4.2%	3.2%
Non-statin monotherapy[b]	0.5%	0.4%
No statin or non-statin treatment[b]	4.8%	4.2%

[a]p<0.05; [b]results were not statistically significant.

Conclusion: Concomitant DM had no influence on the physicians' LLT choice. Lower LDL-C in patients with DM indicates a different lipid profile with smaller lipoprotein particles. LDL-C target value attainment was low in both groups calling for increased urgency to treat.

Acknowledgement/Funding: The study was funded by Merck & Co, Inc., Kenilwort, NJ. DL, PB, and BA are employees of Merck & Co, Inc. or one of its subsidiaries.

P831 | BEDSIDE
High prevalence of early coronary calcifications linked to cholesterol burden in young patients with familial hypercholesterolemia

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Background: Heterozygous Familial Hypercholesterolemia (HeFH) is an autosomal dominant disorder associated with early coronary heart disease (CHD) due to exposure to high LDL-c levels. In those patients cardiovascular Risk (CVR) assessment is challenging and Coronary Artery Calcification score (CAC) has never been evaluated.

Purpose: To assess the prevalence of elevated CAC in HeFH patients and to correlate it to lifelong Total Cholesterol Burden (TCB).

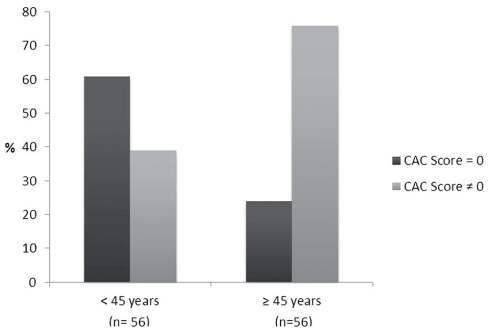
Methods: 112 non diabetic genetically assessed HeFH patients aged between 20 and 60 years regularly followed from diagnosis, in primary prevention, were recruited between May and December 2015. For each patient, CAC was assessed using multi-detector Scan and TCB was calculated from files as the sum of annually assessed total cholesterol.

Results: Non-zero CAC score prevalence was 39% among HeFH patients below 45 years (n=56) and 76% after 45 years (Figure; p<0.001). In comparison to patients with a zero CAC score, patients with a non-zero CAC score exhibited significantly higher TCB (Table). This difference was due to a significantly higher TCB at diagnosis because of higher Total Cholesterol (TC) levels (no difference was found in the age of diagnosis). In multivariate analysis, TCB remained an independent correlate of CAC Score after adjustment for other CVR factors (r^2=0.29; p=0.000).

TCB in young HeFH patients

Age <45 years (n=56)	CAC=0 (n=34)	CAC ≠0 (n=22)	p
Sex, males (n)	16	13	NS
TCB (mmol/l-years)	2.55±0.9	3.5±0.7	0.001
TCB at diagnosis (mmol/l-years)	1.03±0.68	1.73±1.11	0.009
TC at diagnosis (mmol/l)	8.7±1.95	10.2±2.21	0.01
Age at diagnosis (years)	12.7±8.3	17.3±10.6	NS

TCB, total cholesterol burden; HeFH, heterozygous familal hypercholesterolemia; TC, total cholesterol. Data are expressed as mean ± SD.



Prevalence of CAC in HeFH patients

Conclusion: HeFH patients exhibit early coronary calcifications and atherosclerosis related to an elevated total cholesterol burden. This emphasizes the need for early diagnosis and treatment.

P832 | BEDSIDE
Is low Non-HDL cholesterol, a hallmark of low CHD risk and long-term survival, a harbinger of increased dementia among old age survivors?

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Background: Blood concentrations of non-HDL cholesterol (non-HDLC) are associated with an approximate 1.50-fold risk of subsequent coronary heart disease (CHD) per 1 SD increment. Trials have indicated an amelioration of the burden of CHD by decreasing LDL- and non-HDLC levels. However late-life ramifications of non-HDLC remain unclear.

Patients and methods: We looked at rates of 21-yr fatal CHD in a study of 10,000 working men, aged 42–70 in 1965, and at the prevalence of dementia among survivors of these men 35 years later, in relation to serum total and non-HDLC cholesterol. Age-and multivariate-adjusted odds ratios for dementia, associated with blood cholesterol and cholesterol based indices, were estimated using logistic regression. Corresponding hazard ratios (HR) for long-term fatal CHD were estimated using Cox's egression.

Purpose: To examine and compare the association of non-HDLC with dementia among late life survivors to that with fatal CHD.

Results: Over 21 years, encompassing 263155 person years (PY), 1649 men with known total and serum HDLC levels died of CHD. Age-adjusted mortality rates were 37, 55, 68 and 97 per 1000 person-years (PY) in the first to fourth quartile of total serum cholesterol; and 34, 54, 68 and 96 per 1000 PY in corresponding quartiles of non-HDLC, respectively. Upon further adjustment for reported smoking habits, measured blood pressure and diabetes assessed at baseline, the corresponding CHD mortality hazard ratios for total cholesterol and non-HDLC, were: for total cholesterol 1, 1.39, 1.72 and 2.32; and for non-HDLC 1, 1.46, 1.82 and 2.57, both trend tests p<0.0005) in corresponding quartiles.

Dementia prevalence rates among men (N=1714, including 307 demented) who survived till 1999/2000, exhibited no association with total cholesterol assessed 35 years earlier. However, within approximate quartiles of non-HDLC, ORs for dementia were 21.2, 16.7, 13.6 and 16.2% (p for trend=0.04) for dementia and the corresponding ORs, adjusting for age, height, and baseline diabetes were consistent with a dose-response association: 1, 0.88 (0.62–1.24), 0.73 (0.51–1.07) and 0.68 (0.45–1.03), p for trend=0.034.

Comment: Apparently conflicting relations of CHD long-term mortality on the one hand and survivors' dementia rates on the other hand with mid-life non-HDLC are intriguing. Research among other large population samples on mid-life blood lipids and, when available, the incidence rather than prevalence of late life dementia, may shed light on the current obscure putative conflict between these outcomes.

P833 | BEDSIDE
Discordance between low-density lipoprotein cholesterol and other atherogenic lipid measurements by levels of high-sensitivity C-reactive protein: the very large database of lipids study 23

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Background: A recent post-hoc analysis of the Improved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT) trial showed that individuals achieving dual targets of low-density lipoprotein cholesterol (LDL-C) <1.8 mmol/L and high-sensitivity C-reactive protein (hsCRP) <2 mg/L had lower risk for cardiovascular events compared with those who achieved either one target or neither target. However, it is uncertain to what extent this finding is explained by: (1) hsCRP itself or (2) hsCRP serving as a biomarker of elevated circulating atherogenic lipids beyond Friedewald-estimated LDL-C (LDLf-C).

Purpose: To examine discordance between LDLf-C and other atherogenic lipid measurements in individuals with and without elevated hsCRP (≥2 mg/L).

Methods: We analyzed a subset of 83,829 adults from the Very Large Database of Lipids whose lipoproteins were fractionated by ultracentrifugation and had hsCRP measurement. We stratified individuals by hsCRP levels.

Results: Patients were 57.9±14.9 years old (44% men). A total of 5269 individuals had hsCRP <2 mg/L and LDLf-C<1.8 mmol/L, among whom 1102 (19.6%), 3077 (54.7%) and 1147 (20.4%) had discordantly high levels of direct LDL-C,

Abstract P833 – Lipid levels by hsCRP and LDLf-C

		N (%)	Triglycerides	HDL-C	Non-HDL-C	TC/HDL-C	Direct LDL-C
hsCRP <2 mg/L	LDLf-C <1.8 mmol/L	5,629 (6.71)	103 (72–154)	48 (39–59)	80 (71–90)	2.65 (2.27–3.16)	62 (54–58)
	LDLf-C ≥1.8 mmol/L	32,985 (39.35)	104 (75–148)	55 (45–67)	136 (114–163)	3.49 (2.89–4.29)	114 (94–138)
hsCRP ≥2 mg/L	LDLf-C <1.8 mmol/L	5,434 (6.48)	123 (85–186)	45 (37–55)	84 (74–95)	2.86 (2.40–3.45)	64 (56–70)
	LDLf-C ≥1.8 mmol/L	39,780 (47.45)	128 (92–179)	50 (42–61)	145 (122–172)	3.87 (3.20–4.74)	120 (99–144)

Values are reported as median (25th–75th percentile). Differences between medians were statistically significant (p<0.0001).

TC/HDL-C, and non-HDL-C, respectively. In contrast, among 5434 individuals with hsCRP ≥2 mg/L and LDLf-C<1.8 mmol/L, 1499 (27.6%), 3562 (65.6%) and 1587 (29.2%) had discordantly high levels of direct LDL-C, TC/HDL-C, and non-HDL-C, respectively. Among individuals with LDLf-C<1.8 mmol/L, those with hsCRP ≥2 mg/L had modestly higher levels of triglycerides, non-HDL-C, direct LDL-C and TC/HDL-C, and lower HDL-C than those with hsCRP<2 mg/L (p<0.0001) (Table).

Conclusions: High-sensitivity C-reactive protein is a marker of discordance between LDL-C and other atherogenic lipid and lipoprotein measurements. These changes in lipoprotein measures may explain some of the excess risk attributable to elevated hsCRP.

P834 | BEDSIDE

Usefulness of lipoprotein (a) for predicting clinical outcomes after peripheral endovascular intervention for atherosclerotic lesions in the aortoiliac artery

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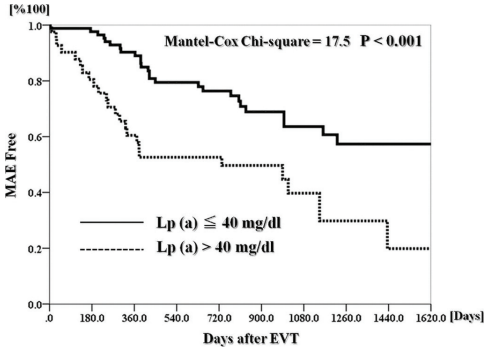
Background: The serum lipoprotein (a) level is genetically determined and remains consistent during a person's life. Previous studies have reported subjects with a high lipoprotein (a) level are at high risk of cardiac events. We investigated an association between lipoprotein (a) levels and clinical outcomes after endovascular therapy (EVT) for peripheral artery disease (PAD) due to aortoiliac artery.

Methods and results: We measured the serum lipoprotein (a) concentrations on admission in the consecutive 147 PAD patients due to aortoiliac artery underwent successful EVT. Patients were divided into two groups based: LOW group with the level<40 (n=100) and HIGH group>40 (n=47). After EVT, incidence of major adverse event (MAE) including major adverse limb event (MALE) and any-cause death were analyzed. At the median follow-up of 26 months (19–39 months), MALE occurred in 40 patients (27.2%) and 14 patients (9.5%) died. MAE-free survival rate was significantly worse in patients with HIGH lipoprotein (a) group than LOW lipoprotein (a) group (42.6% vs 73.0%, long-rank test χ^2=17.5; p<0.001). Cox proportional hazards analysis showed HIGH lipoprotein (a) levels (HR, 3.09; 95% CI, 1.72 to 5.56; p=0.001) and critical limb ischemia (HR, 3.38; 95% CI, 1.66 to 6.89; p<0.001) were independent predictors of MAE after EVT.



Conclusions: HIGH lipoprotein (a) level was associated with the higher incidence of MAE after EVT for the patients with PAD due to aortoiliac artery.

P835 | BEDSIDE

Do blood lipids correlate to body mass index? Findings from 52.916 statin treated patients

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Background: The correlation of body mass index (BMI) to blood lipids has been disputed in the past.

Purpose: We aimed to identify the influence of BMI on low density lipoprotein cholesterol (LDL-C), high density lipoprotein cholesterol (HDL-C), and triglycerides (TG) in a representative, real world cohort of 52.916 statin treated patients across the globe.

Methods: DYSIS was performed as a cross-sectional, observational, multicenter study in 30 countries around the world. The setting was primary care. Inclusion criteria were an age of ≥45 years, treated with statins for ≥3 months, and at least one fasting blood lipid profile available within the last 6–12 months while on statins. They were consecutively enrolled. Mean statin dose was a simvastatin equivalent of 33.5±25.1 mg per day. We used SAS 9.3 to calculate the non parametric Spearman rho correlation between BMI and LDL-C, HDL-C, and triglycerides, respectively. The variables were treated as continuous variables. Cochran-Armitage test was used to determine trend wise differences between lipoprotein and TG levels per BMI category as defined by the world health organization (WHO).

Results: 1.1% of the patients were underweight (BMI<18.5), 33.1% had normal weight (BMI 18.5–24.9), 41.5% overweight (BMI 25.0–29.9), 17.1% suffered from class I obesity (BMI 30.0–34.9), 5.0% from class II obesity (BMI 35.0–39.9), and 2.1% from class III obesity (BMI ≥40.0). Mean age was 65.4 years, 45% were female. Mean LDL-C was 103.21±38.26 mg/dl with no significant differences between the BMI categories (p=0.5443). Median HDL-C was 47.95 (Interquartile range, IQR 39.83, 58.00) with a significant decrease per BMI category (p<0.0001). Median triglycerides were 130.20 (IQR 93.89, 182.46) with a significant increase per BMI category (p<0.0001). Spearman rho for LDL-C was 0.00283, for HDL-C -0.14718 and for TG 0.17001.

Conclusion: No significant correlation or influence between BMI and LDL-C could be identified. However, there is a significant correlation between BMI and HDL-C and triglycerides, respectively. This influence ranges around 2–3%. Our finding was identified in a representative cohort of >50.000 statin treated patients from North America, Europe, the Middle East, Africa and China.

Acknowledgement/Funding: The study was funded by Merck & Co, Inc., Kenilworth, NJ. DL, BA and PB are employees of Merck & Co or one of its subsidiaries.

P836 | BEDSIDE

Prevalence of xanthelasma palpebrarum in general population and its association with lipid levels. Results from the Moli-Sani Study

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Xanthelasma palpebrarum is the most common form of cutaneous xanthoma. It is characterized by one or more soft, yellowish plaques on the medial aspect of the eyelids. Similarity between cholesterol-accumulating xanthomas and atheroma formation does exist, at least experimentally. Aim of this study was to evaluate prevalence of xanthelasma in general population from South-Central Italy and its association with lipid levels.

Methods: 7612 consecutive subjects (>35 y. old) participating on a large epidemiological Moli-Sani study in Italy and recruited during a limited time period were examined for presence of xathelasma. Serum lipid levels were measured from overnight fasting venous blood. Only non treated subjects were considered for analyses which included lipid levels.

Results: Xanthelasma was present in 1.85% (n=141) of all subjects, significantly more often in women than in men (2,34% vs 1,33%, p<0,01). Higher prevalence was noted also in higher age groups. Treatment for dyslipidemias was more frequent in those with xanthelasma (14.2 vs 8.3%, p<0.05). Mean levels of cholesterol and LDL were significantly higher in subjects with xanthelasma (6.0±0.1 vs 5.7±0.01, p<0,01 for cholesterol, and 3.8±0.08 vs 3.55±0.01 mmol/l, p<0,01 for LDL, mean±SE). However, 25% and 34,45% of subjects with xanthelasma still had cholesterol levels <5.2 mmol/l and LDL <3.4 mmol/l, respectively. There was no difference in Tg and HDL levels.

Conclusion: Prevalence of xanthelasma was significantly higher in women. Even that significant proportion of subjects with xanthelasma had normal levels of cholesterol, presence of xanthelasma in physical examination is important indicator of elevated total and LDL cholesterol levels.

P837 | BEDSIDE

Assessment of the risk factors in angiographically proven CAD and correlation of the Lp(a), apo A, apo B with the severity of the CAD

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Background: Indians develop coronary artery disease (CAD) at a much younger age. Conventional risk factors do not fully explain the high risk of premature and severe CAD in Indian population. Though the newer risk factors had been studied

in the CAD cohort, their role in the younger Indian population was not properly explored.
Purpose: To assess the risk factors in the patients with angiographically proven CAD and to assesss the correlation of apo A, apo B and Lp(a) with the severity of the CAD.
Methods: A total of 1200 patients (1000 cases, 200 controls) undergoing coronary angiography were included in the study. The cohort was divided into cases and controls based on the presence or absence of the CAD on the coronary angiogram respectively. Patients were further stratified according to their age into following groups: Group I (n=599) with age above 55 years (mean age: 64.68±5.8 years), group II (n=351) with age 41–55 years (mean age: 50.36±3.7 years) and group III (n=50) with age ≤40 years (mean age: 35.28±4.3 years). The baseline characteristics including the conventional risk factors, lipid profile including Lp(a), apo A and apo B levels were compared with the severity of the CAD.
Results: Among the conventional risk factors, hypertension was the commonest risk factor present in 55.6% of the patients while smoking accounted to 40.6% and 40.3% were diabetics. Hypertension and diabetes were more common in group I & II while smoking and positive family history of premature CAD was higher in group III. Acute coronary syndromes were more common in the younger age group while chronic stable angina was more common in the old. Angiographic study revealed that very severe CAD was the most common form of the involvement in all the three age groups although calcification was more common in the older groups I and II. HDL was lower and the LDL/HDL ratio, VLDL and Lp (a) significantly higher in group III viz a viz group I & II. Apo A, apo B, their ratio apo A/apo B and Lp(a) were highly significantly associated with the severity of the CAD ($p<0.001$).
Conclusion: The risk profile, clinical presentation , lipid abnormalities and the angiographic picture varies according to the age of the patient. Young CAD (age ≤40 yrs) comprised 5% of the total cases. Although these patients had a lower incidence of the conventional risk factors like diabetes and hypertension, they had a significantly higher rate of smoking, positive family history and a more atherogenic lipid profile including higher levels of the genetic risk factor Lp(a). Apo A, apo B, apo A/apo B ratio and Lp(a) levels were very significantly associated with the severity of the CAD

AORTIC VALVE DISEASE

P838 | BEDSIDE
Aortic valve gradient and mortality in patients undergoing transcatheter aortic valve implantation for severe aortic stenosis

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Background: Mortality of patients undergoing Transcatheter Aortic Valve Implantation (TAVI) remains high, making optimal patient selection for this costly procedure extremely important. We aimed to evaluate the relationship between baseline aortic valve gradients (AVGs) and mortality post TAVI and assess the role of AVG in risk stratification for TAVI candidates.
Methods: We analyzed data on 1,186 consecutive patients with severe Aortic Stenosis (AS), who underwent TAVI at 3 tertiary centers from 2008 through 2014. The relation between AVG and mortality was evaluated among all patients and in subgroup of patients with high AVGs using the Cox proportional hazard model adjusting for multiple prognostic variables. Peak AVG was categorized as: <60mmHg, 60–100mmHg, >100mmHg and assessed as a continuous measure.
Results: Patients had a peak AVG of (mean+SD) 75+24 mmHg, mean AVG of 47 +17 mmHg, and aortic valve area of 0.7+0.2 cm^2. During a mean follow up of 1.8 years, baseline AVG was inversely associated with mortality (Figure). By multivariable analysis, patients with AVG 60–100 mmHg and >100 mmHg had a respective 30% (p=0.02) and 70% ($p<0.001$) reduction in mortality compared to patients with AVG<60%. Every 10 mmHg increase in peak AVG was associated with 9% reduction in mortality (HR 0.914, p=0.003). Subgroup analyses among patients with left ventricular ejection fraction (LVEF) >40%, or peak AVG≥60 mmHg yielded similar results (HR 0.910, p=0.003 and HR 0.905, p=0.025, per 10 mmHg increase in peak AVG respectively). Analyses using mean AVGs yielded consistent results to those of peak AVG.

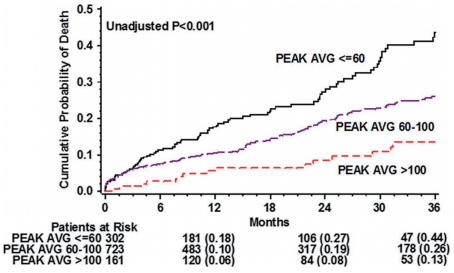

Figure 1. 3 year mortality according to

Conclusions: Baseline AVGs are directly associated with improved survival post TAVI. These results were consistent also in patients with high gradient AS, suggesting that AVG can be used to select patients most likely to benefit from TAVI.

P839 | BEDSIDE
Postprocedural pacemaker rate is related to implantation depth and calcium distribution pattern after Sapien 3 implantation

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Background: The Edwards Sapien 3 valve has undergone significant design modifications to reduce periprocedural complications. Initial results showed significantly reduced paravalvular regurgitation (PVR), however at the cost of an increased rate of AV conduction disturbances requiring new permanent pacemaker implantation (PPMI).
Aims: This retrospective study investigated the influence of final valve position and calcium distribution patterns of the device landing zone (DLZ) on the occurrence of AV conduction disturbances requiring new PPMI in 184 patients treated with a Sapien 3 valve.
Methods: Assessment of valve implantation depth was based on off-line evaluation of a single still frame of post-deployment aortic angiograms. Preoperative contrast-enhanced multidetector computed tomography data was used for the assessment of DLZ calcium distribution patterns.
Results: PPMI rate was 14.7%. Valves in patients requiring PPMI were implanted significantly deeper into the LVOT than in patients not requiring PPMI. On average, the ventricular portion of the total valve stent frame length was 26.7±13.5% in patients requiring PPMI compared to 19.8±5.5% in patients without need for pacemaker implantation (P=0.008). Deep valve implantation into the LVOT was associated with significantly higher pacemaker rates. A deep implantation with a ventricular portion of more than 30% of the total stent frame length resulted in a PPMI rate of 38.1%. In contrast, high implantation (ventricular portion <20%) resulted in a PPMI rate of 9.1%, while an intermediate implantation depth (ventricular portion 20–30%) yielded a pacemaker rate of 17.0%. Relative risk for PPMI after low vs. high implantation was 4.2 (CI 1.9–9.4, P=0.002).
Analysis of calcium distribution patterns revealed an elevated calcium load of the LVOT in the area below the left coronary cusp in patients with need for PPMI (Median calcium 12.0 mm^3 vs. 2.1 mm^3, P=0.025). A calcium load over 5.1 mm^3 was associated with a significantly elevated PPMI rate (24.6% vs. 9.9%, P=0.03). Multivariate regression analysis identified implantation depth (OR 17.9, CI 3.9–82.1, $P<0.001$) and LVOT calcium load in the area below the left coronary cusp >5.1 mm^3 (OR 3.3, CI 1.1–9.8, P=0.029) as independent predictors of PPMI.
Conclusion: Implantation depth and LVOT calcium load in the area below the left coronary cusp are independent predictors for the need of PPMI post-TAVI. A high implantation with a ventriculo-aortic ratio of less than 20/80 might lower the risk of conduction disturbances and is associated with a significantly decreased pacemaker rate. An initial positioning of the central marker at least 1 mm above the aortic annulus seems to be beneficial to achieve finally a ventriculo-aortic ratio of less than 20/80. This minor modification of the currently used implantation technique may reduce the number of patients requiring PPMI post TAVI without increasing the risk for PVR.

P840 | BEDSIDE
Endothelial and platelet derived microparticles in patients undergoing transcatheter aortic valve implantation (TAVI)

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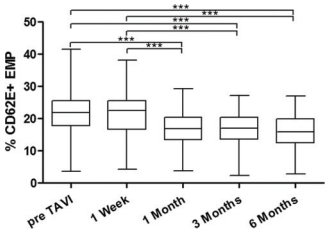
Introduction: Degenerative severe aortic stenosis (AS) is the most frequent form of acquired valvular heart disease worldwide. AS is known to entail endothelial dysfunction caused by increased mechanical shear stress leading to elevated circulatory levels of microparticles. Endothelial and platelet microparticles (EMP and PMP) are small vesicles that originate from activated cells and thrombocytes. The hypothesis of our study was to evaluate whether transcatheter aortic valve implantation (TAVI) procedure would elicit beneficial effects on endothelial function by reducing circulating EMP and PMP.
Materials and methods: 92 patients undergoing TAVI procedure for severe AS were included in this study. Samples were obtained at each visit before TAVI and after one week, one, three and after six months. The collected samples were stained with antibodies against CD31, CD42b, CD62E and Annexin in order to analyze circulatory levels of CD31+/Annexin+, CD31+/Annexin-, microparticles using flow cytometry.
Results: Clinical and functional results after TAVI procedure were good as shown by significantly reduced Vmax, MPG and PPG ($p<0.001$). Also a slight improvement in ejection fraction was documented during follow-up, from 55.9% (±18.4 SD) before TAVI to 62.6% (±14.3 SD) after six months ($p<0.01$).
CD62E+ EMP concentration before TAVI was 21.11% (±6.6% SD) and declined to 20.99% (±6.8% SD) after one week, to 16.63% (±5.4% SD, $p<0.0001$) af-

ter one month, to 17.08% (±4.6% SD, p<0.0001) after three months and to 15.94% (±5.4% SD, p<0.0001) after six months (see Figure). CD31+/CD42b-, CD31+/Annexin +/– EMP remained unchanged.
Furthermore, pre TAVI levels of CD31+CD42b- and CD31+ Annexin- correlated with maximum velocity (0.258 and 0.245, p<0.05), mean pressure gradient (0.301 and 0.288, p<0.01) and peak pressure gradient (0.230 and 0.219, p<0.05). CD62E+ EMP and CD31+CD42b+ PMP correlated with EF (0.228 and 0.248, p<0.05).



Conclusions: Apart from a procedure related improvement in echocardiographic parameters, TAVI procedure also led to amelioration in endothelial dysfunction as shown by a decline in CD62E+ EMP. The reduction in transvalvular pressure gradients with less hemodynamic shear stress seems also to have beneficially affected endothelial homeostasis.
As the shedding of microparticles is also associated with systemic inflammation and endothelial activation, a vicious circle of hemodynamic shear stress and endothelial dysfunction is present in the pathophysiological setting of AS. It was shown that inflammation might play a fundamental part in the progression of degenerative AS and microparticles also seem to play a role as signaling factors within the vascular compartment mediating inflammation, angiogenesis and coagulation. As levels of CD62E+ EMP were significantly reduced during follow-up, one could argue that one factor for the progression of vascular dysfunction was taken out of the equation, thusly leading to an improvement in endothelial function.

P841 | BEDSIDE

The impact of the development of TAVI on the management of severe aortic stenosis in high-risk patients: treatment strategies and outcome

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Background/Introduction: Transcatheter Aortic Valve Implantation (TAVI) has reoriented the treatment of aortic stenosis (AS) for high-risk patients. Little is known on late outcome after TAVI, surgical aortic valve replacement (AVR) or medical treatment in a single centre.
Purposes: We report patients' characteristics, early and 6-year survival rates after the 3 therapeutic strategies, and the evolution over time. We also analysed predictive factors of mortality after TAVI or surgical AVR.
Methods: Between October 2006 and December 2010, 478 high-risk consecutive patients were referred for severe symptomatic AS. After Heart Team evaluation, 253 underwent a TAVI, 102 a surgical AVR and 123 medical treatment including 33 who had a compassionate Percutaneous Balloon Aortic Valvuloplasty (PBAV). Follow-up was complete in 98% of patients.
Results: Medically-treated patients had higher risk scores than the 2 other groups. They presented a significantly worse survival (p<0.001), with a 1-year rate of only 30%. The 33 patients who underwent compassionate PBAV presented with the lowest survival rate, even lower than patients receiving drug therapy alone.
In the TAVI group, patients had more comorbidities than in the surgical group, as assessed by a higher Charlson index. There was no difference in 30-day survival rates (91±2% for TAVI and 88±3% for surgical AVR; p=0.32). Predictive factors of 30-day mortality were post-intervention complications illustrated by higher troponin levels and severe infection. The 6-year survival rates were 31±4% and 40±6% for TAVI and surgical AVR respectively (p=0.03) but the difference was no longer significant after adjustment on the Charlson index (p=0.68). Predictive factors of late mortality were patients' comorbidities for both groups and paraprosthetic aortic regurgitation ≥2/4 for the TAVI group.
Finally, the number of interventions (TAVI or surgery) increases over years, driven by the amount of TAVI procedures but without any surgical AVR decrease.
Conclusions: In this single-centre study, medically-treated patients with severe AS have a higher risk profile than those undergoing surgery or TAVI. Their survival is particularly poor and not improved by compassionate PBAV. When comparing TAVI and surgical AVR, there was no difference in 30-day and 6-year survival rates after adjusting for comorbidities.

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Treatment options in intermediate-high risk patients with aortic stenosis and renal disfunction: the European multicenter propensity match study comparing tavr versus conventional avr surgery

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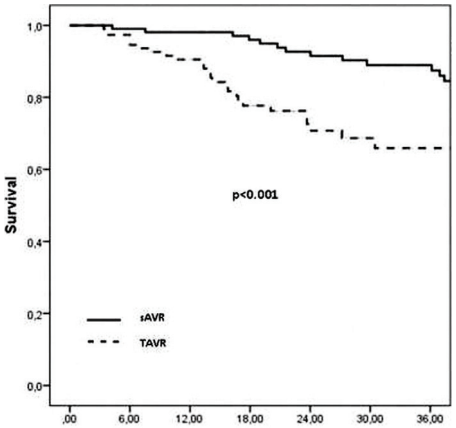
Background: Surgical Aortic Valve Replacement (sAVR) still represents the gold standard therapy for patients with severe aortic stenosis. Transcatheter Aortic Valve Replacement (TAVR) is becoming an attractive strategy in inoperable or extremely-high patients, albeit a its use is expanding also in those patients patients with intermediate-high risk profile with one or more organ disfunction.
Purpose: Renal dysfunction has been identified as an independent predictor of perioperative morbidity and mortality in patients undergoing TAVR. We therefore sought to investigate the impact of pre-operative renal dysfunction (GFR<60ml/min) in patients with intermediate-high risk profile undergoing either surgical AVR or TAVR.
Methods: From 2007 to 2014, 700 patients with isolated severe aortic stenosis and an intermediate-high risk profile (STS Score >4 and logistic EuroSCORE I>10) were collected from 7 European centers. Among the study population, 433 patients had preoperative renal dysfunction: 197 underwent surgical AVR (G1), and 236 TAVR (G2). A propensity score analysis was performed in order to obtain two homogeneous groups of 126 patients the most common pre-operative risk factors (STS score and others continuous and discrete variables). Primary end points were 30-day mortality and overall survival at 36-month follow-up; the secondary end point was survival freedom from a composite end point of major adverse cardiac events (MACCE) defined as cardiac-related mortality, myocardial infarction, CVA, major hemorrhagic events and periprosthetic regurgitation > grade II.
Results: There were no significant differences in 30-day mortality between the groups (sAVR = 3.2% vs TAVR = 6.1%; p=0.092). The incidence of post-procedural PM implantation was 3.6% in sAVR group vs 16.6% in TAVR group (p=0.004), peripheral vascular complications 0% in sAVR group vs 9.5% of TAVR patients (p<0.001). There were no differences in terms of post-operative acute renal failure (sAVR = 11.9% vs TAVR =13.5%; p=0.767) and need of dialysis (sAVR = 3.7% vs TAVR =5.3%; p=0.332). At 36-months follow-up, overall survival (sAVR= 86.0% ± 2.4% vs TAVR = 65.9% ± 4.3%; p<0.001) and survival freedom from MACCE (sAVR = 74.7%±3.7% vs TAVR = 52.5%±7.5%; p<0.001) were significantly better in patients undergoing surgical aortic valve replacement than in TAVR patients (Figure 1). Multivariate Cox regression analysis depicts TAVR as an independent risk factor for all-cause of death hazard ratio (HR: 3.4; confidence interval, 1.7–6.6; p<0.001) and MACCEs (HR: 5.1; confidence interval, 2.6–9.6; p<0.001).



FOLLOW-UP timepoints	Groups			
	SAVR		TAVR	
12-Months	98.1%	(96.7%-99.5%)	90.5%	(87.9%-93.4%)
24-Months	91.5%	(88.6%-94.4%)	70.8%	(65.4%-76.2%)
36-Months	86.0%	(82.2%-89.8%)	65.9%	(59.9%-71.9%)

Figure 1. Overall Survival

Conclusion: Surgical AVR yields excellent outcomes at short and mid-term follow-up even in patients with renal dysfunction. In this multicenter propensity matched study the use of TAVR apparently worsened outcome in this subset population indicating that further Randomized Controlled Trials are mandatory before extending the use of TAVR in intermediate-high risk patients.

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The incidence and severity of aortic plaque in patients with aortic stenosis and its relation with severity of aortic stenosis

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Objectives: The pathogenesis of aortic plaque is similar to aortic stenosis (AS), thus it is expected that the incidence of aortic plaque is high in patients with AS. Severe aortic plaque is thought to be the risk factor for embolic events, especially during open heart surgery or cardiac catheterization. Recently, transcatheter aortic valve replacement (AVR) has emerged as an alternative to surgical AVR and it is important to predict the risk of subsequent embolic events in patients with AS. However, current guidelines do not recommend the screening for aortic plaque in patients with AS. The purpose of this study is to clarify the incidence and severity of aortic plaque in patients with AS.
Methods: We retrospectively investigated 1812 transesophageal echocardiographic examinations between 2008 and 2015 in our hospital. Among 1812 patients, 247 consecutive patients (mean age; 75.1±7.8 years) who showed maximal aortic jet velocity (AV-Vel) ≥2.0 m/s by transthoracic echocardiography were investigated. We defined these patients as AS group. We also picked up age- and sex- matched 100 patients (mean age; 74.6±5.3 years) as non-AS group among the remaining 1565 patients. AS group were classified into 3 groups according to AV-Vel; mild AS (AV-Vel; 2.0–3.0m/s), moderate AS (AV-Vel; 3.0–4.0m/s), and severe AS (AV-Vel; >4m/s). We compared clinical factors and the severity of aortic plaque between AS group and non-AS group. Severe aortic plaque was defined as protruding plaques ≥4mm thickness and/or complex plaque such as mobile plaque and ulceration.
Results: Among 247 patients in AS group, there were 34 patients (14%) with mild AS, 65 patients (26%) with moderate AS, and 148 patients (60%) with severe AS. The incidence of severe aortic plaque was 13.0% in non-AS group, 29.4% in mild AS group, 38.5% in moderate AS group, and 37.1% in severe AS group, respectively. With regard to the incidence of complex plaque, it was seen in 1.0% in non-AS group, 14.7% in mild AS group, 16.9% in moderate AS group, 12.0% in severe AS group. There was the association between the severity of AS and the severity of aortic plaque. ($p<0.01$)
Conclusion: The incidence and severity of aortic plaque were related to the severity of AS. In patients with moderate to severe AS, severe aortic plaque was observed in about 40%. The screening for aortic plaque may be needed among patients with moderate to severe AS.

P844 | BEDSIDE

Comparison of balloon-expandable versus self-expandable transcatheter prostheses with regard to the degree of calcification of the aortic valve and aortic root: Do we need more than one TAVI device?

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Background: Severe calcification of the aortic valve is known to be associated with worse procedural results in transcatheter aortic valve replacement (TAVR). This pertains to both self-expandable (s-exp) and balloon-expandable (b-exp) transcatheter heart valves (THV); however, a direct comparison of these valve types is lacking.
Purpose: Using MSCT we sought to compare results of s-exp versus b-exp THV with regard to the degree of calcification of aortic roots/annuli, with emphasis on immediate clinical outcome.
Methods: Consecutive patients with severe native aortic stenosis who underwent TAVR in our institution with available MSCT of the aortic root were retrospectively analyzed. The calcification of the aortic valve (AVCS) was quantified using native scans via the Agatston method and 3 different degrees of calcification were defined: severe (>75. percentile), moderate (25.-75. percentile) and mild calcification (<25. percentile). Peri-procedural outcome of s-exp (Medronic Corevalve; St. Jude Portico, Symetis Acurate TA/TF) and b-exp (Edwards SAPIEN XT/3) THVs was evaluated with respect to the grade of calcification.
Results: In total 1116 (b-exp.=521, s-exp.=595) patients were included. In the group with severe calcification (>75. percentile), the use of b-exp THV was associated with a lower rate of procedural failure according to VARC-2 criteria (4.7% vs. 16.7%; p=0.001), post-procedural aortic regurgitation ≥2° (15.3% vs. 25.8%; p=0.03), and post-dilatation (10.2% vs. 53.2%; p<0.001) as compared to s-exp THVs - without increased risk of annular rupture. In the group with mild calcification (<25. percentile), permanent pacemaker implantation was significantly less frequent after b-exp versus s-exp THVs (9.1% vs. 16.2%; p=0.05). These differences were mainly driven by CoreValve and Portico s-exp THVs. Only in the group with moderate calcification (25.-75. percentile) outcome was independent of the prosthesis type.
Conclusions: B-exp THVs may have advantages over s-exp devices 1) in patients with severely calcified aortic valves due to lower rates of procedural failure (VARC-2), residual aortic regurgitation ≥2°, and post-dilatation, without increasing the risk of annular rupture, and 2) in cases with mild calcification given the less frequent need for pacemaker implantation, which was mainly attributed to the CoreValve and the Portico prostheses.

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Persistent pulmonary hypertension after transcatheter aortic valve implantation: impact on 3-year mortality

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Objective: Severe aortic valve stenosis leads to increased pulmonary arterial systolic pressure. A controversy still remains regarding the impact of persistent pulmonary hypertension (PHT) on prognosis of patients undergoing transcatheter aortic valve implantation (TAVI).The aim of our study was to elucidate the impact of persistent PHT on 3-year all-cause mortality of patients with severe aortic stenosis undergoing TAVI.
Methods: Patients with severe and symptomatic aortic stenosis (effective orifice area [EOA]≤1cm^2), who were scheduled for TAVI with a self-expanding valve at our institution, were consecutively enrolled. Prospectively collected echocardiographic data before and after TAVI were retrospectively analyzed in all patients. Pulmonary artery systolic pressure was estimated as the sum of the right ventricular to the right atrial gradient during systole and the right atrial pressure. PHT following TAVI was classified as normal if <35mmHg and persistent if ≥35mmHg. Primary clinical end-point was cumulative mortality defined according to the criteria proposed by the Valve Academic Research Consortium-2.
Results: We included 157 patients (mean age: 79.9±6.9 years) in the study. The primary clinical end point occurred in 41 patients (26.1%) during a follow-up period of 26.8±20.7months. Mean pulmonary artery systolic pressure was reduced in all patients following TAVI (43.1±11.3 versus 40.6±8.7mmHg, $p<0.01$). Mortality rate was higher in patients with persistent PHT compared to patients with normal PHT after TAVI (39.3% versus 10.95%, $p<0.001$). Patients that reached the primary clinical end point had a higher post procedural mean systolic pulmonary pressure (43.5±7.7 versus 39.6±8.8mmHg, p=0.01). In multivariate regression analysis, persistence of PHT [(OR: 3.218, B=1.169 (95% CI: 1.311–7.899, p=0.001)] was an independent predictor of cumulative mortality.
Conclusions: The persistence of pulmonary hypertension after TAVI is associated with long term mortality. Identifying the population that will clearly benefit from TAVI is still need to be validated by further trials.

P846 | BEDSIDE

Novel left ventricle contractility index is a predictor of a deterioration of ejection fraction in patients with severe aortic stenosis and preserved left ventricular ejection fraction

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Introduction: The maximal rate of change of pressure-normalized wall stress, dσ*/dtmax, is a novel load-independent index of left ventricular (LV) global contractility. Its role in aortic stenosis (AS) has not been studied. We evaluated the capacity of dσ*/dtmax to predict a deterioration in LV ejection fraction (EF) and major adverse cardiovascular events (MACE) in subjects with severe AS and preserved LVEF (≥50%).
Methods: 128 consecutive patients with isolated severe AS (aortic valve area <1cm^2) with preserved EF underwent echocardiographic examination (>180 days apart) to characterise LV dimension, function and dσ*/dtmax. Patients with intervening myocardial infarction were excluded. Baseline demographic, clinical and echocardiographic parameters were analysed. Cardiovascular mortality and admission for heart failure on 5-year follow-up were collected. Univariate

Table 1

Parameter	Group A (n=23)	Group B (n=105)	Mean difference/ Odds ratio (95% CI)*	P value
Clinical parameters				
Age	71.9 (±12.9)	66.8 (±13.6)	5.1 (–1.0 to 11.1)	0.101
Male (%)	36	38	0.93 (0.36 to 2.41)	0.879
Diabetes mellitus (%)	52	29	2.62 (1.04 to 6.59)	0.037
Hypertension (%)	87	26	18.93 (5.18 to 69.21)	<0.001
Hyperlipidaemia (%)	61	33	3.11 (1.22 to 7.91)	0.014
Previous myocardial infarction (%)	17	5	4.13 (1.01 to 16.79)	0.035
Echocardiographic parameters				
Days between studies	812 (±859)	1009 (±892)	–197 (–603 to 208)	0.329
Initial LVEF (%)	61.70 (±7.54)	65.12 (±4.78)	–3.43 (–5.87 to –0.99)	0.006
Septal E/E'	22.55 (±12.64)	15.85 (±8.70)	6.7 (1.94 to 11.46)	0.006
Aortic valve area (cm^2)	0.82 (±0.13)	0.82 (±0.16)	–0.002 (–0.068 to 0.063)	0.946
Transaortic peak velocity (cm/s)	366.3 (±65.4)	398.8 (±94.9)	–32.4 (–65.7 to 0.8)	0.056
Global LV contractility index	1.63 (0.69)	2.75 (1.11)	–1.12 (–1.60 to –0.64)	<0.001

Group A: patients with LVEF deteoriation on subsequent echocardiography; Group B: all other patients with preserved LVEF ≥50% on subsequent echocardiography. *Odds ratios presented for categorical variables while mean difference (S.D.) presented for continuous variables.

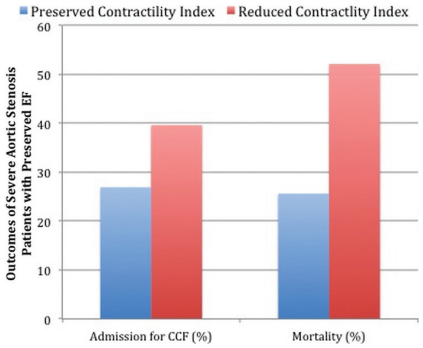

Figure 1

and multivariate analyses were performed to identify predictors of EF deterioration (to <50%) and a ROC curve was used to evaluate optimised cut-off values.
Results: Group A consisted of subjects with LVEF deterioration to less than 50% (Table). Multivariate analysis showed that a lower dσ*/dtmax independently predicted EF deterioration (OR 0.10, 95% CI 0.01–0.90, p<0.05). A ROC curve identified an optimised cut off of dσ*/dtmax<2.00 s^{-1} to predict EF deterioration. Subjects with reduced dσ*/dtmax were found to have higher heart failure admission rates (OR 1.78, 95% CI 0.83–3.82, p=0.138) and higher mortality (OR 3.15, 95% CI 1.47–6.75, p=0.003) (Figure).
Conclusion: dσ*/dtmax predicts LVEF deterioration in isolated severe AS, and may represent subclinical myocardial dysfunction despite preserved EF in the initial study.

P847 | BEDSIDE
The impact of hypertension and LV dimension on LV subclinical dysfunction in more than moderate to severe asymptomatic AR with normal LV systolic function: multilayer speckle tracking echocardiography

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Background: Left ventricular (LV) systolic function and end-systolic, end-diastolic LV dimension (LVESD, LVEDD) are regarded as important parameters when considering aortic valve (AV) surgery for patients with asymptomatic AR. Patients with asymptomatic AR show subclinical LV longitudinal axis dysfunction, with more attenuation demonstrated in hypertensive than in normotensive patients.
Purpose: The aims of our study were to detect signs of subclinical LV dysfunction and to determine the impact of hypertension and LV dimension on LV systolic dysfunction in patients with chronic asymptomatic AR using multilayer-speckle-tracking echocardiography (MSTE).
Methods: Conventional echocardiography and 2D MSTE were performed in 37 normal patients and 85 patients (mean age 53.6±13.6 yrs) with more than moderate to severe chronic AR (vena contracta >0.6 cm, ERO >0.3 cm^2 or regurgitant volume >60mL) and normal LVEF (≥50%) and without overt coronary artery disease. Multilayer-Global longitudinal strain (GLS) was calculated by 2D MSTE.
Results: Patients were divided into each of four groups by the 65mm of LVEDD or the 50mm of LVESD by the current ACC/AHA VHD guideline; group 0: LVESD ≤50mm or LVEDD ≤65mm and HTN (–), group 1: LVESD ≤50mm or LVEDD ≤65mm and HTN (+), group 2: LVESD>50mm or LVEDD >65mm and HTN (–), group 3; LVESD >50mm or LVEDD >65mm and HTN (+). Clinical characteristics, IVSd and LVPWd were no significant differences between four groups. LVMI was the largest in the LVEDD >65mm or LVESD >50mm and HTN group. And, GLS was the lowest in the LVEDD >65mm or LVESD >50mm and HTN group. GLS of

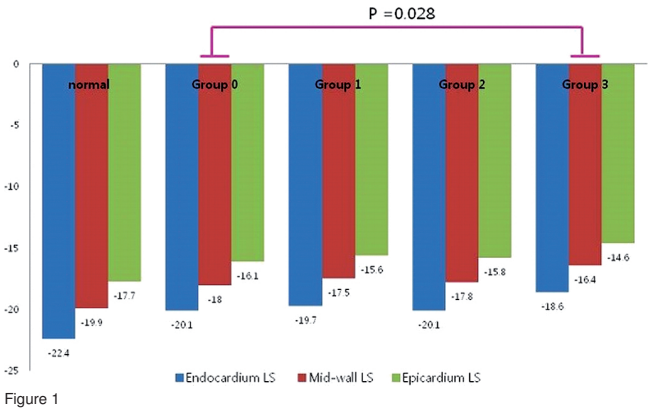

Figure 1

endocardium, mid-wall, and epicardium was reduced when the LVEDD was more than 65mm or LVESD was more than 55mm. And, multilayer-GLS was reduced when patients with AR was associated with HTN.
Conclusions: Patients with asymptomatic chronic AR showed subclinical LV longitudinal axis dysfunction, with more attenuation demonstrated in hypertensive than in normotensive and with the LVEDD>65mm or LVESD>50mm. Our results suggest that MSTE may compliment evaluation of patients with asymptomatic chronic AR.

P848 | BEDSIDE
Von willebrand factor for bedside diagnosis of aortic regurgitation in cathlab and prediction of outcome during TAVR

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Background: Post-procedural aortic-regurgitation is a major clinical problem occurring in 10–20% of patients with aortic stenosis undergoing transcatheter-aortic-valve-replacement (TAVR). We hypothesized that measurement of the loss of high-molecular-weight (HMW)-multimers of von-Willebrand-factor or its bedside assessment could monitor occurrence and fate of aortic-regurgitation during TAVR.
Methods: 183 consecutives patients undergoing TAVR were enrolled. Aortic-regurgitation after initial implant, as identified by trans-esophageal-echocardiography, led to post-dilatation to attempt to correct aortic-regurgitation. HMW-multimers and PFA-100Ò-closure time using adenine-diphosphate (ADP) cartridges (CT-ADP) were measured at baseline and 5 minutes after each step of the procedure. Mortality was evaluated at 1 year. A validation-cohort (n=201) was designed to validate the use of CT-ADP to identify patients with aortic-regurgitation.
Results: After initial implant, HMW-multimers normalized in patients without aortic-regurgitation (n=137). Normalization was delayed to after post-dilatation in patients in whom aortic-regurgitation was corrected by post-dilatation (n=20) and was absent in those with persistent aortic-regurgitation (n=26). Similar time course was observed with CT-ADP.
HMW-multimers and CT-ADP at the end of TAVR had an AUC of the ROC curve>0.90 to identify patients with aortic-regurgitation. A CT-ADP-cut-off>170s had sensitivity, specificity and negative-predictive-value of 91%, 91% and 98%, respectively. A CT-ADP AUC=0.92 (95% CI: 0.86–0.97) was also found in the validation cohort. HMW-multimers or CT-ADP at the end of TAVR were associated with 1-year-mortality by multivariable analysis.
Conclusion: A defect in HMW-multimers and its bedside assessment using PFA-100Ò can monitor TAVR procedures, recognize the occurrence of aortic-regurgitation and its correction, while its value at the end of the TAVR-procedure predict long-term outcome.

P849 | BEDSIDE
Moderate to severe mitral regurgitation is associated with worse long term survival in patients undergoing TAVI

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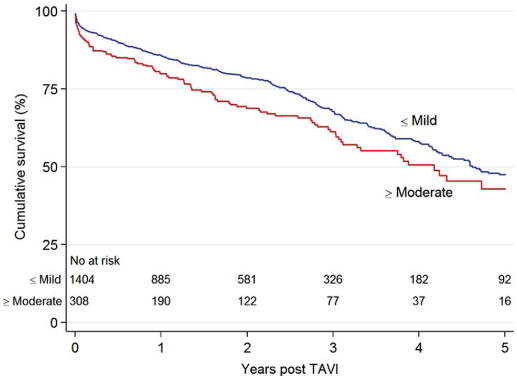
Background: Several studies have shown increased mortality during the first year in patients with significant mitral regurgitation (MR) who undergo transcatheter aortic valve implantation (TAVI). Less is known of the influence of MR on long-term survival beyond the first years after TAVI.
Purpose: We aimed to study short and long-term survival in patients with moderate/severe MR who undergo TAVI.
Methods: The Swedish TAVI Registry enrolled 1712 consecutive TAVI patients between 2008 and 2014. Baseline characteristics, echocardiographic data at baseline and within 7 days after TAVI, and survival data were obtained. Patients with MR were dichotomized into no/mild and moderate/severe MR.
Results: Of 1712 patients undergoing TAVI, 1404 had no/mild MR, and 308 had moderate/severe MR at baseline. No difference in mortality rate was observed during 30 days (p=0.09) after TAVI, whereas moderate/severe MR conferred a higher mortality rate during 1 year follow-up (adjusted HR 1.43, CI 1.03–1.97, p=0.03) and 5 years of follow-up (adjusted HR 1.29, CI 1.0–1.65, p=0.04). Within a week after TAVI, moderate/severe MR had improved in 47% to no/mild MR. Improved MR after TAVI lead to a lower mortaliy rate during 5 year follow-up (unadjusted HR 0.65, CI 0.43–0.99, p=0.045) compared to persisting moderate/severe MR.

Selected baseline characteristics

	No/mild MR	Moderate/severe MR	p-value
Female	679 (48%)	177 (58%)	0.004
Age	81.3±7	82.3±6	0.025
BMI	26.5±5	25.3±5	<0.001
Recent MI	88 (6%)	10 (3.2%)	0.04
Diabetes	324 (23%)	56 (18%)	0.06
Hypertension	1012 (72%)	210 (68%)	0.17
COPD	296 (21%)	50 (16%)	0.06
Afib	460 (33%)	157 (51%)	<0.001
NYHA class 3–4	1289 (92%)	297 (96%)	0.001
EF >50%	878 (63%)	131 (43%)	
EF 40–49%	241 (17%)	57 (19%)	
EF 30–39%	185 (13%)	69 (22%)	
EF <30%	100 (7%)	51 (17%)	<0.001

BMI = body mass index; MI = myocardial infarction, Afib = atrial fibrillation.



Kaplan-Meier curves for all cause mortality

Conclusions: Moderate/severe MR in patients undergoing TAVI is associated with an increased mortality rate during 5 years of follow-up. Improved MR after TAVI is associated with better survival compared to persisting moderate/severe MR.

P850 | BEDSIDE
Transcatheter aortic valve replacement with the self-expanding CoreValve prosthesis performed using clinical best practices: impact on clinical outcomes to six months. The ADVANCE II study

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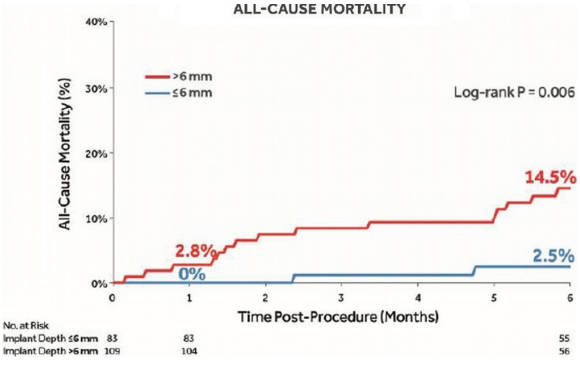
Background: Best clinical practice recommendations include control of implant depth to 6 mm or less relative to the aortic annulus, valve size selection based on MSCT images, and management of post-transcatheter aortic valve replacement (TAVR) conduction disturbances according to international guidelines.
Objective: To assess outcomes in TAVR patients treated in accordance with best clinical practices for CoreValve implantation.
Methods: Patients with severe aortic stenosis at high risk for surgery were enrolled in the multicenter, prospective, observational ADVANCE II study and followed for 6 months. All imaging and ECG data were analyzed by an independent core laboratory. Safety-related adverse events were adjudicated to valvular academic research consortium-2 (VARC-2) definitions by an independent clinical events committee.



Results: From October 2011 to April 2013, 200 patients were enrolled, and 194 were implanted. The mean age was 80.2±6.7 years, 47.5% were male, and the mean STS-PROM was 7.2±6.8%. At 6 months, all-cause mortality was 9.2%, stroke was 2.6%, and permanent pacemaker implantation (PPI) was 19.2% for class I and II indications. In patients with implant depth ≤6 mm, both mortality and PPI were lower than in patients with depth >6 mm (2.5% vs. 14.5%, p<0.01 and 18.1% vs. 31.7%, p=0.03, respectively). The rate of moderate and severe paravalvular leak (PVL) decreased over time from was 9.8% at 7 days post-TAVR, to 4.3% at 6 months (p=0.02).
Conclusions: Findings from the ADVANCE II study reinforce that adherence to best clinical practices has a strong positive impact on patient outcomes.
Acknowledgement/Funding: Medtronic

P851 | BEDSIDE
Conduction abnormalities after Sapien-3 transcatheter aortic valve implantation. What is more important: valve sizing or implantation height?

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Aims: To analyze the influence of valve sizing and implantation height on the development of new conduction abnormalities after transcatheter aortic valve implantation (TAVI) using the third-generation balloon-expandable SAPIEN-3 (S3) valve.
Background: Our group has previously reported that the implantation height of the valve was a predictor of new conduction abnormalities and pacemaker implantation rate (PMIR) in patients receiving the S3 valve. The potential role of valve sizing in this context remains unknown.
Methods: The first 206 patients treated with S3 were analyzed. Patients with prior PMI or ICD, transapical and valve-in-valve procedures were excluded from the analysis. All patients were monitored for at least 7 days. Previous and new conduction abnormalities were documented and prosthesis implantation height assessed. The valve size selection was at the discretion of the operators who were aware of the multidetector computed tomography (MDCT) size recommendation provided by the vendor specifications. The prosthesis was considered oversized when the S3 nominal area was greater than the systolic MDCT annular area. The percentage of oversizing (positive percentage) or undersizing (negative percentage) was calculated using the following formula: % oversizing = (S3 nominal area/MDCT area– 1) × 100. In addition, to further analyze a possible effect of the sizing of the valve on the PMIR we also categorized patients by the degree of MDCT area oversizing/undersizing percentage in the following categories: below 0% (undersizing); 0% to 10%; 10% to 20%; and above 20% (oversizing).
Results: The mean implantation height was significantly lower in patients requiring PMI (67%/33% vs. 72%/28% aortic/ventricular stent extension, p=0.032). Mean area oversizing was 7.4±11.1% (range –18.4 to 48.1%). Undersizing was present in 42 patients (27.8%). MDCT area oversizing percentage of 0% to 10%, 10% to 20%, and above 20% was present in 46 (28.4%), 46 (28.4%), and 17 patients (10.4%), respectively. Mean area oversizing was 6.6±10.5% in those patients who did not require PM (range –18.0 to 33.2%) and 10.9±12.9% in those patients who required PM (range –18.4 to 48.1%) with no significant difference between groups (p=0.06). On multivariate logistic regression analysis including presence of a pre-existing right bundle branch block, implantation height, valve sizing, age and gender, implantation height remained the only independent predictor of the need for PMI (OR 0.94 [95% CI 0.90–0.99], p=0.009).
Conclusions: Valve under- or oversizing did not influence the development of new conduction abnormalities and the requirement of PM implantation. After including valve sizing in our model, an implantation height over 70% seems to be the only operator modifiable factor that prevents an excess in PM implantation.
Acknowledgement/Funding: This study was supported by a research grant from the EMAH Stiftung Karla Voelm, Krefeld, Germany

P852 | BEDSIDE
Do we need antiplatelet therapy before transcatheter aortic valve implantation?

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Background: The clinical benefit of pre-procedural antiplatelet therapy before transcatheter aortic valve implantation (TAVI) has not been established.
Objective: The aim of this study is to evaluate the incidence of adverse events in patients undergoing transfemoral TAVI with and without pre-procedural antiplatelet therapy using multicenter cohort data.
Methods: OCEAN-TAVI registry is a prospective, multicenter, observational cohort registry, enrolling 749 patients who underwent TAVI from October, 2013 to August, 2015 in Japan. Of 749 patients, we identified 540 patients (median age 85 years, 68.1% female) undergoing transfemoral TAVI without pre-procedural antiplatelet therapy (n=80) and with antiplatelet therapy (n=460). The clinical endpoints were any bleeding (life-threatening, major, and minor bleeding) and thrombotic event (stroke, myocardial infarction and valve thrombosis) during hospitalization.
Results: The prevalence of heart failure on admission, diabetes mellitus, and previous percutaneous coronary intervention were higher in antiplatelet therapy than in no antiplatelet therapy (86.1% vs. 58.8%, p<0.001; 26.7% vs. 11.3%, p=0.001; 31.1% vs. 1.3%, p<0.001). The puncture approach and median Logistic EuroSCORE II were lower in antiplatelet therapy (47.4% vs. 80.0%, p<0.001; 3.25 vs. 4.17, p=0.004). The patients with antiplatelet therapy had significantly higher incidence of any bleeding than those without antiplatelet therapy (p=0.024). No antiplatelet therapy before TAVI did not increase the risk of thrombotic event. In multivariate logistic regression analysis, dual antiplatelet therapy (DAPT) before TAVI significantly increased the risk of any bleeding than no antiplatelet therapy (Odd ratio, 2.35; 95% confidence interval, 1.15–4.80). The risk of bleeding was not different between single and no antiplatelet therapy before TAVI.
Conclusion: In current study, DAPT before TAVI increased the risk of bleeding. In modern TAVI era, it might be acceptable to perform TAVI on pre-procedural single or no antiplatelet therapy without the increase of adverse events.

P853 | BEDSIDE
Impact of mixed aortic valve disease in long-term mortality after transcatheter aortic valve implantation

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Background: The negative impact of significant aortic regurgitation in patients with severe aortic stenosis is well known.
Purpose: To investigate the impact of mixed aortic valve disease (MAVD) in patients undergoing transcatheter aortic valve implantation (TAVI) with a self-expanding valve.
Methods: Patients with severe and symptomatic aortic stenosis who were scheduled for TAVI were prospectively enrolled. Prospectively collected echocardiographic data before and after TAVI were retrospectively analyzed in all patients. Primary clinical end-point was 4-year all-cause mortality. All outcomes were evaluated according to the VARC-2 criteria. Patients with no aortic regurgitation (AR) were considered to have pure aortic stenosis (AS) and patients with mild/moderate/severe AR were considered to have MAVD.
Results: We included 133 patients (age: 82±8 years; logistic EuroSCORE 21±8%; 59% females; NYHA III 81%) in the study. Twenty-one patients (16%) had pure AS and 112 patients had MAVD (84%). The primary clinical end point occurred in 3 patients with pure AS and in 26 patients with MAVD (14% versus 23% respectively, p=0.5). No major differences were observed concerning cardiovascular death (10% versus 17%, p=0.5), stroke (10% versus 3%, p=0.1) and acute kidney injury (8% versus 4%, p=0.2) in pure AS and MAVD patients respectively. Post TAVI AR was higher in the MAVD group compared to the pure AS group (moderate AR: 77% vs 71% and severe AR: 12% vs 0%, p<0.007 for all measurements).
At univariate analysis, predictors for mortality were: severe AR before TAVI (p<0.03, OR: 16, 95% CI: 2.634–9.7), mean gradient >40 mmHg (p=0.24, OR: 0.369, 95% CI: 0.156–0.875), female gender (p=0.26, OR: 1.629, 95% CI: 0.691–3.838), age (p<0.04, OR: 1.091, 95% CI: 1.003–1.188) and logEuroscore (p<0.004, OR: 1.058, 95% CI: 1.018–1.099). At multivariate analysis, age (p<0.022, OR: 1.116, 95% CI: 1.018–1.224), mean gradient >40 mmHg (p<0.003, OR: 0.214, 95% CI: 0.077–0.593) and severe AR (p<0.004, OR: 18, 95% CI: 2.591–13.4) were independent predictors of long-term mortality.
Conclusions: Mixed aortic valve disease with severe aortic regurgitation before TAVI is associated with increased long-term mortality and further studies are needed in order to explore possible implications in patient selection.

P854 | BEDSIDE
Mean transvalvular gradient and indexed stroke volume have superior prognostic value than ejection fraction in patients submitted to TAVI

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Background: The severity of aortic valve stenosis has been associated with prognosis after transcutaneous aortic valve intervention (TAVI).
Purpose: Our objective was to evaluate the influence of indexed stroke volume (SVi), mean gradient and ejection fraction (EF) on 1-year mortality in severe aortic stenosis patients who underwent TAVI.
Methods and results: We selected 175 consecutive patients with symptomatic severe aortic stenosis who were submitted to TAVI between November/2008 and November/2015, in a single center. We defined three groups of patients (according to the American Heart Association recommendations): D1 – "high gradient" [maximum velocity (Vmax) ≥4m/s or mean gradient ≥40mmHg]; D2 – "low-flow, low-gradient with reduced EF" [Vmax <4m/s, mean gradient <40mmHg, SVi <35 mL/m^2, EF <50%]; D3 – "low-gradient with preserved EF/paradoxical low-flow" (Vmax <4m/s, mean gradient <40mmHg, SVi <35mL/m^2, EF ≥50%). Univariable analysis was performed for clinical and echocardiography variables. Variables with p<0.05 in the univariable analysis were included for multivariate analysis according to Cox proportional hazards regression model – backward Wald to identify independent predictors of mortality. The primary endpoint was defined as all-cause death. Mean age was 81±7.6 years and 43% were male. Mean EuroScore II was 6.8±5.4%. Global 1-year mortality was 14.9% (n=26). The groups with reduced mean gradient (D2 and D3) had higher mortality than the group with elevated mean gradient (D1: 11.6%; D2: 31.6%; D3: 30%; p=0.027) – see figure 1. Multivariable analysis identified male gender [HR=2.5; 95% Confidence Interval (CI): 1.1–5.5; p=0.027], diabetes (HR=3.7; 95% CI: 1.6–8.5; p=0.002) and group D2 (HR=3.7; 95% CI 1.4–9.7; p=0.006) as independent predictors of mortality.

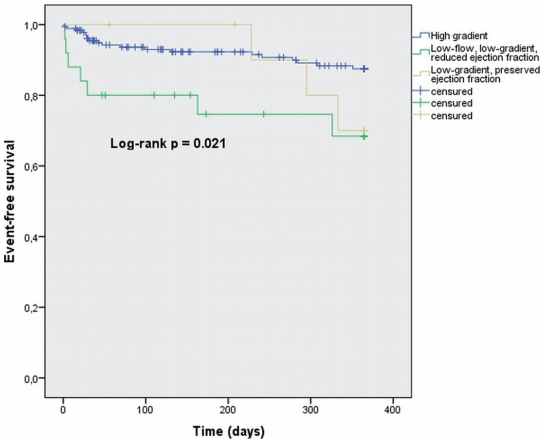

Figure 1. Survival curve analysis

Conclusions: In this population we found that patients with "low-flow, low-gradient, reduced ejection fraction" and "low-gradient, preserved ejection fraction" aortic stenosis had higher mortality when compared with patients with "high-gradient" aortic stenosis submitted to TAVI. Male gender, diabetes and group D2 ("low-flow, low-gradient, reduced ejection fraction") were independent predictors of 1-year mortality.

P855 | BEDSIDE
Estimation of a new simple echocardiographic parameter for mitral regurgitation severity

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Background: Generally, the severity of mitral regurgitation (MR) is evaluated with proximal isovelocity surface area (PISA) or volumetric methods. However, these methods are time consuming and there are some anatomical difficulties and limitations for the quantification of MR severity and integrated approaches using echocardiography are recommended. Recently, left ventricular early inflow-outflow index (LVEIO index), which is calculated by dividing the mitral E-wave velocity by the LV outflow velocity time integral has been proposed but its usefulness remained unclear to differentiate the severity in various etiology of MR.
Purpose: The aim of this study was to evaluate the usefulness and determine ideal threshold of LVEIO index to diagnose severe MR in different backgrounds.

Methods and results: We reviewed 76721 transthoracic echocardiographic reports performed at our institution from January 4, 2008 to May 15, 2015. MR severities were evaluated according to the guideline of the American Society of Echocardiography and the European Association of Echocardiography. Cases with moderate or severe aortic valve regurgitation, any mitral stenosis, prior mitral valve surgery, congestive heart diseases, LV assist device, or any arrhythmias were excluded. Also cases with inadequate or missing LV inflow or outflow Doppler recordings were excluded. Finally we evaluated 18692 cases and classified them as 17961 of no, trivial, or mild MR (Grade 0/1), 600 of moderate MR (Grade 2), 82 of moderate to severe MR (Grade 3) and 49 of severe MR (Grade 4). The average LVEIO index of Grade 0/1, Grade 2, Grade 3 and Grade 4 were 3.4±2.7, 5.5±5.0, 6.7±6.2 and 9.1±5.6, respectively. For diagnosis of moderate to severe or severe MR, area under the curve for LVEIO was 0.93 by receiver operating characteristic analysis. When we used LVEIO ≥8 as the threshold according to the previous report, the sensitivity was 90% and the specificity was 49% to detect moderate to severe or severe MR. The optimal threshold of LVEIO was 5.4 to distinguish moderate to severe or severe MR from non-severe MR (sensitivity 84%, specificity 91%). There were no differences in the significance of LVEIO index between the cases with reduced LV ejection fraction (<50%) and preserved LV ejection fraction (≥50%), which area under the curves were 0.94 and 0.92, respectively. Secondary MR had greater average of LVEIO than primary MR and mitral valve tethering was the most common etiology of MR among the group of LVEIO ≥8, suggesting the need of the specific assessment for MR severity by LVEIO in the different etiologies.
Conclusion: LVEIO is a simple and useful method to diagnose severe MR by using adequate thresholds regardless of LVEF.

P856 | BEDSIDE
Quantitative evaluation of mitral regurgitation using ventricular volumes by 3D transesophageal echocardiography

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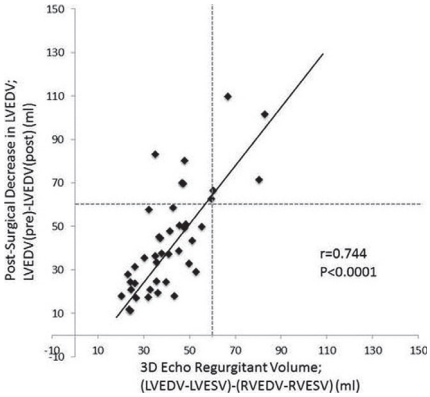
Background: Our aim was to evaluate the ability of 3D echocardiography to quantify the mitral regurgitation (MR) severity.
Method: This study included 42 patients who had isolated mitral valve surgery for MR. Exclusion criteria included patients with more than moderate other valvular disease and atrial fibrillation. We performed 2D transthoracic echocardiography (TTE) and 3D transesophageal echocardiography (TEE) before surgery, and we also performed 2DTTE within a week after surgery. We analyzed the 3D TEE datasets offline on a dedicated workstation (4D LV Analysis, 4D RV Function; Tom Tec v1.2, Tom Tec Imaging Systems, Germany). We evaluated the preoperative regurgitant volume (ReV) using 3 different methods; 2D volumetric methods by TTE, 2D proximal isovelocity surface area (PISA) methods by TTE and 3D volume methods by TEE: left ventricular total stroke volume – right ventricular total stroke volume = (left ventricular end-diastolic volume (LVEDV) – left ventricular end-systolic volume (LVESV)) – (right ventricular end-diastolic volume (RVEDV) – right ventricular end-systolic volume (RVESV)). We compared 2D volumetric methods, 2D PISA methods and 3D volume methods in the assessment of ReV using post-surgical decrease in LVEDV as the reference standard; LVEDV (preoperative) – LVEDV (postoperative).
Result: There was no correlation between post-surgical LV remodeling and ReV as assessed by 2D PISA methods (r=0.094, p=0.560). Post-surgical LV remodeling had a correlation with ReV as assessed by 2D volumetric methods (r=0.539, p=0.0002). Notably, there existed a strong correlation between post-surgical LV remodeling and ReV as assessed by 3D volume methods (r=0.744, p<0.0001). The Bland–Altman plots revealed that post-surgical LV remodeling showed good agreement with ReV as assessed by 3D volume methods (mean difference ± 2SE: -5.77 to 3.13ml).
Conclusion: Quantification of mitral regurgitation severity can be accurately performed by 3DTEE.



P857 | BEDSIDE
Are there any differences between primary and secondary mitral regurgitation? Is there a gap to be filled for a mixed group?

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Background: Even though Carpentiers classification addresses all forms of mitral regurgitation (MR), a simplified classification in primary versus secondary is frequently used in clinical practice. The characteristics of these groups and of a third group of mixed forms are not well defined.
Purpose: To evaluate the burden of mitral regurgitation attending to frequency, severity, aetiology and mechanism.
Methods: From February to June 2015, a total of 39855 consecutive echocardiographic studies performed in nine hospitals were prospectively included. Patients with moderate to severe MR were selected for analysis. MR was classified according to aetiology as primary, when structural abnormalities were described or secondary otherwise. In patients with both, LV remodelling and resulting tethering of the mitral valve a structural lesions of the valve, MR was classified as mixed.
Results: Moderate to severe MR was detected in 1608 studies (4.03%). According to aetiology, 58.2% of cases were classified as primary MR, 24.2% as secondary, and 17.5% were described as mixed forms of MR. Degenerative disease was the most common cause of primary MR (68.6%), followed by rheumatic disease (14.3%), endocarditis (3.0%), congenital disease (1.0%) and other causes (13.2%). 27.6% of degenerative MR cases were classified as Barlow disease. Patients with mixed MR ranged from 1.6 to 33.6% among hospitals. Significant differences were noted between groups with younger male patients seen in the secondary MR groups compared to the older age of patients in the other two groups and female predominance in primary MR. Secondary MR patients, as expected, showed larger left ventricle with lower ejection fraction. Mixed forms represent the older group with an intermediate profile according to echo parameters.
Conclusions: Most mitral regurgitations are of degenerative origin. Primary, secondary and mixed forms of mitral regurgitation differ significantly in their presentation with regard to gender, age and ventricular function. Mixed MR is not specified in the guidelines and this fact has probably led to a diversity of criteria used for its definition. There appears to be a gap for this entity though further studies are needed.

P858 | BEDSIDE
The importance of prolapsing volume in predicting left ventricular function post mitral valve repair

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Purpose: Post mitral valve repair (MVR), the left ventricular ejection fraction (EF%) can be mildly lower than before surgery. Therefore, we investigated whether, post MVr, we can predict the LV end systolic volume (LVESV) and the post-op LVEF%, by measuring the preoperative LV end-systolic volume, correcting for it using the prolapsing volume derived from 3D Echo and using the corrected volume in the calculation of LVEF%.
Methods: We analyzed 31 patients who underwent MVrbecause of mitral valve prolapse. We measured the pre-op LV volumes and pre-op EF% using biplane Simpson's method and the MV prolapsing volumes by using 3D Echo data and Mitral Valve Navigation software. Then, based on the Pre-op LVESV plus the MV

Abstract P857 – Table 1. Groups comparison

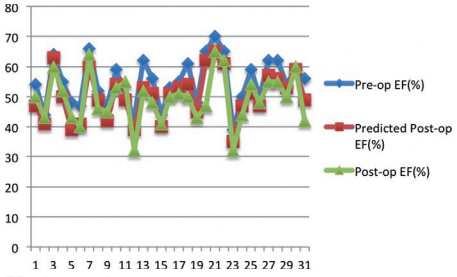
	Primary (n=913)	Secondary (n=380)	Mixed (n=275)		Primary (n=913)	Secondary (n=380)	Mixed (n=275)
Age (years)	71 (SD=14)	68 (SD=13)	74 (SD=11)	LV end systolic diameter (mm)	34 (SD=8)	49 (SD=13)	43 (SD=11)
Gender (female %)	56.7	29.8	42.3	LV end systolic volume (ml)	51 (SD=31)	116 (SD=65)	85 (SD=55)
Sinus rhythm (%)	59.0	53.7	53.6	LV end diastolic volume (ml)	115 (SD=49)	173 (SD=73)	142 (SD=66)
Left atrial volumen (ml)	110 (SD=59)	104 (SD=47)	127 (SD=69)	LV ejection fraction (%)	62 (SD=11)	39 (SD=15)	46 (SD=17)
LV end diastolic diameter (mm)	52 (SD=8)	62 (SD=10)	57 (SD=9)	Pulmonary systolic pressure (mmHg)	44 (SD=17)	45 (SD=16)	48 (SD=15)

LV: left ventricle.

prolapsing volume (PV), we made an estimation of the predicted LV EF (EFp) after the MVR, calculating it using as the pre-op EDV and the corrected pre-op ESV (the sum of the pre-opESV and the PV). These were compared to the actual post-op parameters.
Results: In order to test the prediction accuracy we executed Student's t-test with equal variances examining whether the null hypothesis (Mean prep-op EF% – Mean Predicted EF% = 0) is supported.
The two-tailed P value equals 0.6238. By conventional criteria, this difference is considered to be not statistically significant (a=0.05), which means that the estimated predicted EF% values were almost similar to the actual post-op EF% values. However there was no correlation comparing the pre-opEF% with the post-opEF% (the two-tailed P value was <0.01 which by conventional criteria is considered to be statistically significant) (a=0.05).
The good correlation between the predicted LVEF and the post op actual LVEF can be also demonstrated in the line-histogram below.

Table 1

	Predicted EF (%)	Postop EF (%)
Mean	50.42	49.42
Sdev	7.68	8.03
N	31	31



EF values graph

Conclusion: This demonstrates that the MV prolapsing volume in patients undergoing MV Repair is an important contributor towards the apparent reduction in EF post surgery.

P859 | BEDSIDE
Five years efficacy and durability of transcatheter edge-to-edge mitral valve repair in significant mitral regurgitation patients

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Background: The efficacy of transcatheter edge-to-edge mitral valve repair using the MitraClip device for significant mitral regurgitation (MR) has been demonstrated in several studies. However, there is a paucity of long-term clinical and echocardiographic outcomes. In this study, 5-year efficacy and durability of the MitraClip device was investigated in a single-center experience.
Methods: This study population included 109 patients (65 patients with functional MR and 44 patients with degenerative MR) who underwent the MitraClip procedure from November 2005 to January 2011. Clinical and echocardiographic follow-up was scheduled at 30 days, 6 months, and annually up to 5 years after the procedure.
Results: Clinical 5-year follow-up was completed in 91.7%. All-cause mortality was 11.1% at 1 year and gradually went up to 41.2% at 5 years. The proportion of New York Heart Association functional class III/IV was 72.5% at baseline, 6.9% at 1 year, and 6.0% at 5 years. The rate of grade 3+/4+ MR was 13.1% at 1 year and 17.8% at 5 years follow-up. Whereas the cumulative incidence of grade 3+/4+ MR or re-intervention was 27.8% at 1 year and 44.9% at 5 years, it was 15.9% from 1 to 3 years and 7.9% beyond 3 years in landmark analysis. Among 16 patients requiring re-intervention, 7 underwent 2nd MitraClip procedure, and no mitral valve surgery was performed beyond 3 years. Among 42 matched patients, left ventricular end-diastolic volume and end-systolic volume were reduced at 1 year compared with baseline (154.4±29.2 ml to 131.3±27.2 ml, $p<0.001$; 68.6±24.6 ml to 63.9±22.7 ml, p=0.09), and further reductions were observed from 1 to 5 years (to 122.7±31.6 ml, p=0.03; to 54.9±21.9 ml, p=0.03). Forward stroke volume significantly increased from 50.4±9.3 ml at baseline to 56.1±13.5 ml at 1 year (p=0.007), and the improved stroke volume was sustained at 5 years (to 55.3±11.1 ml, $p>0.99$).
Conclusion: The MitraClip therapy was effective and durable during 5 years follow-up with low incidence of recurrent MR and re-intervention in chronic phase. The symptomatic improvement and positive echocardiographic changes were preserved up to 5 years.

P860 | BEDSIDE
Prosthetic valve endocarditis in patients with two prosthesis, but only one infected. What is better to do?

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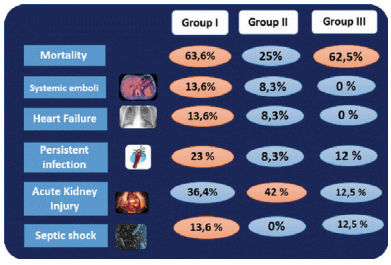
Purpose: Prosthetic valve endocarditis (PVE) account for 10–30% of all cases of infective endocarditis (IE), and it is the most severe form. Although surgical treatment is frequently necessary, there are few data available about the management of patients with two valve prostheses and only one infected. Our aim was to evaluate the management and outcome of these patients.
Methods: From 248 episodes of PVE prospectively recruited between 1996 and 2014, we studied 42 episodes of PVE in patients with two prostheses in whom infection was present in only one. They were classified in three groups: Group I (n=22), no surgery; Group II (n=12), replacement of the infected prosthesis; and Group III (n=8), replacement of both prosthetic valves. A comparison of in-hospital outcomes was performed.
Results: From 42 PVE, 37 were mitral and 5 aortic. The majority (64%) were community-acquired IE and portal of entry was known in 43%. Among the general characteristics: 43% were diabetics and 21% had renal failure. Acute onset prevailed (60%) and the principal initial manifestations were fever (88%), cardiac failure (47%) and systemic symptoms (26%).
In Group I surgery was not performed due to: high risk (64%), good clinical evolution (23%), death before surgery (9%) and patient's rejection (4%).
Total mortality rate was 52.4%, it was significantly lower in group II (Figure). During hospitalization, patients from Group I developed systemic embolisms more frequently than groups II and III (13.6% vs. 8.3% and 0%, p=0.3). Previously to surgery, heart failure (13.6% vs. 8.3% and 0%, p=0.3), new signs of infection (22.7% vs. 8.3% and 12.5%, p=0.5) and septic shock (13.6% vs. 0% and 12.5%, p=0.2) were more common in Group I as well (Figure). New renal failure was more frequent in group II (36.4% vs. 41.7% and 12.5%, p=0.3)
Among the surgical groups, the outcome was worse in Group III. Comparing Groups III and II, mortality (62.5% v. 25%, p=0.1) and events after surgery: heart failure (87.5% vs. 25%, p=0.02), renal failure (50% vs. 25%, p=0.3), fever (50% vs. 33.3%, p=0.6) and septic shock (37.5% vs. 0%, p=0.04) were more frequent in Group III. There were no differences in systemic emboli.



Conclusions: In this preliminary study of patients with two prostheses but only one infected, those in which replacement of the infected prosthesis was performed had a better outcome than those in which the two prosthesis were replaced.

P861 | BEDSIDE
Prosthetic valve endocarditis: a disease with a poor prognosis

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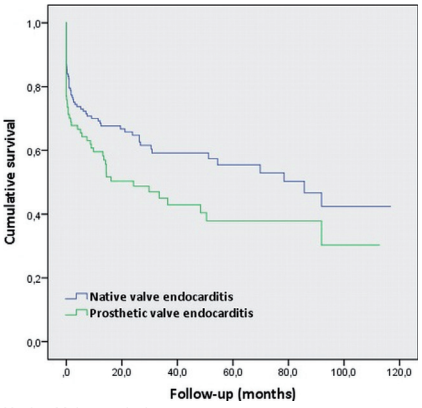
Introduction: Infective endocarditis (IE) is a condition associated with high morbidity and mortality, prosthetic valve endocarditis (PVE) being the form with the worse prognosis.
Purpose: To compare the characteristics of PVE with those of native valve endocarditis (NVE).
Methods: Retrospective analysis of consecutive IE patients (pts) who underwent transoesophageal echocardiography in a single tertiary centre between 2006 and 2014. Demographic, clinical, echocardiographic, treatment and prognostic data were obtained. A subanalysis of the PVE cases was made, comparing early (EPVE) and late prosthetic valve endocarditis (LPVE). EPVE and LPVE were defined as occurring in the 12 months before surgery or later, respectively. Complicated IE was defined as having at least one of the following: heart failure, perivalvular extension and cerebral or peripheral embolism.
Results: 238 pts (69.3% males, mean age 63.3±15.4 years; mean follow-up 28.5±30.9 months) were evaluated. 39.5% had PVE and 48.8% of these had EPVE. The aortic valve was most commonly affected (55.9%), followed by the mitral valve (38.2%). The most frequently isolated microorganisms were Staphylococcus spp. (27.5%) and Streptococcus spp. (16.4%). 67.0% had a complicated course and 36.9% were submitted to surgery during or immediately after

the acute phase of IE. The in-hospital mortality was 16.3% and the long-term mortality after discharge was 17.2%. Comparing the two groups, PVE more frequently involved the aortic valve (64.9% vs. 50.0% p 0.024) and less frequently the tricuspid valve (3.2% vs. 10.4% p 0.046). Vegetations were identified in almost all cases of NVE (97.9% vs. 83.0% p<0.001). Staphylococcus spp. was associated with PVE (36.7% vs. 21.9% p 0.020) and non-HACEK-Gram-negative bacilli with NVE (8.7% vs. 1.3% p 0.032). Pts with PVE had more heart failure (45.9% vs. 31.6% p 0.047) and perivalvular extension (41.8% vs. 15.3% p<0.001). There was no difference in regard to surgery or in-hospital mortality. However, the long-term survival was worse in the PVE group (58.3% vs. 67.7% at 12 months and 48.8% vs. 64.8% at 24 months; log rank p 0.031) (image 1). In the subanalysis of PVE, EPVE was more frequently associated with aortic valve (75.6% vs. 53.5% p 0.034), bioprothesis (63.4% vs. 30.2% p 0.002), abscess (34.1% vs. 11.6% p 0.014) and Staphylococcus spp. (48.6% vs. 23.1% p 0.022). The incidence of cerebral embolism was greater in LPVE (33.3% vs. 14.7% p 0.069). There was no difference in regard to surgery and mortality when comparing EPVE and LPVE.



Kaplan Meier survival curves

Conclusion: PVE was common in this population and was associated with aortic valve involvement, Staphylococcus spp. and worse prognosis, with increased incidence of complications and decreased long-term survival. EPVE was related to bioprothesis, perivalvular abscess and Staphylococcus spp., and LPVE to cerebral embolism, although no difference in mortality was found.

P862 | BEDSIDE
Clinical characteristics and association with shunt flow in mural infective endocarditis

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Mural infective endocarditis (mural IE) is rare clinical manifeststion in the course of IE and confused to appropriately diagnose, with or without valve involvement. The aim of our study was to evaluate the clinical characteristics of mural IE and to determine independent clinical factors for diagnosis.
Among the 604 cases reviewed, 59 cases were classified as mural IE (forming mass or spreading the endocardium). Compared with non-mural type IE, patients with MIE were younger (p=0.004) and associated with congenital condition of shunt flow (p<0.001) among the congenital heart disease. More patients with mural IE had central intravenous catheters (p=0.001), and multiple site of vegetation was also common finding in the TTE (p<0.001). In addition, multiple involvement of vegetation was 35 cases, and right and left both involvement were 14 cases among them. In the patients with mural IE, shunt flow was larger incidence in the right and left both side involvement (p=0.016), and slightly associated with the both side involvement (r=0.344, p=0.008).

Table 1

	Right or left side (n=44)	Right and left both side (n=15)	p-value
Age (year ± SD)	47.6±18.2	43.7±15.9	0.46
Gender (male)	21 (47.7%)	3 (20.0%)	0.07
Nosocomial infective endocarditis	11 (25.0%)	2 (13.3%)	0.48
Definite infective endocarditis	35 (79.5%)	14 (93.3%)	0.43
Underlying cardiac condition			
Congenital heart disease	12 (27.3%)	8 (53.3%)	0.11
Shunt flow (right through left)	8 (18.2%)	8 (53.3%)	0.016
Prosthetic valve	3 (6.8%)	1 (6.7%)	1.00
Normal valve	30 (68.2%)	13 (86.7%)	0.20
Central intravenous catheter	10 (22.7%)	3 (20.0%)	1.00
Echocardiographic finding			
Severe regurgitation	12 (27.3%)	5 (33.3%)	0.75
Large vegetation (>1cm)	23 (52.3%)	10 (66.7%)	0.38
Perivalvular abscess	8 (18.2%)	4 (26.7%)	0.48
Perforation	5 (11.4%)	2 (13.3%)	1.00

Because of the difficulty of differential diagnosis, we should pay attention to accurate diagnosis and proper management of mural IE, especially for the findings such as shunt flow underlying congenital condition, central intravenous catheters, and multiple involvement of vegetation.

P863 | BEDSIDE
Tricuspid regurgitation, prevalence and classification of a large single center population

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Background: Tricuspid regurgitation (TR) has historically been shadowed by left heart diseases. Mild TR is common and usually benign. Moderate or severe TR can lead to irreversible myocardial damage and adverse outcomes, however there is not much information about prevalence, associations, and management of this valve disease. Our purpose was to assess the prevalence and classification of patients with severe TR in a large single center population study.
Methods: Echocardiographic data of consecutive patients who had undergone a transthoracic echocardiogram (TTE) between June 2012 and January 2016 were included. TR severity was evaluated according to ASE guidelines. Final statistical analysis was made considering, gender, severity, associated left heart valve disease (LHVD), significant pulmonary hypertension (PHT) (>50 mmHg), presence of a prosthetic valve or an implanted cardiac device.
Results: A total of 41471 patients were included, TR was present in 13071 (31.5%), 52.9% were women. TR was mild in 10642 patients (81.4%), moderate in 1471 (11.3%) and severe in 958 (7.3%). Mean left ventricular ejection fraction was 66.37% (DS 13.24), being above 60% in all patients with severe TR. Among patients with severe TR 121 (12.6%) presented isolated TR (defined by the absence of concomitant moderate or severe LHVD, valve prosthesis, significant PHT and cardiac devices). Severe TR in the context of moderate or severe LHVD was present in 417 (43.5%): 203 had concomitant mitral regurgitation (43.5%), 30, mitral stenosis (3.1%), 94, aortic regurgitation (9.8%), and 90, aortic stenosis (9.3%). 216 (15.51%) patients with concomitant valve prosthesis and 102 (15.7%) with implantable cardiac devices presented severe TR. Mean TAPSE was 2.2 in mild group (DS 0.45), 1.97 in moderate group (DS 0.47) and 1.89 in severe group (DS 0.46).
Conclusion: Management of severe TR is an object of debate and assessment of its prevalence and associations is crucial for the patient's management. In this single center population with a large cohort of TR patients, we found a significant number of patients with moderate or severe TR. Most patients with severe TR has concomitant LHVD, however the prevalence of patients with isolated or device related severe TR was not negligible.

P864 | BEDSIDE
Risk factors of severe tricuspid regurgitation after left-sided valve surgery

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Background: Tricuspid regurgitation (TR) sometimes deteriorated late after left-sided valve surgery. According to the recent guidelines, we aggressively have been encouraged to perform tricuspid annuloplasty at the same time as the left-sided valve surgery. However, little is known about the pathophysiology that leads to severe TR after left-sided valve surgery.
Purpose: We sought to clarify the risk factors of the patients with severe TR after the left-sided valve surgery. (Method)
We retrospectively investigated consecutive 483 patients diagnosed as severe TR from June 2004 to September 2015 at our hospital. Clinical background, echocardiographic parameters were evaluated. We examined the following factors by checking the previous clinical charts: age, electrocardiograms, type of left-sided valve surgery, underlying valve diseases and history of pacemaker or ICD implantation.
Result: 95 patients out of 483 patients were postoperative state of the left-sided valve. The mean age at diagnosis was 74±10 years old, and 28 patients were male (29%).
The surgical indications were as follows: mitral valve stenosis (71 patients, 75%), mitral valve regurgitation (39 patients, 41%), aortic valve stenosis (34 patients, 36%) and aortic regurgitation (25 patients, 26%), respectively. Among those patients, 89 patients (93%) had atrial fibrillation (AF), 75 patients (79%) were diagnosed as rheumatic heart disease, 54 patients (57%) had pulmonary artery hypertension (PH) and 21 patients (22%) were performed permanent pacemaker or ICD implantation. There are only 6 patients who had severe TR without AF. Four of six patients without AF had PH, 2 of those had anatomical abnormality (malignant cardiac tumor or the double chambered right ventricle). Of 4 patients with PH without AF, one had extremely high pulmonary artery resistance, and one had pacemaker lead interference with tricuspid valve closure. The other 2 patients had similar characteristics: extremely aged (>90), female, small left ventricle, di-

lated left atrium, and post aortic valve replacement. Of the total, 47 patients (49%) underwent regular echocardiographic follow-up. Patients developed severe TR at a mean of 11.7 years after surgery in this sub analysis.
Conclusion: Almost all patients with severe TR after left-sided valve surgery present with AF, and prevalence of rheumatic heart disease were about 80 percent in patients with severe TR after left-sided valve surgery. All of patients without AF had PH or anatomical abnormality that could cause severe TR. The most important risk factors of the patients with severe TR after the left-sided valve surgery might be AF and history of rheumatic heart disease. Concomitant tricuspid valve repair might be aggressively taken into account patients with AF and/or history of rheumatic heart disease.

P865 | BEDSIDE
Prognostic value of exercise left ventricular end-systolic volume index in patients with asymptomatic aortic regurgitation: exercise echocardiography study

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Background: Surgical timing of chronic aortic regurgitation (AR) remains a matter of debate because of limited data. This study assessed the prognostic value of exercise echocardiography in patients with asymptomatic AR.
Methods: This prospective study included consecutive asymptomatic 74 patients with isolated moderate or severe AR (mean regurgitant volume = 57.0±12.5 ml) and preserved ejection fraction who underwent exercise echocardiography. The clinical outcomes were defined as the presence of 1) indication for AVR more than class IIa in the current guideline and 2) major adverse cardiovascular events (MACE).
Results: During the average follow-up of 636 days, 11 patients suffered from the clinical events, including 9 patients (15%) indicating for AVR and 2 patients (3%) developing MACE. No difference in LVEF at rest was found between the patients with and without clinical events. The indexed left ventricular (LV) diameters and LV volumes were significantly dilated in the patients with clinical events. The Cox proportional hazards regression analysis resulted that the exercise LV end-systolic volume index (LVESVi) was most significantly associated with the clinical outcomes (HR, 1.095; P=0.001). The ROC analysis indicated that exercise LVESVi, cut-off value of 40 $\geq$ ml/m^2, could predict the clinical outcomes with the sensitivity of 91% and the specificity 80%.
Conclusion: Exercise LVESVi is an independent predictor for future prognosis in patients with asymptomatic AR.

P866 | BEDSIDE
The importance of a "heart team" in infective endocarditis diagnosis. A preliminary study evaluating whether cardiologist involvement in patient assessment improves diagnostic yield in endocarditis

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Background: The European Society of Cardiology (ESC) recommends the early involvement of a cardiologist, for the diagnosis, treatment and management of infective endocarditis (IE). IE has significant mortality and morbidity, which may be due to diagnostic delays caused by the non-specific signs and symptoms associated with the disease.
Objective: To investigate whether cardiologist involvement in patient evaluation improves the accuracy of the diagnosis and increases the yield of Transthoracic Echocardiography (TTE) for IE.
Method: A retrospective study reviewing all in-patients referred for TTE over a 1-year period, for IE, at two UK hospitals within the same NHS trust, with differing diagnostic protocols. Patient diagnosis at Site A is aided by a cardiologist during an "IE ward-round", whereas at Site B this does not occur. All patient's clinical notes were reviewed for the presence of IE predictors (adapted from the Duke Criteria and the ESC guidelines), cardiologist involvement, TTE outcome and IE diagnosis confirmation
Results: The number of in-patient TTE performed, with IE as the indication, at Site A was 66/1302 (5%) and 120/2295 (5%) at Site B. 33/66 (50%) patients at Site A were reviewed by a cardiologist prior to TTE referral compared to only 11/120 (9.2%) at Site B (P<0.001). IE was confirmed in 18 patients (27.3%) at Site A and only 5 patients (4.2%) at Site B (P<0.001). A significantly greater number of patients at Site A were assessed for and therefore found to have IE clinical predictors, prior to TTE referral. Therefore, more patients at Site A, when referred for TTE were febrile, had appropriately taken positive blood cultures, had pre-existing cardiac disease and were identified with vascular and immunological stigmata. Subsequently, leading to 11 patients (16.7%) at Site A and 8 patients (6.7%) at Site B having positive TTE. Inconclusive TTE's were found in 14 patients (21.2%) at Site A and 7 patients (5.8%) at Site B, in whom further testing was required for IE confirmation. Multivariate analysis found that cardiologist input in establishing diagnosis increases the likelihood of confirming IE presence by 11-fold.
Conclusions: This study highlights how a formal "endocarditis team", including a cardiologist, limits the inappropriate use of echocardiography, enhances the diagnostic yield of echocardiography and provides the patient with an earlier confirmed diagnosis. All due to better patient assessment for IE clinical signs. This strategy is supported by the ESC and should be of interest to all acute hospitals providing cardiac services; as it has the capacity to improve the rapidity of patient diagnosis and treatment; as well as being more cost effective.

P867 | BEDSIDE
Choice of prosthesis for endocarditis of the aortic valve - a retrospective single centre experience

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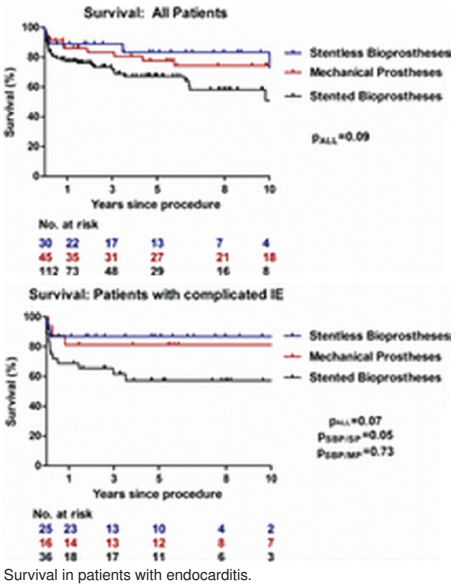
Background: The choice of adequate substitute during aortic valve replacement (AVR) for infective endocarditis (IE) is still widely debated.
Purpose: To retrospectively review all patients treated surgically for IE of the aortic valve from 2000–2015 and compare groups according to substitute received.
Methods: During the observational period, 188 patients underwent AVR for IE using either stentless bioprostheses as root replacement (SBP, n=30), mechanical prostheses (MP, n=45) or stented bioprostheses (SP, n=112). Mean follow-up was 4.6 years (maximum 15.4 years) and survival data were 100% complete.
Results: MP patients were significantly younger (57.2±16.9y [SBP] vs. 42.5±10.7y [MP] and 59.1±14.1y [SP], p<0.01). Rates of intravenous drug use and chronic dialysis were not significantly different (p=0.76 and 0.44 respectively). SBP patients were more likely to have root involvement (RI) (83.3% vs. 33.3% [MP] and 25.9% [SP], p<0.01) and prosthetic valve endocarditis (PVE) (53.3% vs. 6.7% [MP] and 12.5% [SP], p<0.01). Thus, cardiopulmonary bypass time was longer in SBP patients (174.0±114.4mins vs. 110.3±42.6mins [MP] vs. 108.5±49.8mins [SP], p<0.01). Rate of in-hospital complications and length of stay was not significantly different between the groups. Mortality at 30 days was 13.3% [SBP] vs. 6.7% [MP] and 12.5% [SBP] (p=0.53). Long-term survival was best in SBP patients (83.3% at 5 years vs. 77.6% [MP] vs. 67.1% [SP], p=0.09). In patients with complicated IE (presence of RI or PVE, n=77), survival advantage in SBP patients became more apparent (86.9% at 5 years [SBP] vs. 81.3% [MP] vs. 57.2% [SP], p=0.07 and pSBP/SP=0.05). No early re-infection (<90 days) occurred in SBP patients, versus 4.4% in MP and 7.1% in SP (p=0.29). At latest follow-up, rate of re-operation for re-infection was 6.7% [SBP] vs. 11.1% [MP] and 12.5% [SP] (p=0.67). Prosthesis failure occurred in 3.3% in SBP and 1.8% in SP patients (p=0.52).



Survival in patients with endocarditis.

Conclusions: Use of SBP provides favourable outcomes in patients with IE with low rates of re-infection and valve deterioration. Despite a more advanced age and a higher risk profile in SBP patients, long-term survival compares favourably to patients who received MP and SP. This is likely due to a more radical excision of infected tissue. SBP should be favoured especially in patients with complicated IE.
Acknowledgement/Funding: King's College Hospital Charity.

CHRONIC PULMONARY HYPERTENSION

P868 | BEDSIDE
Prognostic relevance of pulmonary arterial compliance after therapy initiation or escalation in patients with pulmonary arterial hypertension

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Background: Conventional hemodynamic parameters are considered to be the gold standard indices of outcome in pulmonary arterial hypertension (PAH); on the contrary, few data support the hypothesis that the pulsatile component of right ventricular afterload provides important prognostic information.
Purpose: The aim of the study was to investigate the prognostic significance of pulmonary arterial compliance (PCa) and of its change after therapy initiation or escalation in PAH patients.
Methods: A cohort of 419 consecutive PAH patients (308 naive and 111 prevalent) underwent right heart catheterisation (RHC) prior to initiating or escalating PAH targeted therapy. RHC was repeated in 255 patients (61%) after 4 to 12 months of therapy as 62 patients died and 102 (24%) did not undergo a follow-up RHC within the first year.
Results: After the follow-up RHC, 63 patients died over a median follow-up period of 39 months. At multivariate analysis, age >50 yo, male gender, etiology associated with systemic sclerosis, persistence of WHO class III/IV and reduced PCa at follow-up RHC were the independent parameters significantly associated with poor prognosis. At ROC analysis the optimal cut-off point of PCa to predict survival was 1.4 ml/mmHg (AUC 0.73, sensitivity 81.8%, specificity 58.8%).
Conclusions: In PAH patients hospitalized to initiate or to escalate PAH specific therapy, failure to improve PCa after therapy is a strong hemodynamic predictor of poor prognosis.

P869 | BEDSIDE
Follow-up haemodynamic assessment as a predictor of survival in scleroderma-associated pulmonary arterial hypertension

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Background: Scleroderma-associated pulmonary arterial hypertension (SSc-PAH) has higher mortality than other types of pulmonary hypertension (PH). It is suggested that cardiac index (CI) and pulmonary vascular resistance (PVR) 4 months post-treatment predict survival (1). In this single-center retrospective study, we examined this hypothesis and other haemodynamic predictors of survival in a larger cohort of SSc-PAH.
Methods: Patients with SSc-PAH undergoing right heart catheterization (RHC) at baseline and 3–6months from 2005–2015 were included. Survival analysis was performed using Kaplan-Meier method. Comparison between groups was assessed by log-rank test.
Results: 175 patients were included with median follow up of 5.25 years (Table 1). Females had better 3-year survival (79.1% vs 59.3%, p=0.007) but this balanced out at 5 years (65.4% vs 59.3%, p=0.133). Mean pulmonary artery pressure (mPAP) 25–35mmHg at baseline carried better 5-year survival than mPAP>35mmHg (Figure 1a). CI>2.7L/min/m^2 at 3–6 months, rise in CI greater than 50%, and fall in PVR all showed a trend towards improved survival without reaching statistical significance (Figures 1b,c,d). Change in mPAP and right atrial pressure (RAP) showed no correlation with survival.
Conclusion: In our cohort, no haemodynamic parameters at 3–6months predicted survival. This may be due to escalation of treatment in those with poor haemodynamic response. Predicting outcomes in SSc-PAH using invasive haemodynamics remains challenging. Non-invasive tools, such as cardiac magnetic resonance, warrant further investigation as an alternative for monitoring progress (2).

Table 1. Characteristics & haemodynamics

Characteristics		
Total number, n	175	
Female, n (%)	146 (83.4)	
Deaths, n (%)	74 (42.2)	
Median follow up, years (Q1; Q3)	5.3 (2.7; 7.1)	
Haemodynamics	**Baseline, mean ± SD**	**3–6 months, mean ± SD**
RAP, mmHg	8.42±4.82	7.73±3.85
mPAP, mmHg	42.0±11.48	39.15±11.78
PCWP, mmHg	10.52±3.39	10.92±3.02
Cardiac index, L/min/m^2	2.74±0.70	2.96±0.73
PVR, dyn.s/cm^5	597.74±316.76	495.9±281.20
Body surface area, m^2	1.71±0.21	1.70±0.21

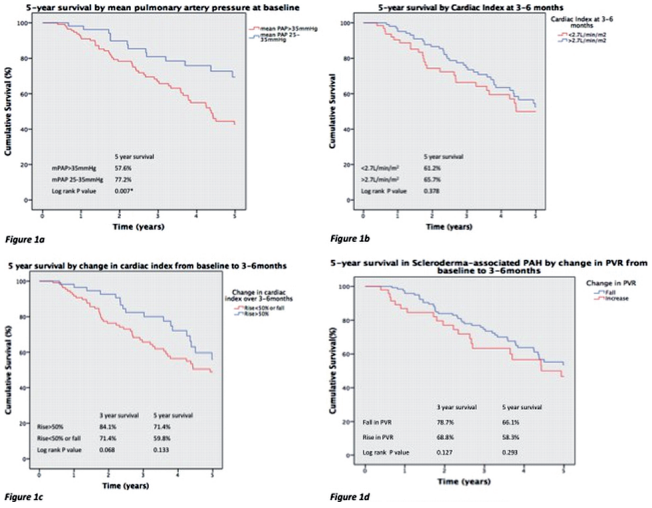

Figure 1

P870 | BEDSIDE
Borderline pulmonary pressure elevation is associated with worse prognosis in patients at risk for pulmonary hypertension

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Introduction: According to recent guidelines pulmonary hypertension (PH) is defined as an elevation of mean pulmonary arterial pressure (mPAP) ≥25mmHg. Under physiological conditions normal mPAP is considered to be 14±3mmHg. The prognostic relevance of mPAP under 25mmHg has not been systematically addressed.
Methods: We retrospectively analysed hemodynamics and survival data of patients undergoing right heart catheterization between 2006 and 2014 at our clinic. Patients were clustered into 4 mPAP groups (≤17mmHg: lower normal-, 18–20mmHg: upper normal-, 21–24mmHg: borderline PAP; ≥25mmHg: PH). Baseline characteristics including number of cardiopulmonary comorbidities were assessed. Parametric and non-parametric ANOVAs were performed to check for significant differences between mean PAP groups. Kaplan-Meier- and multivariate COX-Regression analysis for survival were performed.
Results: 547 patients were analysed (64% female, age 62±14yr, mPAP 29.6±15.1mmHg). Kaplan-Meier analysis revealed worse survival in patients with upper normal- and borderline PAP as compared to patients with lower normal PAP ($p<0.05$). Patients with PH had worse survival than patients with normal or borderline PAP ($p<0.01$). In addition, number of comorbidities was a significant predictor for survival in univariate analysis ($p<0.005$). Multivariate Cox Regression analysis revealed that mPAP ($p\leq0.001$; 18–20 mmHg: HR 1.91 95% CI 0.9–4.3; 21–24 mmHg: HR 2.2 95% CI 1.1–4.6; ≥25mmHg: HR 4.6 95% CI 2.6–8.2) was an age independent predictor for survival, whereas number of comorbidities was not. In multivariate analysis there was no significant difference between the lower-normal and upper-normal PAP groups (p=0.12). However, borderline PAP elevation still showed significantly worse survival as compared to lower-normal PAP (p=0.03).
Conclusion: Borderline-PAP elevation is associated with worse prognosis in patients at risk for PH. Upper-normal PAP is associated with significant worse survival as compared to lower-normal PAP in univariate but not in multivariate analysis (corrected for age and number of comorbidities).

P871 | BEDSIDE
Comparison of different types of pulmonary hypertension in patients with connective tissue disease

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Background: Pulmonary hypertension (PH) is a well-known complication in connective tissue disease (CTD) and can be due to distal pulmonary arteries obstructive disease (pulmonary arterial hypertension – PAH-CTD), left heart diseases (LHD) or lung diseases (LD). The prognostic impact of PAH is well known in CTD patients but few data are available on the survival of CTD patients with PH due to other conditions.
Purpose: To compare survival of CTD patients with PAH, PH-LHD or PH-LD.
Methods: Consecutive CTD patients with PAH, PH-LHD and PH-LD referred to our center underwent baseline right heart catheterization, 6-minute walk distance (6MWD) and echocardiographic evaluation. Patients were treated according with current PH guidelines. Data were analysed by Kruskal-Wallis test. Kaplan-Meier curves were used to estimate survival.

Results: We included 242 patients with CTD (170 PAH, 37 PH-LHD, 35 PH-LD). Baseline characteristics are shown in the table. Survival at 1, 2 and 5 years were: 77%, 64% and 32% in PAH patients, 90%, 78% and 43% in PH-LHD patients and 84%, 65% and 33% in PH-LD patients (p-value= 0.563).

Median (interquartiles)	PAH n=170	PH-LHD n=37	PH-LD n=35	p-value
Age (years)	65 (55–72)	69 (61–78)	69 (60–75)	0.056
Male sex (%)	13	14	40	<0.001
NYHA III/IV (%)	88	59	60	<0.001
6MWD (m)	319 (233–400)	368 (292–409)	344 (238–400)	0.548
RAP (mmHg)	7 (4–12)	10 (8–13)	5 (2–6)	<0.001
mPAP (mmHg)	48 (39–55)	31 (29–42)	31 (27–40)	<0.001
PAWP (mmHg)	8 (6–10)	20 (18–21)	8 (7–11)	<0.001
Cardiac index (l/min/m^2)	2.4 (1.9–3.0)	2.5 (2.0–3.1)	2.9 (2.4–3.4)	0.003
PVR (WU)	10 (7–14)	3 (2–5)	5 (4–7)	<0.001
RV diastolic area index (cm^2/m^2)	16 (13–18)	12 (10–14)	14 (11–17)	<0.001
LV diastolic volume index (ml/m^2)	29	49	41	<0.001
LVEF (%)	71	62	69	<0.001

EF: ejection fraction; LV: left ventricle; PAP: pulmonary artery pressure; PAWP: pulmonary artery wedge pressure; PVR: pulmonary vascular resistance; RAP: right atrial pressure.

Conclusions: CTD patients with PAH have the worst functional, hemodynamic and echocardiographic characteristics. Despite remarkable clinical, functional and haemodynamic heterogeneity, no differences in survival were found between patients with PAH, PH-LHD and PH-LD outlining the prognostic relevance of the underlying systemic disease.

P872 | BEDSIDE
The clinical characteristics and long-term prognosis of pulmonary arterial hypertension associated with hereditary hemorrhagic telangiectasia (HHT-PAH): a case series

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Background: Hereditary hemorrhagic telangiectasia (HHT) is a rare autosomal dominant inherited vascular disorder resulting in multiple arterial venous malformations. Pulmonary arterial hypertension (PAH) is increasingly recognized as a severe complication of HHT, however little is known about the clinical characteristics and prognosis of HHT-PAH.
Purpose: We aimed to describe the baseline clinical, echocardiographic and hemodynamic characteristics, treatment options and follow-up data in 11 HHT-PAH patients.
Methods: Newly diagnosed HHT-PAH patients in a single pulmonary hypertension expert centre between October 2007 and April 2015 were prospectively recruited and followed every half year. The clinical diagnosis of HHT was made according to Curaçao criteria and PAH was confirmed by right heart catheterization (RHC). The baseline clinical, echocardiographic and hemodynamic parameters and treatment options were recorded.
Results: 11 HHT-PAH patients were finally enrolled, and female was predominant (81.8%) with mean age of 34.0 years (range 22–49 years). Patients all had spontaneous recurrent epistaxis, eight had multiple telangiectasias at characteristic sites, five had visceral lesions and eight had at least one first degree relative with HHT. Among them, 9 patients had a definite HHT diagnosis, while 2 patients had a possible HHT diagnosis. Their world health organization functional class (WHO-FC) distributed as 9.1%/36.4%/54.5% (I/II/III) and 6-minute walk distance was 413±53 meters. Hemodynamic parameters assessed by RHC showed a right atrial pressure (RAP) of 7.8±6.1 mmHg, a mean pulmonary artery pressure of 55.8±20.3 mmHg, a right ventricle end diastolic pressure (RVEDP) of 12.36±6.58 mmHg, a pulmonary capillary wedge pressure of 8.1±3.4 mmHg, a pulmonary vascular resistance of 10.3±6.4 wood, and a cardiac index of 3.86±1.25 ml/min. Only one patient had a positive acute vasoreactivity test result. Echocardiographic parameters showed a RV/ left ventricle (LV) end diastolic diameter ratio of 87.68±30.89%, and three patients had pericardial effusion. All patients received PAH supportive therapy including digoxin and diuretics. 9 patients received PAH specific therapy. The mean follow-up time was 2.7±1.6 years (range 0.77–5.89 years). At the end, 3 patients died while 8 patients survived. The 1- and 2- year survival rates were 90.9% and 77.9% respectively. Comparing with survivors, deceased patients tended to have higher RAP (p=0.044), RVEDP (p=0.002) and total bilirubin (p=0.012), but lower prothrombin time activity percentage (PTA, p=0.010) and partial pressure of carbon dioxide (pCO2, p=0.006) at baseline. However baseline WHO-FC distribution, PAH specific therapy and pericardial effusion showed no difference between two groups.
Conclusion: The survival rates and hemodynamic characteristics of HHT-PAH were similar with idiopathic PAH. HHT-PAH with higher RAP, RVEDP, total bilirubin, and lower PTA, pCO2 may have worse prognosis.
Acknowledgement/Funding: National Key Technology R&D Program, China (project number: 2011BAI11B15)

P873 | BEDSIDE
BMPR2 mutations in patients with pulmonary arterial hypertension. Implications for outcome

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Background: Pulmonary arterial hypertension (PAH) is a rare disorder characterised by progressive remodelling of the small pulmonary arteries resulting in increased pulmonary vascular resistance and ultimately right ventricular failure and death. Mutations in the gene encoding the bone morphogenetic protein receptor type II (BMPR2) are the commonest genetic cause of PAH. Recently, it has been shown that these mutations are associated with an increased risk of death or transplantation and all-cause mortality.
Purpose: To describe the epidemiology of BMPR2 mutations and the association with outcome in patients treated in a single North Italian referral center for PAH.
Methods: Since November 2013, 64 patients with idiopathic PAH and 16 family members have undergone genetic testing at our center. DNA was extracted from peripheral blood using standard procedures and specific primers were used to amplify the BMPR2 coding regions. Sanger sequencing was performed to identify disease-causing mutations. Preliminary data are available in 39 patients and 9 family members (mean age 47±4 years, 64% female gender, 15% in WHO class III).
Results: BMPR2 mutations have been observed in 10 patients (26% of the entire population). Mutations have been detected in the exons 1,3,7,8 and 11. Seven out of ten mutations were missense substitutions while 3 mutations lead to a truncated protein. Seven mutations are unpublished and are for the first time related to idiopathic PAH. Idiopathic PAH patients carrying BMPR2 mutations were more frequently of female gender (60%), had a more severe disease (30% were in WHO class III, 40% in triple combination therapy with 2 included in the lung transplant list) and a more severe haemodynamic profile (60% had a cardiac index <2 l/min/ mq).
Conclusions: The preliminary data of this single Italian referral center study are in agreement with literature data that idiopathic PAH patients with BMPR2 mutations present with more severe disease, and are at increased risk compared to those without BMPR2 mutations. Genetic counselling and BMPR2 mutation screening should be offered by referral center to patients with idiopathic PAH.

P874 | BEDSIDE
Right ventricular longitudinal peak systolic strain predicts survival in precapillary pulmonary hypertension

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Background: The use of two-dimensional speckle tracking in the assessment of right ventricular dysfunction in patients with precapillary pulmonary hypertension (pPH) has been recently introduced. Thus, little is known on the prognostic value of right ventricular longitudinal peak systolic strain (RV-LPSS) in patients with pPH.
Purpose: The aim of the current study is to evaluate RV-LPSS as an independent associate of survival and to investigate the additive role of RV-LPSS in the prognostic significance of already recognized markers of survival in pPH.
Materials and methods: All consecutive adult patients with pPH classified as group 1 or 4 according to current guidelines were prospectively included. They underwent six minute walk test (6MWT), assessment of NT-proBNP serum levels and echocardiographic evaluation in the day of enrollment. Speckle-tracking analysis of the RV was performed from the apical 4-chamber view images. Time from enrollment to death due to pPH was recorded for all patients. In order to further evaluate the additive prognostic value of RV-LPSS, three different regression models were built using each one of the following known predictors of survival in pPH patients (NT-proBNP, WHO functional class and distance walked in 6MWT).
Results: In total, 40 patients with pPH (13 men, 51.2±15.6 years) were studied. Over a median follow-up period of 31.3 months (IQR 27.7–37.9 months), 10 patients died. Univariate Cox proportional hazard analysis showed that WHO

Model comparisons

	Multivariable analysis			Model comparison			
	HR	95% CI	p value	–2LL	χ^2	p value	c-statistic
Model A (6MWD)	3.769	1.204–11.795	0.023	56.381	16.997	<0.0001	0.712
Model A + RV-LPSS	–	–	–	54.288	17.762	<0.0001	0.796
6MWT	2.928	1.001–9.226	0.011	–	–	–	-
RV-LPSS	5.391	1.467–19.814	0.014	–	–	–	-
Model B (NT-proBNP)	5.817	1.297–26.100	0.021	65.901	5.420	0.02	0.704
Model B + RV-LPSS	–	–	–	61.808	8.525	0.014	0.760
NT-proBNP	1.001	1.001–1.003	0.043	–	–	–	–
RV-LPSS	1.133	1.004–1.279	0.042	–	–	–	–
Model C (WHO class)	10.010	2.931–34.190	<0.0001	62.862	6.961	0.008	0.705
Model C + RV-LPSS	–	–	–	60.153	9.662	0.008	0.780
WHO class	4.193	1.119–15.721	0.033	–	–	–	–
RV-LPSS	1.102	1.002–1.235	0.045	–	–	–	–

6MWD: distance walked in 6 minute walk test, RV-LPSS: right ventricular longitudinal peak systolic strain, HR: hazard ratio, CI: confidence interval, –2LL: -2 likelihood ratio, χ^2: chi squared, p: statistical significance.

functional class, 6MWT distance, NT-proBNP and RV-LPSS were significant predictors of survival. RV-LPSS remained an independent predictor of survival in multivariable Cox proportional hazard regression analysis after adjusting for WHO functional class, 6MWT distance and NT-proBNP respectively (Table). Addition of RV-LPSS to each one of the regression models resulted in a significant improvement in χ^2 and increase in c-statistic, suggestive of improved survival prognosis (Table).
Conclusion: RV-LPSS is an independent predictor of survival in patients with pPH.

P875 | BEDSIDE
Effects of human immunodeficiency virus infection on pulmonary artery pressure in children

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Background: Pulmonary hypertension is a potential complication of HIV infection and may result in right ventricular failure and premature death. There are no data of the effects of vertically acquired HIV infection and/or antiretroviral therapy (ART) on pulmonary artery pressure.
Methods: We performed a cross-sectional study of 112 HIV infected children (48 ART-naïve, 54 ART-exposed) and 51 HIV uninfected controls to estimate pulmonary artery pressure using the following echocardiography parameters: tricuspid valve jet regurgitation peak velocity (TVR jet velocity), left ventricular (LV) systolic and diastolic eccentricity indexes, and right ventricular (RV) function, which was assessed by measuring tricuspid annulus plane systolic excursion (TAPSE). The association between either ART-naive or ART-exposed HIV infection was explored using general linear modelling with adjustment for potential confounders and intermediary variables.
Results: ART-exposed HIV infected children had higher mean TVR jet velocity both in unadjusted (difference 0.36 m/s, 95% CI 0.07 to 0.40, p=0.003) and adjusted analyses (difference 0.36 m/s, 95% CI 0.12 to 0.60, p=0.003) as well as higher eccentricity index (adjusted difference 0.06, 95% CI 0.01 to 0.11, p=0.02), indicating higher pulmonary artery pressure than controls. ART-naive HIV infected children, had a lower TAPSE (adjusted difference -2.2 mm, 95% CI -3.73 to -0.71, p=0.004), indicative of reduced RV systolic function, despite no statistically significant differences in TVR jet velocity (crude difference 0.17 m/s, 95% CI -0.07 to 0.40, p=0.17; adjusted difference 0.18 m/s, 95% CI -0.06 to 0.43, p=0.14). The LV eccentricity index in these ART-exposed children was significantly higher than normal however, lower respiratory tract infection (LRTI) seemed to partially account for the effect, also for the association between ART-naïve HIV infection and reduced RV systolic function.
Conclusions: ART-exposed HIV infection is associated with higher pulmonary artery pressure, while ART-naïve HIV infection appears to be associated with reduced RV systolic function. LRTI partially mediates the associations found in both ART-naïve and ART-exposed HIV infected children.

P876 | BEDSIDE
Pulmonary hypertension in patients with transposition of great arteries or pulmonary atresia

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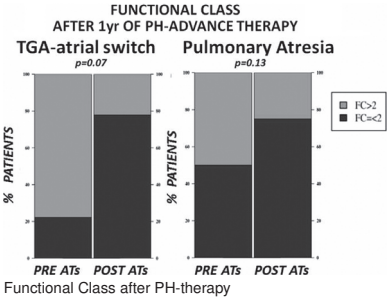
Background: There is clear evidence on benefit of advance therapy (AT) in Eisenmenger syndrome relating to simple cardiac defects. Little is known however on the effect of AT in pulmonary hypertension (PH) for patients with complex congenital heart disease (CHD), such as transposition of great arteries after atrial switch procedure (TGA-AS) or pulmonary atresia (PA).
Purpose: To study long-term safety and clinical efficacy of ATs in TGA-AS and PA.
Methods: All adult patients with TGA-AS or PA diagnosed with precapillary PH (in the absence of other causes) followed-up in our Centre between 2004 to 2014 were identified; demographic, clinical data and investigations were retrospectively reviewed.
Results: Fourteen TGA-AS patients (pts) had PH; their median age 40 [range 26–48] years (yrs), 57% male, age at AS procedure 2.5 [0.06–27] yrs. Six (42.9%) pts had a non-restrictive VSD and underwent a palliative mustard procedure. Nine (64.3%) pts received AT (6 phosphodiesterase type 5 inhibitor [PDE5i], 3 endothelin receptor antagonist [ERA]). At short-term follow-up (median 1.0 [0.75–1.5] yrs), there was trend towards improving functional class (p=0.07), but no change on 6MWT or BNP. At long-term follow (median 4.5 [1.6–8.3] yrs), one patient died of congestive heart failure. Three (33%) pts required combination AT at a median 3 [2–5] yrs from initiation (PDE5i+ERA±prostanoid). BNP and 6MWT remained unchanged.

Twenty-six pts with PA had PH (median age 36.5 [18–51] yrs, 19% male, major aorto-pulmonary collateral arteries were present in 88.5% of pts); 20 (77%) of them received AT (16 PDE5i, 4 ERA). At short-term follow-up (median 0.87 [0.25–1.4] yrs), there was trend towards better functional class (p=0.13), but no changes on 6MWT or BNP. During long-term follow-up 2.6 [0.6–6.8]yrs, 6 (30%) pts required combination AT (PDE5i+ERA), while 4 pts developed intolerance and were switched to a different AT class. There was no change in FC and 6MWT or any deterioration in left ventricular function, but BNP (n=13) increased from 49 ng/dL[10.5–360.5] to 78 [19–1219] ng/dL, p=0.01. Five (25%) pts died at a median 2.9 [1.6–7.6]yrs from commencing AT, 2 of haemoptysis, 1 of brain haemorrhage, 1 of heart failure and 1 cause unknown; 3 pts were on combination ATs at the time of death.



Functional Class after PH-therapy

Conclusions: PH in pts with PA and TGA-AS is not uncommon and should be promptly diagnosed and managed, as it is associated with significant mortality. ATs appear to be safe and maybe associated with functional benefits and disease stabilization. Larger prospective studies are warrant in this complex area.

CARDIOMYOPATHIES

P877 | BENCH
Effects of treatment with methotrexate associated to lipid nanoparticles on diabetic cardiomyopathy in rats

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Background: Diabetic cardiomyopathy is characterized by increased myocardial stiffness, myocyte hypertrophy, myocardial fibrosis, cell death and diastolic dysfunction. Previously we showed that lipid nanoparticles, that bind to lipoprotein receptors, have the capability to concentrate carried drugs in sites with inflammation and atherosclerotic lesions. The treatment with metothrexate (MTX) associated with LDE reduces inflammation and tissue proliferation in atherosclerotic lesions in rabbits.
Purpose: To investigate in rats the effects of LDE-MTX association on diabetic cardiomyopathy induced by streptozotocin (STZ).
Methods: Male Wistar rats were submitted to diabetes mellitus (DM) induction by a single dose i.v. of STZ (50mg/kg) dissolved in 1M citrate buffer. After two weeks we checked the blood glucose levels and animals with glucose $<$300 mg/dL were excluded. DM rats were divided into 3 groups: DM-LDE, treated only with LDE; DM-MTXc treated with commercial MTX; DM-LDE-MTX treated with LDE-MTX. MTX dose was 1 mg/kg, i.p., weekly. SHAM group (without DM) received citrate buffer injection and animals were treated with saline solution once a week for 6 weeks. Six weeks after the blood glucose evaluation, echocardiography was performed. The animals were then euthanized for morphological analysis and protein expression by Western blot.
Results: Compared to DM-LDE and DM-MTXc groups, treatment with LDE-MTX markedly improved blood glucose (634±65 mg/dL; 557±99 mg/dL and 469±97 mg/dL, respectively) and insulin secretion (11±4 U/L; 8±3 U/L and 86±17 U/L respectively). LDE-MTX reduced ($p<0.05$) inflammation, cardiac hypertrophy and left ventricular myocardial fibrosis. Moreover, LDE-MTX significantly ($p<0.05$) decreased the expression of macrophages, TNF-α, collagen I and pro-apoptotic factors caspase 3 and BAX. The expression of antioxidant enzymes catalase and SOD1 was also higher compared to DM-LDE and DM-MTXc groups. The animals treated with LDE-MTX showed no toxicity.
Conclusion: The treatment with the association LDE-MTX improved blood glucose levels, insulin secretion, cardiac hypertrophy, myocardial fibrosis and the inflammatory process. These results were achieved without observable toxicity, so that this new therapeutic approach should be considered for future clinical trials.
Acknowledgement/Funding: FAPESP and CAPES

P878 | BEDSIDE
NT-proBNP: a potent parameter of clinical success of PTSMA in patients with HOCM

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Background: Percutaneous transluminal septal myocardial ablation (PTSMA) performed in symptomatic patients with hypertrophic cardiomyopathy (HOCM) creates a micro-infarction by administering pure ethanol in a suitable septal coronary branch. The corresponding myocardium is believed to subsequently heal and remodel itself with resulting gradient reduction and symptom relief.
Methods: Blood samples of 47 symptomatic consecutive patients (mean age: 57±12 years; 31 male; admission: Oct. 2013 - Sept. 2014; without any history of septal reduction therapies) were taken at rest before early rising the day of PTSMA, at discharge and again at 3- and 12-month-follow-up visit.
Results: The extent of myocardium infarction after PTSMA was estimated with blood-testing for maximum Creatinkinase output, reaching 992 U/l (IQR: 670–1296 U/l).
Three months after PTSMA overall NT-proBNP levels were significantly lower (p=0.000015) compared to baseline, only to be underscored significantly (p=0.000016) once again at 12-month-follow-up. In 9 patients without satisfactory gradient reduction and indication for re-PTSMA or myectomy at follow-up, there was no significant (p=0.21) reduction of NT-proBNP levels at 3-month-follow-up (Median: 1307 pg/ml; IQR: 459–1956 pg/ml) compared to baseline (Median: 1284 pg/ml; IQR: 382–2941 pg/ml). Eventually, one of these patients received a myectomy and 4 such patients had a re-PTSMA performed during follow-up. In contrast, the other 36 patients with good haemodynamic results already showed a significant (p=0.000025) reduction of NT-proBNP levels at 3 months (Median: 309 pg/ml; IQR: 129–486 pg/ml) compared to their baseline-levels (Median: 503 pg/ml; IQR: 190–1092 pg/ml).
NT-proBNP 3-month-levels correlated significantly with interventricular septum-thickness (r=0.35; $p<0.05$) and LVOT-gradient at rest/after Valsalva-manoeuvre (r=0.43/r=0.49; $p<0.05$).

	Baseline (N=47)	3 months (N=45)	12 months (N=34)
NYHA	2.7±0.6	1.5±0.7	1.4±0.6
VO2max [ml/min/kg]	20.1±5.0	20.8±4.5	21.5±5.3
IVSd [mm]	19±4	16±4	14±4
LVOT-gradient (at rest / after Valsalva) [mmHg]	56±37 / 100±43	25±29 / 48±44	26±30 / 39±36
NT-proBNP [pg/ml]	586 (IQR: 237–1284)	364 (IQR: 200–586)	214 (IQR: 88–637)

Conclusion: In patients with symptomatic HOCM who underwent PTSMA, a significant fall in NT-proBNP levels during follow-up seems to correlate with objective haemodynamic and clinical improvement. In this sense, NT-proBNP could be a useful marker of clinical success after septal reduction treatment for HOCM.

P879 | BEDSIDE
Technetium pyrophosphate cardiac imaging in asymptomatic variant transthyretin-related cardiac amyloidosis

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Background: Transthyretin-related cardiac amyloid (ATTR-CA) is an increasingly recognized cause of heart failure with preserved ejection fraction (HFpEF). In single center studies, technetium pyrophosphate (99mTc-PYP) cardiac imaging has been shown to noninvasively identify ATTR-CA with a quantitative heart-to-contralateral chest (H/CL) ratio threshold >1.5. While 99mTc-PYP is well characterized in patients with overt cardiomyopathy, the utility of 99mTc-PYP in patients with variant TTR genotype (TTRm) without signs or symptoms of heart failure remains undetermined.
Purpose: To assess the utility of 99mTc-PYP cardiac imaging in patients with variant TTR genopositivity without heart failure in a single center experience.
Methods: Forty patients who underwent clinical examinations, echocardiography, measurement of cardiac biomarkers, and 99mTc-PYP scintigraphy (planar imaging) were subsequently subdivided into three groups: (1) patients with non-amyloid HFpEF, n=8 (2) asymptomatic TTR mutation carriers, n=12 and (3) TTR mutation carriers with symptoms of heart failure (ATTRm), n=20. Cardiac retention of 99mTc-PYP was assessed using both a semi-quantitative visual score (range: 0 [no uptake] to 3 [uptake greater than bone]) and a H/CL ratio on planar images. Continuous and categorical variables were compared between the groups.
Results: TTR mutation carriers appeared phenotypically normal as compared to patients with ATTRm cardiac amyloidosis as determined by left ventricular ejection fraction (61±8 vs 51±14, p=0.02), interventricular septal thickness (0.9±0.3 vs 1.5±0.3, $p<0.001$) and E/e' (8.1±1.5 vs. 18.1±8.9, $p<0.001$). However, abnormal 99mTc-PYP uptake was observed in the 12 asymptomatic TTR mutation carriers without heart failure as follows, grade 1 (n=3), grade 2 (n=3) and grade 3 (n=4). In addition, 99mTc-PYP uptake was increased among asymptomatic carriers as compared to patients with HFpEF (H/CL ratio 1.5±0.4 vs 1.2±0.1, p=0.02), but lower as compared to symptomatic ATTRm (H/CL ratio 1.5±0.4 vs 1.8±0.4, p=0.02).
Conclusion: 99mTc-PYP scintigraphy demonstrated abnormal uptake by both quantitative and semi-quantitative methods among asymptomatic carriers of TTR mutations. These data suggest that abnormal 99mTc-PYP may be the first measurable manifestation of ATTR cardiac amyloidosis.

P880 | BEDSIDE
Clinical features and prognosis of pediatic patients with left ventricular noncompaction

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Introduction: Left ventricular noncompaction cardiomyopathy (LVNC) is characterized by a left ventricle with a prominent trabecular meshwork. Long-term prognosis of LVNC has not been fully elucidated yet.
Purpose: The aim of this study is to clarify the difference between infantile and juvenile cases and identify the risk factor of poor prognosis of LVNC in the largest series to date.
Methods: Based on nationwide surveys of LVNC in Japanese children, we compared the clinical features and anatomical properties of infantile cases of LVNC (<2 years: 85 cases) with that of juvenile cases (2–15 years: 73 cases). In addition to the standard noncompacted to compacted layer (N/C) ratio, we developed an echocardiographic criteria which represents an average of N/C ratios in five wall segments to estimate the severity of LVNC.
Results: The duration of follow-up ranged from 15 days to 22 years (median 5 years). Although most patients in the infantile group had clinical signs of severe heart failure at initial presentation (70.1%), the majority of juvenile cases were asymptomatic and identified when screened for cardiac abnormalities, such as ECG screening (55.8%). WPW syndrome was higher in both groups (infantile group: 9.7%, juvenile group: 10.0%) than those reported in adults, but the incidence of LBBB and VT was lower than those reported in adults. On echocardiography the maximum N/C ratio was mostly observed at the apex in both groups. Neither noncompaction score nor N/C score was significantly different between both groups. Left ventricular ejection fraction (LVEF) at initial presentation was significantly lower in the infantile group than in the juvenile group. Although survival analysis showed poor prognosis in the infantile group, the significant risk factor was LVEF below 50% (p=0.0004, hazard ratio = 9.0), rather than age of onset.
Conclusions: LVNC in both infantile and juvenile groups showed poor prognosis when both groups had depressed LVEF at initial presentation, suggesting that the mechanism of developing LVNC in children might be different from that in adults.

P881 | BEDSIDE
Outcome assessment by Tissue Doppler-derived Tei index and/or two-dimensional speckle tracking imaging in patients with AL cardiac amyloidosis

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Background: Both longitudinal systolic and diastolic deformation parameters derived from speckle tracking imaging (STI) and left ventricular (LV) Tei index, a known parameter reflecting combined systolic and diastolic myocardial performance, were previously reported as valuable parameters to predict the outcome of patients with cardiac amyloidosis (CA). In this study, we compared the prognostic values between Tei index and deformation parameters in CA patients.
Methods: LV systolic and diastolic functions including tissue-Doppler-derived LV Tei index and STI-derived deformation parameters were evaluated by echocardiography in 58 consecutive CA patients (age 64±10 years, 55% male). All patients completed a one-year follow-up by clinical visit or telephone interview. The primary end point was all-cause death.
Results: Nineteen (32.8%) out of 58 CA patients died during the one-year follow up (mean 260±132 days). Tei index (0.89±0.29 vs. 0.61±0.16, $P<0.001$) and E to global diastolic strain rate ratio (E/LSRdias) were significantly higher while global systolic strain (LSsys) and strain rate (LSRsys) as well as global diastolic strain (LSRdias) were significantly lower in non-survivors than in survivors (all $p<0.05$). Cox regression survival analysis showed that Tei index [hazard ratio (HR) 47.04, 95% confidence interval (CI) 7.79–284.10, $P<0.001$], global LSsys (HR 1.19, 95% CI 1.06–1.33, P=0.004) and E/LSRdias (HR 1.92, 95% CI 1.19–3.08, P=0.007) were independent predictors of one-year all-cause mortality after adjustment for age, gender, and body mass index. Prediction performance (ROC derived C-statistic) for one-year mortality was 0.85 for Tei index, 0.77 for Global LSsys, 0.72 for E/LSRdias, 0.87 for Global LSsys (%) + Tei index or E/LSRdias + Tei index. Tei index >0.9 and global LSsys absolute value <13% showed excellent prediction performance for one-year all-cause mortality in CA (specificity 1.00). Whereas Tei index <0.8 and global LSsys >13% strongly predicted one-year survival in this high-risk cohort (specificity 0.95, Figure 1).

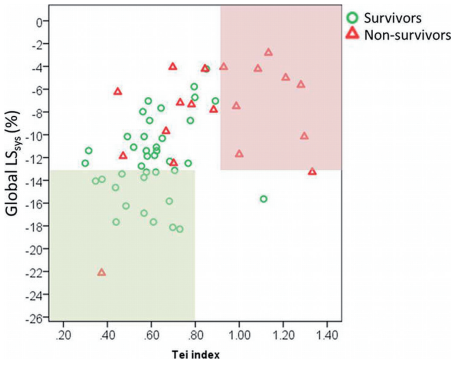

Figure 1

Conclusions: Both deformation parameters and Tei index serve as reliable predictors of one-year mortality in CA patients. The combination of Tei index and deformation parameters provides excellent prediction performance for one-year mortality and survival in CA patients.

P882 | BENCH
Prevalence and pathogenic role of copy number variants in arrhythmogenic cardiomyopathy

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Background: Arrhythmogenic Cardiomyopathy (AC) is an inherited heart muscle disease associated with point mutations in genes encoding mainly components of the cardiac desmosome. Conventional mutation screening fails to uncover approximately 50% of AC genetic variants, whereas growing number of copy number variants (CNVs) have been recently linked to the disease phenotype.
Aim: To search for CNVs involving desmosomal genes in a large cohort of unrelated AC index cases genotype negative for pathogenic point mutations and to determine their pathogenic role by family co-segregation
Methods: 161 AC genotype negative probands for 5 AC-associated genes underwent Multiplex Ligation-dependent Probe Amplification (MLPA) and sequencing on a ABI 3500 (Thermoscientific). MLPA detected deletions were further confirmed by quantitative Real-Time polymerase chain reaction (PCR) on a Light Cycler 480 (Roche).
Results: CNVs analysis revealed 4 different plakophilin-2 (PKP2) gene rearrangements in 9 AC index cases (5.6%), previously undetected by using PCR-based exon-scanning methodologies. Five probands carried a heterozygous deletion carried a deletion of the entire PKP2 gene (122kb), 2 the deletion of the sole exon 4, one the deletion of the region comprising exons 6 to 11 and one carried a duplication of PKP2 exon 1. All probands fulfilled AC definite diagnostic criteria, showing in the majority of cases moderate to severe forms of the disease. Cascade genetic screening identified 13 family members carrying one of these deletions; five of them (38%) fulfilled the diagnostic criteria with presence of a mild form of the disease in 3 and of a moderate form in the remaining two.
Conclusions: Genomic rearrangements are identified in 5.6% of AC probands negative for pathogenic point mutations in desmosomal genes. Our data highlight a role for CNVs analysis to increase the diagnostic yield of AC genetic testing. Preliminary genotype-phenotype correlation in family members shows a relatively low disease penetrance of CNVs, so that their role in the AC phenotype needs further evaluation.

P883 | BEDSIDE
Testing the mayo hypertrophic cardiomyopathy genotype predictor score

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Introduction: Identifying a disease-causing mutation in hypertrophic cardiomyopathy (HCM) permits pre-symptomatic testing to be performed in first degree relatives. The Mayo Clinic have developed a score to determine the likelihood of a genetic mutation being identified based on six parameters. This score has not been tested in other cohorts.
Methods: 196 unrelated patients presenting with a clinical phenotype of HCM were tested for disease-causing mutations in MYBPC3, MYH7, TNNI3 and TNNT2. A retrospective study was performed to obtain: age at diagnosis, family history of HCM and/or sudden cardiac death, maximum left ventricular wall thickness of ≥2.0 cm, echocardiographic reverse curve morphological subtype and hypertension. Each parameter was assigned 1 point (except hypertension = -1). To determine whether significant differences were present between gene positive and negative groups, T-test for the continuous variables and Fisher's exact tests were applied. Receiver operating characteristic analysis was also performed.
Results: Overall, 42 patients were found to have a disease-causing mutation in 1 or more HCM-associated genes. 5 out of 6 clinical markers showed a significant difference between gene-positive and -negative patients, except for maximum left ventricular wall thickness of ≥2.0 cm. The yield increased step wise from 5% for individuals with a score of -1, 8% for those scoring 0, 13% for a score of 1; 20% for a score of 2, 41% for a score of 3 and 82% for a score of 4. When all 5 positive predictors were present the yield declined to 38%. We attribute this to the small numbers of patient present within this subgroup (n=8). The area under the ROC curve for the predictor score was 0.76 (SE=0.04, $p<0.001$).
Conclusions: We have replicated the value of Mayo HCM Genotype Predictor Score in this cohort. Being able to predict the likelihood of a positive result helps inform pre-test counselling and may help to prioritise gene testing.

P884 | BEDSIDE
Speckle tracking derived diastolic strain rate is an independent determinant of cardiac magnetic resonance detected myocardial fibrosis in patients with Fabry disease

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Background: Cardiac involvement is common in Fabry disease (FD) patients and present as replacement myocardial fibrosis in the end-stage of the disease. It is known that cardiac magnetic resonance imaging (cMRI) detected late enhancement (LE) is significantly associated with diastolic dysfunction in various cardiac diseases. The link between diastolic dysfunction and LE in FD remains largely unknown now.
Purpose: This study aimed to investigate the association between echocardiographic diastolic indices including 2D speckle tracking imaging (STI) derived diastolic strain rate and cMRI detected myocardial fibrosis (LE) in FD patients.
Methods: A total of 101 genetically proven FD patients were included (35 male, mean age 38±14 years). All patients underwent both echocardiography and cMRI within 1 week. Global and segmental (18-segment) longitudinal systolic strain (LS_sys) and strain rate (LSr_sys) and diastolic strain rate (LSr_E and LSr_A) by STI were analysed offline. Patients were divided into no-LE (n=63) and LE group (n=38).
Results: Patients in LE group were older and had higher body mass index than those in no-LE group. Cardiac dimensions and systolic function (EF=67±6%) by conventional echocardiography were normal in this cohort. Advanced diastolic dysfunction (pseudonormal or restrictive filling pattern) was found in 12 (11.9%) FD patients and the prevalence of advanced diastolic dysfunction was significantly higher in LE group than in no-LE group (28.9% vs. 1.6%, $P<0.05$). LE was associated with thicker left ventricular (LV) wall (septal wall 11.6±2.8 vs. 9.0±1.4mm), lower lateral mitral annular plane systolic excursion (MAPSE, 13±3 vs. 15±2mm), larger left atrium (36±4 vs. 33±4mm), and higher early diastolic filling velocity to mitral motion velocity ratio (E/E', 14.9±7.7 vs. 9.0±2.9, all $P<0.05$ vs. no-LE). Multivariable from conventional echocardiography regression models showed that LV wall thickness (Odds ratio 1.72, $P<0.001$), lateral MAPSE (OR 0.82, P=0.042) and E/E' (OR 1.26, P=0.003) were independent determinants of LE in this cohort. Global LS_sys and global LSr_E were significantly lower in LE group than in no-LE group. When focusing on segmental strain indices, systolic strain at basal lateral and anterior walls and LSr_E at basal lateral and posterior walls were significantly lower in LE group than in no-LE group (all $P<0.05$). Regression models showed that global LS_sys (OR 1.34, P=0.012), LS_sys at basal lateral (OR 1.16, P=0.008) and anterior (OR 1.13, P=0.034) walls, and LSr_E at basal lateral (OR 0.39, P=0.030) and posterior (OR 0.18, P=0.002) walls were independent determinants of LE while global LS_E (OR 0.67, P=0.59) was not an independent determinant of LE.
Conclusion: Diastolic dysfunction is associated with LE in FD patients. Reduced early diastolic strain rates at basal lateral and posterior walls serve as independent determinants for myocardial fibrosis in FD patients.

P885 | BEDSIDE
Pregnancy in women with a cardiomyopathy: outcomes and predictors from a retrospective cohort

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Background and aim: Pregnancy in women with a cardiomyopathy is considered at high risk for complications but natural history and predictors of evolution are still poorly characterized. We evaluated the prevalence and predictors of maternal and neonatal events during pregnancy in women with a cardiomyopathy, excluding peripartum cardiomyopathy.
Methods and results: In this retrospective study in a referral center for cardiomyopathies, we included 43 pregnancies in 36 women with either dilated cardiomyopathy (DCM, n=10), hypertrophic cardiomyopathy (HCM, n=28), arrhythmogenic right ventricular cardiomyopathy (ARVC, n=3), tachycardia-induced-

cardiomyopathy (TIC, n=1) or non-compacted left ventricle (NCLV, n=1). We observed a major cardiovascular event in 14 women including 3 cardiac deaths, in cases that did not follow our usual multidisciplinary protocol, and 6 congestive heart failure (5 DCM, 1 HCM). CARPREG score was predictive of maternal complication rate (complications: 67%, 33%, 25% in women with CARPREG score of 2, 1 and 0 respectively). However major cardiac complications (heart failure, asymptomatic new systolic dysfunction, pulmonary hypertension) occurred in 3 women with 0 risk factors. LV ejection fraction alone, outflow tract gradient in HCM, ZAHARA or modified WHO scores were less discriminant than CARPREG score for maternal outcome.
There were 1 fetal death (related to maternal cardiac death). We also observed 10 (23%) preterm deliveries and 11 (26%) low neonatal birth weights and similar rate of hypoglycaemia (26%), but all with simple evolution after appropriate management.
Conclusion: Pregnancy in women with a cardiomyopathy is a high risk period for both women and neonates. The highest risk is observed (i) in women who did not benefit from an early multidisciplinary team management, and (ii) in DCM patients compared to HCM. CARPREG score is the best predictor of complications, but might be improved.

P886 | BEDSIDE
Prevalence and impact of pulmonary hypertension on survival in patients with light chains amyloidoisis

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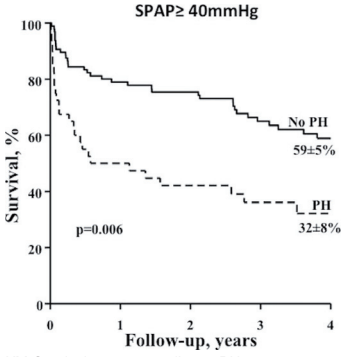
Background: In patients with systemic light chains amyloidosis (AL), the prevalence and prognostic impact of pulmonary hypertension (PH) are unknown. We therefore aimed to investigate the prevalence of PH and its impact on long-term survival.
Methods and results: Between 2000 and 2015, 189 patients (66±11 years, 63% of males) with confirmed AL were studied. PH defined by TTE as estimated sPAP ≥40mmHg, was assessed by the 1st baseline TTE available in 140 patients naïve of any treatment. The mean follow-up was 3.1±3 years (max 14 years).
Overall, 31% (n=43) of patients had PH. No difference was noted in terms of age, gender, cardiac risk factors between patient with and without PH. However, those with PH were more frequently in Mayo clinic stage II (36%) and stage III (61%) than those without PH (stage II (35%), stage III (38%)) p=0.001). They also had larger end systolic LV diameter, lower LVEF, thicker IVS, and larger left atrial volume and higher e/e' ratio (all $p<0.05$).
The 4-year survival was significantly reduced in patients with PH as compared to those without (32±8% vs. 59±5 respectively, p=0.006) (figure). In multivariate analysis, after adjustment for all relevant cofactors including the Mayo Clinic staging, PH was an independent predictor of mortality (hazard ratio=2.05, 95% CI: 1.06–3.97, p=0.03).



KM-Survival curve according to PH

Conclusion: In patients with cardiac systemic AL PH is frequent and is a powerful predictor of 4-year mortality, independently of the disease severity according to the Mayo Clinic staging. Therefore, PH may help to stratify AL patients and should be systematically assessed during TTE

P887 | BEDSIDE
Radical FLNC mutations and high-risk dilated arrhythmogenic cardiomyopathy

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Background: Filamin C (encoded by FLNC gene) is essential for sarcomere attachment to the plasmatic membrane. Mutations in FLNC have been associated with myofibrillar myopathies and cardiac involvement has been reported in some carriers. Accordingly, since 2012 we have included FLNC in the genetic screening of patients with inherited cardiomyopathies and sudden death.
Purpose: The aim of this study was to demonstrate the association between radical mutations in FLNC and the development of a high-risk form of dilated arrhythmogenic cardiomyopathy.
Methods: FLNC has been studied by next generation sequencing in 2,140 patients with inherited cardiac conditions. We have identified a characteristic phenotype in probands with radical mutations in FLNC (predicted to disrupt the protein sequence). A complete clinical and genetic evaluation of 28 affected families was performed.
Results: Twenty-three radical mutations were identified in 28 probands previously diagnosed with dilated, arrhythmogenic, or restrictive cardiomyopathy. Radical mutations in FLNC were absent in patients with other phenotypes, including 1,078 individuals with hypertrophic cardiomyopathy. Fifty-four mutation carriers were identified among 121 screened relatives. The phenotype consisted in left ventricular dilatation (68%) and systolic dysfunction (46%), left ventricular myocardial fibrosis (67%), inferolateral negative T waves on ECG (33%), ventricular arrhythmias (82%), and frequent sudden cardiac death (40 cases in 21/28 families). Clinical skeletal myopathy was not observed. Penetrance was >97% in carriers older than 40 years. Radical mutations in FLNC cosegregated with this phenotype with a dominant inheritance pattern (combined LOD score: 9.5).
Conclusions: Radical mutations in FLNC cause a particular form of dilated arrhythmogenic cardiomyopathy complicated by frequent premature sudden death. Prompt implantation of a cardiac defibrillator should be considered in affected individuals harboring radical mutations in FLNC.

P888 | BEDSIDE
Prognostic significance of global longitudinal strain in extracardiac sarcoid patients with no apparent cardiovascular disease

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Purpose: Global longitudinal strain (GLS) is increasingly accepted as a predictor of mortality in various clinical settings. This study tested the hypothesis that GLS is associated with increased event rate in patients with extracardiac sarcoidosis, who have no overt symptoms of cardiovascular disease and preserved EF.
Methods: We retrospectively studied 117 patients with extracardiac sarcoidosis, who underwent comprehensive echocardiographic study, while GLS was measured by an offline speckle tracking algorithm. Patients who had signs and symptoms of cardiovascular disease at the time of the examination were excluded from the study. Patients were followed for an average of 41.4 months. Major averse cardiac events (MACE) were defined as a composite end point of hospitalizations, heart failure, atrial fibrillation and sudden cardiac death.
Results: The age of patients was 42±6 years old (43 men). Events were recorded in 10 patients (8.5%). Tissue Doppler revealed E/Em 7.9±3.5, while EF was 54.2±3.5%. Global longitudinal strain was 14.4±3% and a cut-off value ≤13.6% for GLS was considered as predictive for MACE (AUC 0.73). After adjustment for multiple potential confounders (age, gender, smoking, hypertension, diabetes, E/Em and EF), GLS remained strongly associated with MACE (odds ratio 0.72, 0.53 to 0.98 95% C.I, p=0.03).
Conclusions: In conclusion, among patients with sarcoidosis and no symptoms of cardiovascular disease, even when EF is preserved, GLS is an important prognostic index of MACE.

P889 | BEDSIDE
Long-term outcomes in the surgical management of left ventricular outflow tract obstruction in hypertrophic cardiomyopathy

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Background: Hypertrophic Cardiomyopathy is the most common genetically inherited cardiac disease affecting 1 in 500 of the population. Dynamic Left Ventricular Outflow Tract Obstruction (LVOTO) caused by systolic anterior motion of the mitral valve is present in up to two thirds of patients.
Purpose: Surgical intervention can alleviate LVOTO and improve symptoms but the risks and long-term outcomes of different surgical strategies are unknown.
Methods: Survival and clinical outcomes were assessed at 1, 5 and 10 years post operatively in 362 patients with HCM undergoing surgical intervention for LVOTO at a specialist cardiomyopathy centre. The primary survival endpoint was all cause mortality.
Results: Group A (n=286) underwent septal myectomy; Group B (n=32) underwent septal myectomy and MV repair; Group C (n=26) underwent myectomy and MV replacement and Group D (n=17) underwent MV replacement without myectomy. There were 93 concomitant procedures including CABG, AVR, MAZE procedure and left atrial appendage closure across groups. Mean follow up was 6.2 years and longest follow up was 46.6 years. NYHA functional class improved from 2.49 to 1.48 postoperatively ($p<0.05$). The mean resting LVOT gradient improved from 72mmHg to 13.6mmHg at 1 year post procedure; 14.4% of patients were operated on because of latent obstruction. There were 16 repeat surgeries including 9 redo myectomies, 6 MV Replacements and 1 MV Repair with a mean time to reintervention of 5.3 years. 28 patients met the primary endpoint of all-cause mortality at a mean of 9.6 years. There were 4 procedural related mortalities and 24 mortalities on late follow up greater than 30 days post procedure. Survival analysis was estimated using Kaplan-Meier curves and log-rank testing. Estimated survival rates post-operatively at 1, 5 and 10 years respectively were 98.9%, 97.5%, 93.7% in group A; 97%, 97%, 32.3% in group B 96.2%, 90.5%, 90.5% in group C; and 93.3%, 80%, 80% in the group D ($p<0.05$).
Conclusion: Different surgical techniques are adopted for the management of LVOTO. Septal myectomy in particular is shown to have good long term outcomes with low rates of reintervention.

P890 | BEDSIDE
Prognosis of patients with hypertrophic cardiomyopathy: a contemporary population record linkage cohort in England

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Introduction: Little is known about the prognosis of patients with hypertrophic cardiomyopathy (HCM) outside specialist centres and about how their outcomes differ from those observed in the general population.
Purpose: In this contemporary population-based cohort, we compared the incidence of 13 cardiovascular diseases (CVDs), gastro-intestinal bleeding and death in patients with and without HCM.
Methods: All patients diagnosed with HCM were identified in the CALIBER dataset, linking primary care, hospital and mortality and disease registries in England, from 1997 to 2010. Patients were matched by age, sex and general practice with up to ten randomly selected patients without HCM. Random effects Poisson models were used to assess the associations between HCM and the incidence of fatal and non-fatal cardiac and vascular diseases. The Kaplan-Meier method was used to estimate cumulative probability of death in patients with and without HCM.
Results: A total of 1,160 patients with HCM and 11,600 non-HCM patients, contributing a median follow-up of 4.0 years were included. Forty-one percent were women and median age was 57 years. Patients with HCM had higher rates of subsequent ventricular arrhythmia (IRR=26.28, [15.01–46.02]), cardiac arrest (IRR=12.74, [8.83–18.39]) and fatal and non-fatal heart failure (IRR=4.33, [3.47–5.40]). They also had increased incidence of angina, myocardial infarction (IRR=4.31 [1.69–11.03]), atrial fibrillation (IRR=4.10, [3.39–4.97]), stroke (IRR=2.00, [1.49–2.68]), transient ischaemic attack (IRR=2.18, [1.45–3.29]), peripheral arterial disease (IRR=2.23, [1.49–3.34]), and gastro-intestinal bleeding (IRR=2.00, [1.60–2.49]). No association was found with abdominal aortic aneurysm, and with a composite endpoint of deep vein thrombosis and pulmonary embolism. Patients with HCM had also higher rates of all-cause (IRR=2.15, [1.87–2.46]; 5-year Kaplan-Meier mortality=22.15% vs. 9.87%), cardiovascular (IRR=2.11, [1.72–2.59]; 5-year mortality=11.36% vs. 3.13%) and COPD-related mortality (IRR=1.95, [1.03–3.71]; 5-year mortality=1.04% vs. 0.4%).
Conclusions: Compared with general population controls, patients with HCM, have higher all cause and cardiovascular mortality. The high relative risks of ventricular arrhythmia, heart failure and stroke highlight the importance of primary prevention strategies in reducing mortality in this disease.
Acknowledgement/Funding: Welcome Trust [WT 086091/Z/08/Z]; the UK National Institute for Health Research (RP-PG-0407-10314); University Academic Fellowship, Leeds University

P891 | BEDSIDE
Factors related to left ventricle reverse remodeling in the elderly undergoing cardiac resynchronization: a two-centre experience

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Background: Little data exist on the benefit of cardiac resynchronization therapy (CRT) in the elderly since the number of these patients was limited in large trials. We aimed to describe predictors of response to CRT in a group of elderly patients ($\geq$75 years old).
Methods: A total of 49 patients undergoing CRT implantation between June 2006 and October 2014 were included in the study. Response was defined by two different parameters to evaluate left ventricular reverse remodelling. First the reduction of $\geq$15% in left ventricle end diastolic diameter (LVEDD) and second the improvement in left ventricle ejection fraction (LVEF) $\geq$15% (relative).
Results: Mean age was 79.2±2.9 years and 20.4% were women. At the time of the implant left ventricle was severely dilated (mean LVEDD 60.4±6.6 mm) and impaired (mean LVEF 23.4±6.7%). The mean QRS duration was 155.4±25 ms and left bundle branch block (LBBB) was present in two thirds of study population. Almost half of the patients suffered non-ischemic cardiomyopathy (51%) and mostly were in NYHA III-IV (54.2%). Medical treatment was optimized (Beta blockers: 87.5%; ACEI (angiotensin-converting enzyme inhibitors) or ARB (angiotensin II receptor blockers): 91.7% and aldosterone antagonists: 68.8%).
After a mean follow up of 37.2±19.3 months, 60.5% of patients were in NYHA I-II. A reduction in LVEDD (57.3±9.3mm) and also an improvement in LVEF (30.8±13.7%) were observed in the whole population. A 55.6% of the sample (25 patients) showed an improvement of $\geq$15% in LVEF; and a decreased of $\geq$15% in LVEDD was observed in 26.8%. After multivariable adjustment improvement of $\geq$15% in LVEF was not related to none of the predictors of response to CRT previously reported (gender, non-ischemic etiology, LBBB, QRS duration). Nevertheless, a positive remodelling estimated by a reduction of $\geq$15% in LVEDD, was significantly greater in female patients (OR 50,5; IC 95%: 1,96–1296,03) and in those with wider QRS (OR 1,1; IC 95%: 1,02–1,19).
Conclusion: Response to CRT in elderly patients is feasible. Up to 55.6% of elderly patients under optimal medical treatment showed a significant improvement in LVEF and in 26.8% left ventricular dilatation reversed. Indications used for CRT in general population must be also followed in patients $\geq$75 years but given the high costs of the implant, defining strategies to select elderly patients who are more suitable for CRT, is necessary. QRS duration and female sex were good predictors of reverse remodelling.

CONGENITAL HEART DISEASE IMAGING

P892 | BEDSIDE
Heart failure severity in Ebstein's anomaly links to left ventricular dyssynchrony, torsion and recoil mechanics: Insights from cardiovascular magnetic resonance imaging

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Introduction: Heart failure development in Ebstein's Anomaly (EA) is characterized by both right and left ventricular deterioration. The mechanisms underlying LV dysfunction and their role in heart failure development are incompletely understood. We hypothesized that LV dyssynchrony and altered torsion and recoil mechanics induced by paradoxical movement of the ventricular basal septum may play a role in heart failure development.
Methods: 31 EA patients and 31 matched controls underwent cardiovascular magnetic resonance (CMR). CMR-feature-tracking (CMR-FT) and 4D-volume analysis was performed employing dedicated software (Diogenes and 4D-LV-Analysis, TomTec, Germany). Circumferential uniformity ratio estimates (CURE) time-to-peak-based circumferential systolic dyssychrony index (C-SDI), 4D volume analysis derived SDI (4D-SDI), torsion (Tor) and systolic (sysTR) and diastolic torsion rate (diasTR) were calculated for the LV. QRS duration, BNP, NYHA and Total R/L-Volume-Index (R/L-Index) were obtained.
Results: EA patients (mean age 31.5 years, controls 31.4 years) had significantly longer QRS duration (119ms±32 vs. 97ms±14, $p<0.01$) and showed more LV dyssynchrony compared with controls (4D-SDI 7.60%±4.58 vs. 2.54%±0.62, $p<0.001$; CURE0.77±0.05 vs. 0.86±0.03, $p<0.001$; C-SDI 8.72%±5.00 vs. 4,17±1.48, $p=0.001$). There were significant associations of LV dyssynchrony with heart failure parameters and QRS duration (Table 1).
Whilst torsion and recoil mechanics did not differ significantly between the groups ($p>0.05$), there was a significant association of torsion and recoil mechanics with dyssynchrony parameters: CURE (sysTR r=–0.426; p=0.017, di-

asTR r=0.419; p=0.019), 4D-SDI (sysTR r=0.383; p=0.044) and C-SDI (diasTR r=–0.364; p=0.044).

Table 1

	NYHA	BNP	QRS duration	R/L index
Dyssynchrony				
4D-SDI	r=0.496; p=0.018	r=0.363; p=0.068	r=0.551; p=0.002	r=0.502;p=0.007
CURE	r=–0.429; p=0.023	r=–0.508; p=0.005	r=–0.495; p=0.005	r=–0.474; p=0.007
C-SDI	r=0.529; p=0.004	r=0.436; p=0.018	r=0.460; p=0.009	r=0.419; p=0.019
Torsion/Recoil				
TOR	r=0.194; p=0.322	r=0.273; p=0.151	r=0.191; p=0.304	r=–0.052; p=0.780
sysTR	r=0.174; p=0.376	r=0.391; p=0.036	r=0.196; p=0.289	r=0.094; p=0.616
diasTR	r=–0.126; p=0.524	r=–0.337; p=0.074	r=–0.228; p=0.218	r=0.038; p=0.837

Conclusions: EA is characterized by LV intra-ventricular dyssynchrony, which is strongly associated with heart failure parameters. Within the Ebstein population increased torsion and recoil mechanics may represent compensatory mechanisms of the dyssynchronous LV. These novel markers are easily assessed with potential utility for future assessment of cardiac function and clinical decision-making in EA.

Acknowledgement/Funding: DZHK (German Centre for Cardiovascular Research), partner site Göttingen, Göttingen

P893 | BEDSIDE
Middle-aged individuals with anomalous coronary artery from the opposite sinus of valsalva - a retrospective matched cohort outcome study

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Background: Anomalous coronary artery originating from the opposite sinus (ACAOS) is a rare finding and associated with adverse cardiac events, especially in the young. It is unclear whether middle-aged patients with untreated ACAOS and possible concomitant coronary artery disease have a worse outcome compared to patients without ACAOS. Therefore, we sought to analyze the outcome in middle-aged patients with newly diagnosed ACAOS in coronary computed tomography angiography (CCTA) compared to a matched cohort.
Methods: We included 68 consecutive patients with newly diagnosed ACAOS by CCTA who were evaluated in our clinic between 2003 and 2015. ACAOS with an interarterial course of the vessel (between aorta and pulmonary artery) were classified as IAC variants, whereas all others were considered ACAOS without IAC. A 1:2 cohort matching based on age, gender, previous revascularization and segment stenosis score (SSS) as obtained from CCTA was performed with 399 controls without ACAOS. Major adverse cardiac events (MACE, i.e. myocardial infarction, elective revascularization and cardiac death) were recorded for all patients and the control cohort.
Results: 66 patients with ACAOS (3% lost to follow up) were included in the final analysis and matched with 132 controls. Mean age of patients with ACAOS was 56 (± 11years) and 73% were male. Forty (65%) patients were classified as having ACAOS with IAC. There were no significant differences in age, gender, cardiovascular risk factors and SSS between the patients and controls. Three (4.5%) patients underwent anomalous vessel related intervention at follow-up. Over a mean follow-up of 49 months, MACE occurred in 17% of all patients with ACAOS variants versus 24% in case controls (log-rank p=0.61) and in 18% of patients with ACAOS and IAC compared to 21% in their matched case controls (log-rank p=0.97).
Conclusion: In middle-aged individuals with newly diagnosed ACAOS and possible concomitant CAD, mid-term outcome is favorable and equivalent to the matched cohort without ACAOS, regardless of whether ACAOS with or without IAC variants are present.

Acknowledgement/Funding: The University Hospital Zurich holds a research contract with GE Healthcare.

P894 | BEDSIDE
Quantification of systemic-to-pulmonary arterial collateral flow in the Fontan circulation with four dimensional flow magnetic resonance imaging

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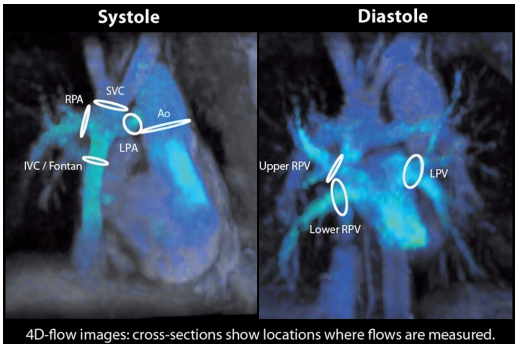
Background: The presence of systemic-to-pulmonary arterial collateral flow (SPCF) is common and likely of clinical significance in patients with a univentricular heart after the Fontan procedure. Two dimensional phase contrast magnetic resonance imaging has been used to estimate SPCF, but this approach is time consuming, the number of flow samples is limited, and the measurement error can be significant. Newer four-dimensional phase-contrast technique (4D-flow) can address these limitations and reliably quantify SPCF.
Purpose: Using 4D-flow measurements, we tested the hypothesis that SPCF in Fontan patients is hemodynamic significant and higher compared to a control group.
Methods: We searched the imaging record for Fontan patients with an available 4D-flow MRI study and control subjects with an anatomically and functionally normal heart. Phase-contrast images were acquired on 1.5T and 3T scanners with a cardiac-gated, respiratory compensated, 3D phase-contrast sequence with velocity encoding in all directions. The imaging volume covered the heart and great thoracic vessels. Flows were measured with dedicated 4D-flow software at the ascending aorta (Ao), left and right pulmonary arteries (LPA, RPA), left and right pulmonary veins (LPV, RPV), and both caval veins (SVC, IVC). SPCF was calculated using 2 formulas: pulmonary estimator=(LPV+RPV)-(LPA+RPA) flow, and systemic estimator=Ao-(SVC+IVC) flow. SPFC values were normalized to BSA, and expressed as percentage of Ao and PV flow. Shunt ratio's=(LPA+RPA)/Ao and PV/Ao flow were calculated. The Mann-Whitney U test was used to test for differences between the groups. Numerical results were expressed as median [25th-75th percentiles].
Results: Ten patients were identified for the Fontan group (age 24 [22–30] years, BSA 1.74 [1.56–1.86] m^2) and ten subjects for the control group (age 23 [10–36] years, BSA 1.54 [1.27–1.68] m^2). SPCF calculated from both estimators was significantly higher for the Fontan group than the control group, pulmonary estimator: 0.33 [0.10–0.52] vs 0.08 [-0.01–0.21] l/min/m^2 (p=0.043), 16%/PV flow vs 2%/PV flow (p=0.009), and 13%/aortic flow vs 2%/aortic flow (p=0.035). Systemic estimator: 0.65 [0.24–0.89] vs -0.07 [-0.16–0.09] l/min/m^2 (p=0.002), 30%/PV flow vs -2%/PV flow (p=0.002), 26%/aortic flow vs -2%/aortic flow (p=0.002). Shunt ratio's for the Fontan group: Qp(LPA+RPA)/Qs=0.71 [0.67–0.79] and Qp(PV)/Qs=0.85 [0.73–0.91], and for the Control group: 0.94 [0.88–1.00] and 0.97 [0.92–1.01] respectively or 1.05 [1.01–1.08] with Qp(main PA]/Qs. The lung flow distribution for the Fontan group was 47% LPA/total PA flow, 47% LPV /total PV flow and 44% left SPCF/total SPCF.



Overview 4D-flow measurements

Conclusions: SPCF comprises a hemodynamic significant amount of cardiac output in the Fontan group and is higher compared to control subjects. 4D-flow is a flexible, efficient, and accurate means of evaluating single ventricular physiology including lung flow distribution and SPCF quantifications.

P895 | BEDSIDE
Function of the systemic ventricle in Fontan patients with a lateral tunnel compared to extracardiac conduit: A magnetic resonance imaging study

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Background and aim: The Fontan procedure dramatically improved outcome in patients with univentricular hearts, and the clinical focus has shifted from decreasing mortality to improving cardiac function. Based on theoretical considerations, extracardiac conduit is considered superior to the lateral tunnel and although comparisons have been inconclusive, the extracardiac conduit is the procedure of choice in most centres today. We consecutively analysed cardiac MRI on thirty-four Fontan patients with extracardiac conduit or lateral tunnels in order to evaluate in cardiac output and function of the systemic ventricle.
Methods: Cardiac MRI scans performed in Denmark between 2010–2014. For each patient a time-volume curve for the systemic ventricle was drawn with 25 cardiac phases and analysed with respect to ejection fraction, ejection rate and peak-ejection and peak-filling rates.
Results: Patients with lateral tunnel (n=23; 48% women, 65% anatomical left ventricle) were similar to patients with extracardiac conduit (n=11; 45% women, 55% anatomical left ventricle) with respect to age, body surface area (BSA), cardiac index, stroke volume indexed too BSA, ventricular end-diastolic volume, peak-filling rates and peak-ejection rates. For both groups peak-filling rates were low at 399±103 ml s^{-1} with no significant difference (normally above 520 ml s^{-1}). Heart rate was higher in the patients with extracardiac conduit 73±13 vs. 82±10

($p<0.05$). Ventricular ejection fraction, stroke volume, and end-systolic volume indexed to BSA where 53±8% and 48±16 mL m-2 in patients with lateral tunnel and 45±7% ($P<0.01$ vs. lateral tunnel) and 61±24 mL m-2 ($p=0.055$) in patients with extracardiac conduit. Patients with indeterminate or anatomical right ventricle had similar ventricular volumes and function as patients with anatomical left ventricles.
Conclusion: Ventricles in all patients were underfilled. At rest Fontan patients with lateral tunnels have a significantly higher ejection fraction compared to patients with extracardiac conduits. Interestingly, Fontan patients with a systemic right ventricle and systemic left ventricles did not differ in function or volumes.

P896 | BEDSIDE
Poor correlation between anatomic and functional imaging in patients with interarterial anomalous right coronary arteries from the opposite sinus

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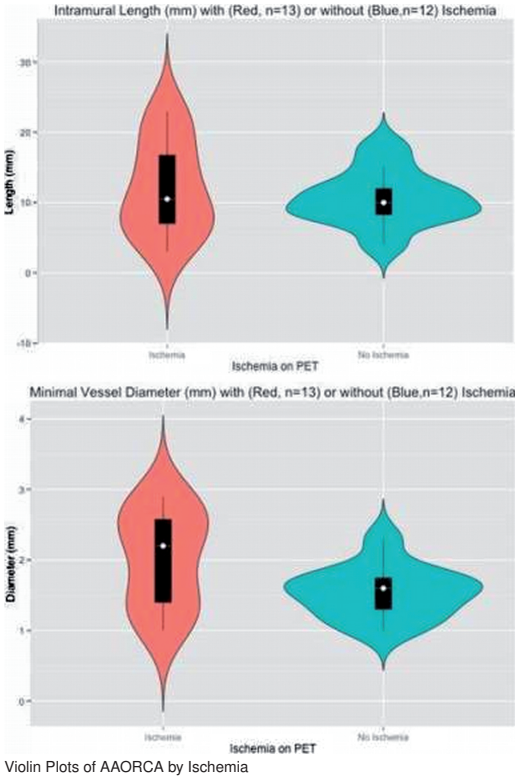
Background: In adults with an interarterial and intramural course of an anomalous right coronary artery from the left sinus (AAORCA), revascularization is recommended in the setting of myocardial ischemia. However, there are limited data regarding whether certain anatomic characteristics such as intramural length and vessel diameter inform which patients are likely to have ischemia on functional testing.
Purpose: The aim of this study was to assess whether the length of the intramural segment or the minimal vessel diameter of the anomalous right coronary artery was associated with ischemia.
Methods: Between July 2008 and December 2014, we identified 25 patients greater than 18 years-old with an interarterial and intramural course of an AAORCA who had exercise N13-Ammonia PET and gated cardaic CT angiography. Our outcome was the association of intramural length and vessel diameter with myocardial ischemia, defined as a reversible perfusion defect. Wilcoxon Rank Sum tests were used for intergroup comparisons with a $p<0.05$ for statistical significance.
Results: Our patients were middle aged (48, 42–58 years), and about half were female (12,48%). Most patients had chest pain (22,88%), 12 (48%) had typical angina, and 15 (60%) had exertional dyspnea. Myocardial ischemia was present in 13 patients (52%), and 11 of these patients had surgery with unroofing of the intramural segment of the anomalous coronary artery. There was no association between the length of the intramural segment and ischemia (10 v. 11 mm, p=0.87) (Figure). There was also no association between minimal vessel diameter and ischemia (1.6 v. 2.2 mm, p=0.13) (Figure).



Violin Plots of AAORCA by Ischemia

Conclusion: In symptomatic patients with an interarterial and intramural AAORCA, anatomic characteristics are not associated with ischemia.

P897 | BEDSIDE
Usefulness of single ventricular function in Fontan patients undergoing feature tracking magnetic resonance strain, strain rate and wall motion delay

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Background: Patients are commonly affected by ventricular dysfunction and heart failure after Fontan palliation. Reliable quantification of ventricular function is of interest but hampered by complex ventricular anatomy and physiology. Cine-based feature tracking strain (FTS) is a new technique to assess cardiac function from cardiac magnetic resonance (CMR). We compared FTS with conventional function parameters in single ventricle subjects with Fontan physiology undergoing CMR.
Objective: The objective of this study was to investigated into cine-based FTS in single ventricle subjects after Fontan palliation undergoing CMR.
Methods: 18 Fontan subjects (mean age 17.6±9.2 years, post Fontan period 14.2±8.2 years, 13/18 morphologic right ventricle, 5/18 morphologic left ventricle) underwent a CMR study. Single ventricular end-diastolic and end -systolic volumes (SVEDV and SVESV), stroke volume (SV), and ejection fraction (EF) were measured offline as conventional function parameters. Offline global longitudinal and circumferential strain/strain rate (GLS/GLSR and GCS/GCSR), and radial strain/SR were performed (TomTec Image Arena, Germany) using FTS. As well, anterior to posterior wall motion delay (<130ms; APWMD) analysis was calculated on the short-axis view at the basal level, and bilateral wall motion delay (<90ms; BLWMD) on the 4-chamber view at the basal and mid levels.
Results: Basal GCS/GCSR were lower than it at the mid (p=0.02 and 0.02) and apical (p=0.001 and 0.003) levels. There were correlations between GLS/GLSR and GCS/GCSR, and SVEDV (r=0.51 to 0.73). At the mid and apical levels, there were correlations between GCS/GCSR and SVESV, and EF (r=0.66 to 0.85 and r=0.52 to 0.79). There was also correlation between GLSR and SV (r=0.73). BLWMD was found for 12 cases (67%) at the basal and 10 cases (56%) at mid levels, and APWMD for 4 cases (22%) at the basal level.
Conclusions: Basal ventricular dysfunction suggested by low GCS/GCSR and BLWMD. Analysis of regional strain/SR may helpful in understanding myocardial mechanics with Fontan physiology in further studies. FTS is independent of inadequate acoustic windows, proposing that this approach could have clinical validity.

P898 | BEDSIDE
Bicuspid aortic valve phenotype and aortic diameter - does it really matter? A systematic review and meta-analysis

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Background: Bicuspid aortic valve (BAV) is the most common congenital heart defect, observed in about 1% of general population. Previous studies have suggested that different BAV phenotypes may differently affect the aortic diameter at various levels.
Purpose: To evaluate the impact of the two most common bicuspid aortic valve phenotypes: right and left cusp fusion (RL) vs right and non-coronary cusp fusion (RN) on the aortic diameter at the level of sinuses of Valsalva and the ascending aorta.
Methods: We have searched the PubMed databases up to 31 December 2014 to identify studies containing information about the aortic diameters and morphology of BAV. Major article inclusion criteria were: the information about the aortic diameters (indexed and/or non-indexed to body size) at the level of sinuses of Valsalva (SVD) and/or at the level of ascending aorta (AAD) together with the information about the morphology pattern of BAV, defined as RL or RN phenotype. Two independent reviewer extracted data on study methods and characteristics.
Results: 12 studies with 2112 patients with indexed and 12 studies with 2012 patients with non-indexed diameter were included into the final analysis of BAV phenotype impact on AAD. Similarly, 7 studies with 1271 patients with indexed, and 14 studies with 2535 patients with non-indexed diameter of aorta at the level of sinuses of Valsalva were included. There was no significant difference in AAD between RN and RL phenotypes of BAV [mean difference in indexed diameter: –0.33 mm/m^2 (95% CI: –1.02 to 0.36 mm/m^2, p=0.35) and mean difference in non-indexed diameter: 0.32 mm (95% CI –1.00 to 1.64 mm, p=0.63)]. Nonetheless, the RL morphology appeared to be connected with significantly larger SVD, as compared with RN bicuspid aortic valve phenotype [mean difference in indexed diameter: 1.63 mm/m^2 (95% CI 0.70 to 2.56 mm/m^2, $p<0.001$) and mean difference in non-indexed diameter: 2.26 mm (95% CI 1.08 to 3.44 mm, $p<0.001$)].
Conclusions: The presented results of our systematic review and meta-analysis clearly indicate, that right and left cusp fusion BAV phenotype is associated with larger aortic diameter at the level of sinuses of Valsalva, with no significant impact of BAV phenotype on the ascending aorta diameter.

P899 | BEDSIDE

Differences in ventricular diastolic dysfunction and dyssynchrony in pulmonary hypertension and repaired tetralogy of Fallot with preserved left ventricular ejection fraction

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Introduction: Pressure overload in pulmonary hypertension and volume overloaded in repaired Tetralogy of Fallot caused right ventricular dilation are common. However, the differences of ventricular diastolic dysfunction and dyssynchrony are unknown in these patients with preserved ejection fraction.
Method: In 69 PH, rTOF and CON (23 age and gender matched subjects in each group), CMR feature-tracking was used to measure mitral annulus velocities in 4-chamber, 3-chamber and 2-chamber views. From 4-, 3- and 2-chamber LV long-axis cine CMR, mitral annular motion was automatically feature-tracked and time-resolved 3D models reconstructed using in-house software. Dividing the annular circumference into 6 parts, segmental sweep surface area velocities (SSAV) or time-derivatives of sweep surface areas (traversed by individual annular segments in the 4D models) were determined at systole (Sssav), early (Essav) and late diastole (Assav); and dyssynchrony indices calculated as standard deviations of time-to-peak SSAV.
Results: (see table 1) The left ventricular volume indexes and ejection fraction were not significant different. Both rTOF and PH had enlarged RV and decreased RVEF. The early diastolic (Essav) and late diastolic (Assav) velocities were lower in rTOF and PH than in control subjects (ANOVA $p<0.05$). Likewise, the early diastolic dyssynchrony (T-Essav-SD-6) index was increased in rTOF and increased more in PH.

Table 1. CMRF measurements in normal control, rTOF with preserved ejection fraction, and PH patients with preserved ejection fraction

	Control (n=23)	rTOF (n=23)	PH (n=23)	ANOVA p value
LVEDVI, ml/m^2	67±8	74±23	67±20	0.325
LVEF, %	65±6	61±8	64±7	0.105
RVEDVI, ml/m^2	71±11	131±35*	109±45*	<0.001
RVEF, %	58±7	48±7*	46±14*	<0.001
S_{SSAV}, cm^2/s	92.8±27.6	106.2±22.7	87.7±33.0	0.077
E_{SSAV}, cm^2/s	127.2±37.3	118.0±47.1	83.4±31.8*#	0.001
A_{SSAV}, cm^2/s	95.9±24.3	87.5±31.9	73.2±28.5*	0.029
T-S_{SSAV}-SD-6, ms	16.9±6.6	22.6±15.2	28.8±23.5	0.060
T-E_{SSAV}-SD-6, ms	17.8±6.2	21.2±13.5	27.7±15.5*	0.028
T-A_{SSAV}-SD-6, ms	14.0±6.9	22.2±29.4	23.9±20.5	0.242

Conclusion: Through the use the CMR feature-tracking analysis, diastolic abnormalities were evident in pulmonary hypertension with preserved ejection fraction, and to a much lesser extent in repaired tetralogy of Fallot with preserved ejection fraction.

MYOCARDIAL-PERICARDIAL IMAGING

P900 | BEDSIDE

Diagnostic and prognostic value of myocardial deformation imaging with cardiac magnetic resonance in patients with hypertrophic cardiomyopathy

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Introduction: Hypertrophic cardiomyopathy (HCM) is an important cause of sudden cardiac death (SCD) and heart failure. Myocardial deformation assessment has demonstrated an incremental diagnostic and prognostic value in other cardiovascular diseases. Feature tracking imaging (FTI) is a new method for evaluating myocardial deformation from cardiac magnetic resonance (CMR) images. Our main aim was to investigate the diagnostic and prognostic value of myocardial deformation assessment in HCM, using FTI-CMR.
Methods: Consecutive HCM patients (pts) evaluated with genetic test, electrocardiogram, echocardiogram, Holter, stress test and CMR. FTI analysis was done on CMR cine images for measurement of radial, circumferential and longitudinal peak strain.
Results: Fifty-seven pts, age 57,4±14,3 years, 35 males (61,4%). Maximal left ventricular (LV) wall thickness (MLVWT) 19,8±5,1 mm, mass 164,4±71,4 g, LV ejection fraction (LVEF) 60,8±11,5%; 66,7% with late gadolinium enhancement (LGE). SCD risk score at 5 years was 2,8±4,4%. Global radial strain (GRS) was 32,5±12,8%, global longitudinal strain (GLS) was -13,7±4,8% and global circumferential strain (GCS) was -16,6±5,2%. In comparison with reference values, 17 pts (29,8%) had a diminished GRS, 14 (24,5%) had a reduced GLS and 14 (24,5%) had a reduced GCS. Six pts (10,5%) had a LVEF <50%. GRS was correlated with LV end-diastolic volume (LVEDV) (-0,34, p=0,014), end-systolic volume (-0,43, p=0,001), LVEF (0,41, p=0,002), MLVWT (-0,34, p=0,016) and mass (-0,50, p<0,0005). Similar correlations were observed for GCS. GLS was significantly correlated with the number of hypertrophied segments (0,34, p=0,02), mass (0,33, p=0,016) and left atrial area (0,42, p=0,005). Basal RS and basal CS were correlated with the SCD risk score (respectively, -0,32, p=0,03 and 0,34, p=0,02). Pts with non-sustained ventricular tachycardia (NSVT) had worse basal and medial RS (26,7±11,3 vs 35,3±12,4%, p=0,04; 23,6±12,5 vs 35,8±13,8%, p=0,012) and worse basal and medial CS (-14,4±4,7 vs -17,9±4,1%, p=0,019; -14.4±6.0 vs -19.2±5.1%, p=0,013). Atrial fibrillation (AF) was more prevalent (27.3% vs 3.1%, p=0,017) in pts with reduced GLS. The presence of LGE was associated with reduced GCS (92,9% vs 64,1%, p=0,04). Blood pressure response to exercise was lower in pts with reduced GCS and reduced GRS (respectively, 4.0±8.4 vs 24.7±30.1mmHg, p=0.003 and 3.6±8.1 vs 25.7±30.3mmHg, p=0.002). A value of ≥ -14,4% of basal CS had a sensibility of 75% and specificity of 81% to predict NSVT (AUC 0,745, p=0,013).
Conclusions: This is the first study on the application of FTI to an adult HCM population. Evaluating myocardial strain with CMR-FTI in HCM is feasible and has additional diagnostic value. Worse myocardial deformation was associated with imaging markers of severity of the disease, arrhythmia and higher SCD risk. Evaluation of myocardial contractility with FTI may prove to be a new prognostic marker in HCM.

P901 | BEDSIDE

Normal ranges of ECV and comparison among cardiovascular diseases: A systematic review and meta-analysis from 2451 subjects

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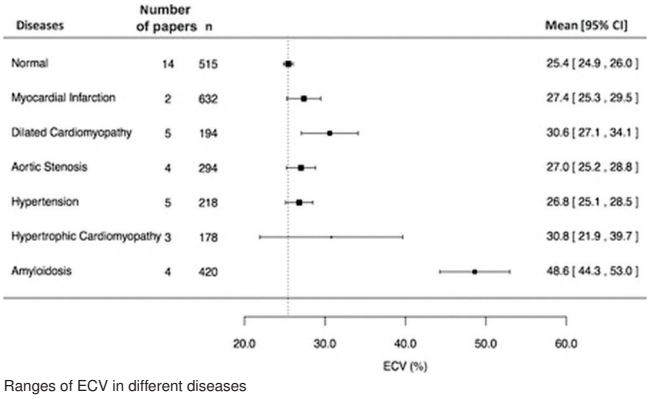
Background: Recent progress in cardiac magnetic resonance (CMR) permits noninvasive quantification of myocardial extracellular volume (ECV) by pre and post contrast T1 mapping and then adjusted for haematocrit. ECV by CMR has been validated against histopathology. ECV promises the detection of diffuse fibrosis that cannot depicted by conventional late gadolinium enhancement (LGE) technique. Modified look-locker inversion recovery (MOLLI) and its shortened analogue (ShMOLLI) are two widely-used sequences in clinical and in research to obtain ECV. However, there are no guidelines or large sample size studies to define normal range or ranges of ECV by these sequences in different diseases. Therefore, we performed a systematic review and a meta-analysis of normal range and ranges of ECV in various cardiovascular diseases.
Methods: Three databases (EMBASE, SCOPUS, MEDLINE) were systematically searched for ECV of the human heart. The key terms were: "ShMOLLI", "shortened modified look locker inversion recovery", "shortened MOLLI", "MOLLI", "modified look-locker inversion recovery", "ecv", "extra cellular matrix", "ecf", "extra cellular fraction", "extra cellular volume", "cmr", "cardiac magnetic resonance" and "cardiac mr". Random effect model was used to pool ECV. Last search was performed on Jan 24 2016. Papers with sample size less than 20 were excluded from the analysis.
Results: 2451 subjects from 25 journal articles were included for the final analysis. Normal range of ECV was derived from 14 articles with 515 healthy subjects and it was 25.4% [95% confidence interval (CI) 24.9, 26.0]. Although no publication bias was identified, significant heterogeneity was found (I2=82.7%). Subsequent meta-regression analyses indicated that none of field strength, sequence, gender, indexed LVEDV, LVEF were the sources of variation of ECV. In comparison among diseases and normal subjects, amyloidosis (48.6% [44.3, 53.0]) has by far large proportion of ECV than any other reported conditions, followed by diabetes (33.3% [31.2, 35.3]) and non-ischemic dilated cardiomyopathy (30.6% [27.1, 34.1]) (Figure). The CIs of ECV of patients with aortic stenosis, hypertension, hypertrophic cardiomyopathy and myocardial infarction demonstrated significant overlaps.



Ranges of ECV in different diseases

Conclusion: Normal ranges of ECV has been identified by meta-analysis. No obvious sources of variations in normal ECV were found. ECV by CMR T1 mapping can be best utilized in amyloidosis, diabetes and non-ischemic dilated cardiomyopathy.

P902 | BEDSIDE

Cardiac magnetic resonance or delayed enhanced computed tomography in patients with symptomatic ventricular arrhythmias and normal coronary arteries: comparison with endomyocardial biopsy

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Background: Symptoms related to the sudden occurrence of ventricular arrhythmias (VA) remain frequently a diagnostic and therapeutic challenge, after the exclusion of coronary artery disease.
Purpose: We aimed to evaluate the role of cardiac magnetic resonance (CMR) and delayed enhanced computed tomography (DECT) in the identification of myocardial disease responsible for VA, comparing imaging findings to histological essays in patients with normal coronary arteries.
Methods: 16 patients (14 males, age 45.1±15.4 y) with sudden occurrence of symptoms (palpitation or syncope) and documentation of previously unknown VA were enrolled. VA included very frequent premature ventricular complexes (trigeminal pattern or PVC >15,000/day), both non-sustained and sustained ventricular tachycardia (NSVT, SVT) and ventricular fibrillation (VF). All of them underwent coronary angiography showing normal epicardial arteries. 13 patients underwent CMR including oedema sensitive T2w-STIR and delayed post-gadolinium IR T1w sequences. Because of contraindication to CMR, the remaining 3 patients underwent DECT including a delayed low-energy (80 kV) scan for scars identification. Blinded, endomyocardial biopsy (EMB) was performed, and results compared to imaging findings.
Results: Symptoms at presentation were cardiac arrest (n=2), syncope (n=3) and palpitation with or without dyspnoea and angina (n=11). Basal 12-leads ECG or continuous telemonitoring showed an underlying VA: VF (n=2), SVT (n=5), NSVT (n=7) or frequent PVC (n=2). After significant epicardial coronary artery disease was excludes by angiography, second level imaging (CMR or DECT) was performed: mean left ventricle (LV) end-diastolic volume was (101.4±28.9) mL/m^2, mean LV mass (59.4±16.7) g/m^2 and mean LV ejection fraction (49.8±5.3) %. In 13/16 patients (81.3%) imaging features were suggestive for inflammatory cardiomyopathy. In particular, 5/13 (38.4%) appeared as acute myocarditis, 7/13 (53.8%) prior myocarditis, and 1/13 (7.8%) cardiac sarcoid. In the remaining three cases cardiac imaging showed cardiac amyloidosis (n=1), left ventricle non compaction (n=1) and initial idiopathic dilated cardiomyopathy (n=1). EMB confirmed the imaging diagnosis in 13 out of 16 patients (81.3%); 1 patient with evidence of focal myocarditis at CMR had a negative EMB, while 2 patients diagnosed as acute myocarditis at CMR had EMB findings suggestive for chronic myocarditis. Imaging findings other than inflammatory cardiomyopathy were all confirmed by EMB (3/3).
Conclusion: Myocarditis is the most frequent diagnosis in patients with acute VA presentation and normal coronary arteries. Although EMB remains the gold standard technique allowing definitive diagnosis and suggesting correct treatment, CMR shows a good concordance with EMB results and thus may help in the management of these patients. When CMR is contraindicated, DECT with delayed low-energy scan is a useful diagnostic tool.

P903 | BEDSIDE

Impact of multiple unfavorable echocardiographic findings in takotsubo cardiomyopathy

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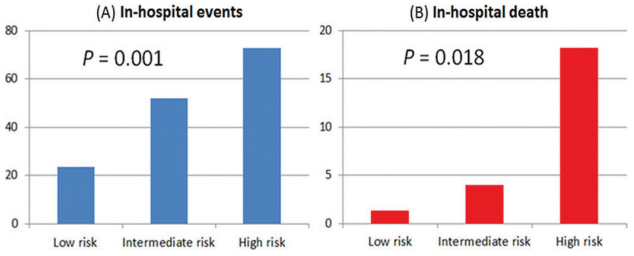
Background: Various unfavorable echocardiographic findings other than apical ballooning, such as right ventricular (RV) involvement, mitral regurgitation (MR), left ventricular outflow tract obstruction (LVOTO), and LV thrombus, occur in takotsubo cardiomyopathy. Occasionally, these findings are observed simultaneously in a single patient. This study was performed to investigate the incidence and prognostic impact of multiple unfavorable echocardiographic findings in takotsubo cardiomyopathy.
Methods and results: We retrospectively reviewed initial echocardiographic images of 113 (72.7±11.5 years old, 29 male) patients with takotsubo cardiomyopathy. Apical ballooning, RV involvement, MR, LVOTO, and LV thrombus were observed in 92 (81.4%), 21 (18.6%), 17 (15.0%), 11 (9.7%), and 3 (2.7%) patients, respectively. The numbers of unfavorable findings were 0–1 in 77 (68.1%) patients (low-risk group), 2 in 25 (22.1%) patients (intermediate-risk group), and ≥3 in 11 (9.7%) patients (high-risk group). The prevalence of the in-hospital events (acute heart failure, shock, ventricular tachyarrhythmia, and in-hospital death) and deaths were significantly different between groups. Logistic regression analysis indicated that being in the high-risk group had significant impacts on in-hospital events (odds ratio 8.74, P=0.003) and death (odds ratio 16.9, P=0.027) vs. being in the low-risk group.
Conclusions: Multiple unfavorable echocardiographic findings in takotsubo cardiomyopathy are not uncommon and are associated with increased rates of in-hospital events and mortality.



In-hospital events and death

CONDITIONS WITH INCREASED CORONARY ARTERY DISEASE RISK

P904 | BEDSIDE

Heart rate variability in diabetic patients with polyneuropathy and Charcot foot

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Background: Diabetic patients with Charcot arthropathy (CA) are characterized by high cardiovascular mortality and morbidity. Autonomic neuropathy and small fiber diabetic polyneuropathy are believed to be important causes of negative outcome. Heart rate variability (HRV) is known to be an early marker of autonomic neuropathy, besides its relation to severe peripheral neuropathy in Charcot foot is less studied.
Purpose: The present study addresses HRV in patients with CA.
Patients and methods: 103 pts with DM type 1 were included. Spectral analysis of heart rate variability (HRV) was performed. 512 successive RR intervals were analyzed. Total power (TP), high and low frequencies (HF, LF) bounds as well as SD of NN intervals were calculated. NDSm score was used for diagnosis of peripheral polyneuropathy. Data on HRV and clinical data were compared in 3 subgroups: 1 – no polyneuropathy, no CA (n=32); 2 – polyneuropathy without CA (n=58); 3 – polyneuropathy with CA (n=13).
Results: Significant differences in all studied groups (1 vs. 2 vs. 3) were revealed for age (28,3±10,3 vs. 40,1±15,7 vs. 45,5±10,6); duration of the DM (9,4±6,0 vs. 19,7±9,9 vs. 22,5±8,8); NDSm score (0 vs. 5,6±2,7 vs. 8,8±1,9) and HbA1c (7,6±2,2 vs. 9,3±1,6 vs. 10,4±1,5). Mean heart rate was maximal in 3 group compared with 1 and 2 groups: 80,9±11,3 vs. 76,3±11,6 vs. 71,6±6,8 beats/s. The same trend for TP was noticed: 117±101 vs. 2365±2486 vs. 551±799. HF progressively decreased from group 1 to groups 2 and 3: 717±854; 142±293; 14±17. LF power decreased in the same way: 1031±1242 vs. 176±221 vs. 33±39. SDNN in 3 group was significantly lower (11,5±4,4) compared with 1 and 2 groups but they did not differed from each other (50,3±25,3 and 48,0±50,1).
Conclusions: Patients with CA demonstrate extremely low HRV possibly contribution to high cardiovascular risk. Both sympathetic and parasympathetic failures are typical for CA patients. The TP of HRV decreased in parallel with increase in the severity of sensory polyneuropathy, duration of DM, age and level of HbA1c. The SDNN is less informative in the studied groups compared with data derived from spectral analyses.

P905 | BEDSIDE

Vital exhaustion and CHD risk: a systematic review and meta-analysis

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Background: Vital exhaustion (VE) and burnout are two related constructs suspected to be independent psychological risk factors for incident and recurrent coronary heart disease (CHD). Despite many decades of research, no systematic review or meta- analysis has previously attempted to collate the empirical evidence in this field.
Purpose: The purpose of this study was to review and quantify the impact of VE and burnout on the development and progression of CHD.
Methods: Studies were derived from PubMed, PsycINFO (1980 to July 2015; published articles in English only), and bibliographies. Only prospective and case-control studies reporting VE or burnout at baseline and CHD outcomes at follow-up were included. Information on aim, study design, sample size, inclusion and exclusion criteria, assessment methods of psychological risk factors, results of crude and adjusted regression analyses were abstracted independently by two authors.
Results: There were few studies of burnout, all using different methods of assessment. 13 prospective and 3 case-control studies on VE were summarized in the meta-analyses. The pooled adjusted risk of CHD in healthy populations was 1.50 (1.22–1.85) for prospective studies, and 2.61 (1.66–4.10) for case-control studies using hospital controls. Risk of recurrent events in patients with CHD was 2.03 (1.54–2.68). The pooled adjusted risk of CHF in healthy populations was 1.37 (1.21–1.56).

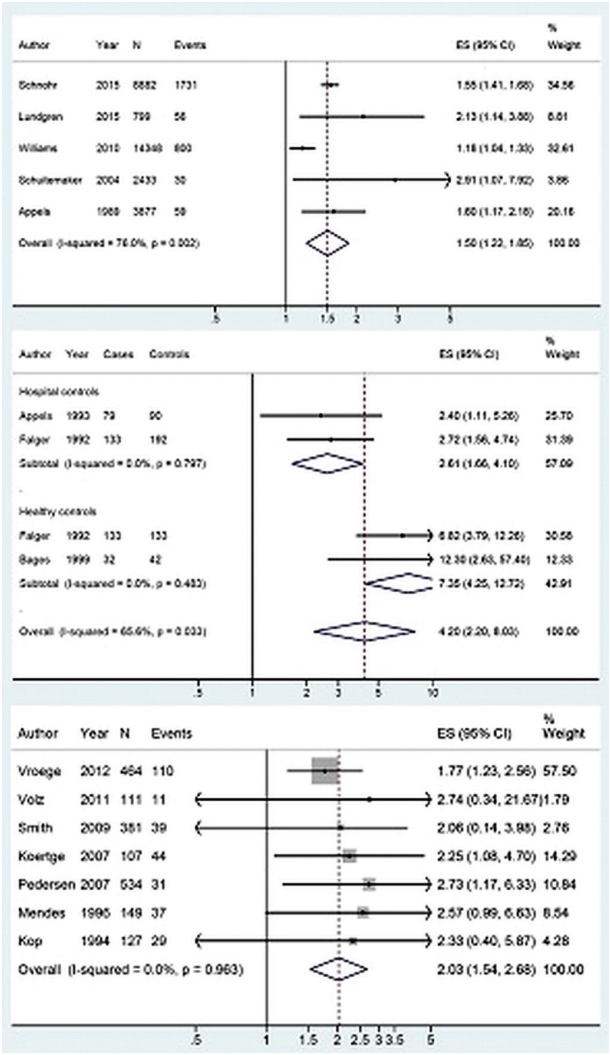

Figure 1. Meta-plots

Conclusions: Vital exhaustion is associated with increased risk of incident and recurrent CHD.

Acknowledgement/Funding: Danish Heart Association, Arvid Nilssons Foundation

P906 | BEDSIDE

The –174 G>C interleukin-6 gene polymorphism is associated with angiographic progression of non-culprit coronary plaques in a 4-year period

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Background: Inflammation is the key process underlying the clinical course of coronary artery disease (CAD). Interleukin-6 (IL-6) is an upstream key regulator of inflammation and acts as biomarker. We sought to examine whether a known single nucleotide polymorphisms (SNP) impacts the progression of CAD, reflecting higher inflammatory activity.

Methods: We evaluated previous coronary angiographies of patients with already established CAD who were re-investigated for stable/unstable angina after a time interval >12 months. We defined progression of CAD as the emergence of a new culprit lesion. We genotyped patients for -174 G>C IL-6 SNP (rs1800795). The probability for CAD progression among the Mendelian randomization groups was evaluated with the Kaplan-Meier method. Results were further analyzed with Cox model including age, hypertension, family history, disipidemia and diabetes mellitus in the model.

Results: A total of 157 patients were included. Genotype distribution was: GG: 30, CC: 55, GC: 72, C variant: 58%, frequencies were in Hardy-Weinberg equilibrium: χ^2=0.54542, p=0.460. Serum levels of IL-6 differed significantly among genotypes. At 48 months, 83 patients (52.9%) versus 74 (47.1%) demonstrated CAD progression. Patients with IL-6 CC genotype demonstrated 61.8% cumulative probability for progression, versus 45.8% for GC versus 13.3% for GG, p=0.005. Carriers of the IL-6 C allele had 52.8% cumulative probability for progression versus 13.3% for G allele, p=0.005. Results were confirmed in multivariate analysis adjusted for relevant clinical factors.

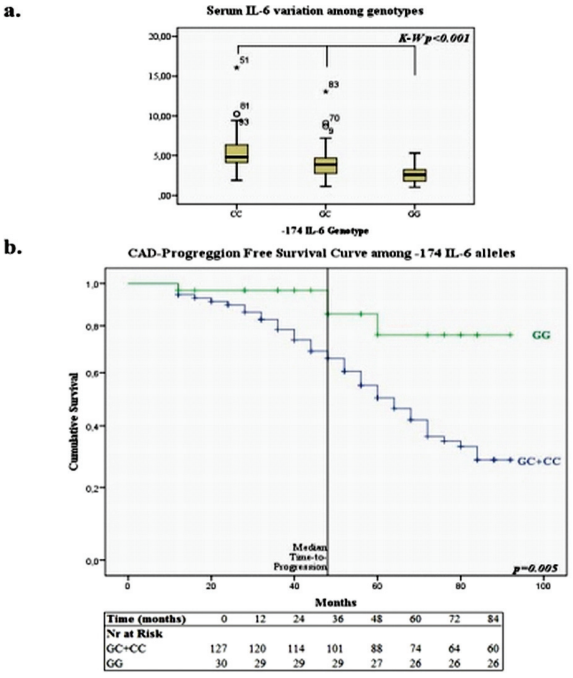

Image: **a.** Serum IL-6 variation among 3 genotypes of -174 G>C SNP (mg/dL), p from Kruskal-Wallis test **b.** Kaplan-Meier curve for CAD-progression among patients carrying G versus C -174 IL-6 allele, p from log-rank test

Conclusions: Patients with established CAD, carrying the -174 C allele of the IL-6 gene, demonstrated increased risk for progression of non-culprit coronary plaques in a 4-year period.

P907 | BEDSIDE

Impact of statins on 5-year clinical outcomes in acetylcholine-induced coronary artery spasm patients without fixed coronary lesions

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Background: Endothelial dysfunction and coronary artery spasm (CAS) are substantially involved in ischemic heart disease. It is known that the use of statin significantly improved endothelial function in vasospastic angina. However, there are limited data regarding impact of statins on long-term clinical outcomes in significant CAS patients (pts) without fixed coronary lesions (FCL).

Methods: A total 2812 pts underwent coronary angiography (CAG) with acetylcholine (Ach) provocation test from Nov 2004 to Oct 2010 were enrolled. Positive CAS test was defined as transient vasoconstriction of more than 70% and the definition of FCL was defined as coronary artery stenosis of less than 30% by quantitative coronary angiography (QCA). The incidence of recurrent angina and major adverse cardio-cerebrovascular accidents (MACCEs) was defined as com-

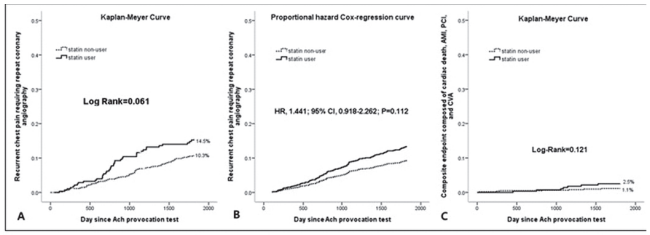

Figure. A: In Kaplan-Meyer curve, the statin user group had the higher incidence in recurrent chest pain (Log Rank=0.061), B: In proportional hazard Cox-regression, statin user had no association with recurrent chest pain, when adjusted by co-variates such as age, gender, hypertension, diabetes, dyslipidemia, cerebrovascular accident, peripheral arterial disease, current smoking, current alcoholics, and drugs including aspirin, clopidogrel, cilostazol, warfarin, calcium channel blocker, diltiazem, nitrate, trimetazidine, molsidomine, nicorandil, beta blocker, and diuretics. C: In Kaplan-Meyer curve, there was no statistic difference in MACCEs between two groups.

posite of cardiac death, myocardial infarction, percutaneous coronary intervention (PCI), and cerebrovascular accident were compared between the Statin non-user (n=631) and Statins user (n=283) were compared up to 5 years.
Results: The statin user group showed higher incidence of hypertension, diabetes, dyslipidemia and older than statin non-user group. The incidence of recurrent chest pain requiring repeat CAG tended to be higher in the statin user group during 5-year follow-up duration (Fig A). However, when adjusted by co-variates, there was no statistical difference in the incidence of recurrent angina (Fig B) and MACCEs between the two groups (Fig C)
Conclusions: In our study, we found that the statin did not play an important role in reducing the incidence of recurrent angina and adverse clinical outcomes in CAS pts without CFL up to 5 years.

P908 | BEDSIDE
Characteristics of young patients with antiphospholipid syndrome who develop acute myocardial infarction

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Background: Antiphospholipid syndrome (APS) is an autoimmune multisystem disorder characterized by thromboembolic events in the presence of persistent antiphospholipid antibodies. The presence of APS is considered a strong risk factor for the development of acute myocardial infarction (MI), especially in young patients, which may be due to coronary thromboembolism or accelerated atherosclerosis leading to plaque rupture. Young patients with MI usually have multiple risk factors for coronary heart disease (CHD), but there are limited data on the features of young patients with APS who develop MI.
Purpose: Understand the characteristics of patients with APS who develop MI.
Methods: A retrospective chart review evaluated patients admitted for acute MI between the years 2000 and 2015 in our facility. Acute MI was defined as the presence of chest pain and ischemic ST-T changes on electrocardiogram in association with increase in cardiac enzymes, leading to coronary angiogram. An age cut-off of 45 years was used to define "young" patients. When patients with APS were identified, we verified that the diagnosis of APS met with the revised Sapporo classification criteria. Hypertension, diabetes mellitus, lipid abnormality, obesity (body mass index over 25) and smoking were used as CHD risk factors.
Results: A total of 395 patients were admitted for acute MI, of which 29 (7%) were young patients. 4 cases were diagnosed as APS which were all young patients (1% of all patients, 14% of young patients), and all were male. In the 4 patients with APS, they all had a history of lipid abnormality, and at least another CHD risk factor. Regarding the etiology of the coronary occlusion, 3 cases were assumed as having plaque rupture from the results of coronary angiogram and intravascular ultrasound, of which 2 cases had a stent implanted. Only 1 case was assumed as having coronary thromboembolism. All APS cases had a prolonged activated partial thrombin time (aPTT) either on arrival or after discontinuation of heparin treatment. None of the remaining young patients had a prolonged aPTT.
Conclusions: Patients with APS who develop acute MI are young, have multiple risk factors for CHD, and may have similar angiographic appearance compared to typical MI patients, leading to a difficulty in distinguishing them from non-APS patients with acute MI. Prolonged aPTT on admission may be a clue in identifying patients with APS. As treatment of these patients may be a clinical challenge due to the thromboembolic predisposition, identifying them on arrival may be helpful.

P909 | BEDSIDE
Prevalence of cancer and its impact on prognosis of acute coronary syndrome population

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Background: Cancer and cardiovascular disease are the two most prevalent diseases worldwide. Few studies have been focused on the relationship between malignancy and acute coronary syndromes (ACS).
Aim: To evaluate the incidence of malignancy and its impact on outcome of ACS population.
Methods: We analyzed retrospectively 1486 ACS patients (pts) admitted, consecutively, in our coronary care unit, from January 2012 to December 2014. They were divided in two groups: group 1 – pts with active cancer (n=58, 3.9%); group 2 – pts without cancer (n=1428, 96.1%). For each group we compared clinical features and adverse events. Primary endpoint was the occurrence of death at 1 year; follow-up was completed in 98% of patients.
Results: Patients with active cancer were older (69±11 vs 63±13; p=0.001), had more prevalence of cerebrovascular (15.5% vs 7.4%; p=0.038) and arterial peripheral (12.1% vs 4.1%; p=0.012) diseases. On admission, they also presented more often anaemia (46.6% vs 23%; p<0.001) and renal insufficiency (eGFR<60 ml/min) (42.1% vs 24.3%; p=0.004). There were no statistically significant differences regarding the type of ACS presented or in the percentage of patients revascularized. About 21% (n=12) of patients who had active cancer were not revascularized, 29% (n=17) were treated with bare metal stent, 28% (n=16) with drug eluting stent, 2% (n=2) with balloon and 20% (n=11) with CABG. Cancer was diagnosed prior to 1 year in 27.6% (n=16) of pts; solid tumors were present in 89.7% (n=52); 22.9% (n=13) were previously treated with chemotherapy and 24.1% (n=14) with radiotherapy. They had higher prevalence of left systolic dysfunction (75.9% vs 54.7%; p=0.002), presenting more frequently acute heart failure (41.4% vs 26.5%; p=0.016), post-infarction angina (12.1% vs 5.1%; p=0.016) and de novo atrial fibrillation (6.9% vs 2.8%; p<0.001). Considering in-hospital mortality there were no differences between groups, but cancer patients had higher 1-year cardiovascular mortality (14.6% vs 3.9%; p=0.006) and all causes mortality (25.5% vs 6.2%; p<0.001).
After adjusting for different baseline characteristics in multivariate analysis, cancer patients had higher risk of overall 1-year mortality compared to those without cancer [OR 2.45, 95% CI (1.33–4.49), p=0.001].
Conclusion: Despite low incidence of malignancy in our population, our study shows that its presence carries an high risk for overall and cardiovascular mortality.

P910 | BEDSIDE
Epicardial adipose tissue contributes to the development of noncalcified coronary plaque: results from a 5-year CT follow-up study

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Background: Epicardial adipose tissue (EAT) has been suggested as a contributing factor for coronary atherosclerosis based on the previous cross-sectional studies and pathophysiologic background. However, the causal relationship between EAT and the development of non-calcified coronary plaque (NCP) has never been investigated in a follow-up study design.
Purpose: We aimed to clarify the impact of EAT on the future development of NCP.
Methods: A total of 122 asymptomatic individuals (mean age, 56.0±7.6 years; male sex, 80.3%) without prior history of coronary artery disease and metabolic syndrome, and without NCP on the baseline cardiac computed tomography (CT) were enrolled. A repeat cardiac CT was performed 5.7±0.5 years apart. Epicardial fat volume index (EFVi; cm^3/m^2) from the baseline cardiac CT were assessed in relation to the development of NCP on the follow-up CT.
Results: Follow-up cardiac CT showed a newly developed NCP in 24 (19.7%) subjects. The mean of baseline EFVi was 79.9±30.3 cm^3/m^2 in the NCP group, which was significantly higher than that of "calcified plaque" group (63.7±22.7 cm^3/m^2; P=0.019 versus NCP group) and the "no plaque" group (62.5±24.7 cm^3/m^2; P=0.021 versus NCP group). Multivariable logistic regression analysis demonstrated that the presence of diabetes (OR, 10.709; 95% CI, 2.076–55.227; P=0.005) and the 3rd tertile of EFVi (OR, 6.397; 95% CI, 1.365–29.982; P=0.019 compared to the 1st tertile) are the significant predictors for the development of NCP on follow-up CT.

Figure 1

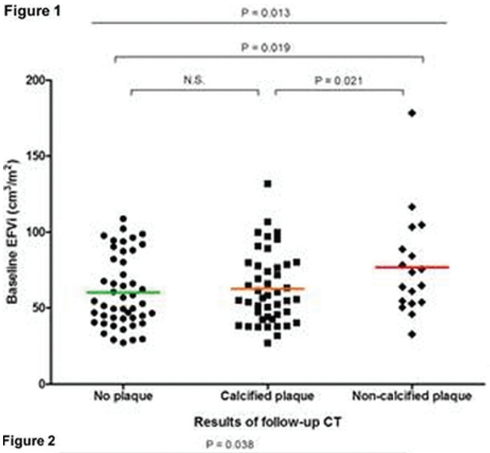
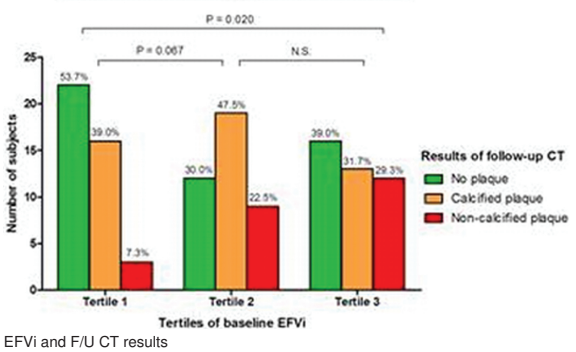


Figure 2



EFVi and F/U CT results

Conclusions: Baseline EFV was an independent predictor for the development

of NCP. Our findings showed the causal relationship between EAT and NCP, suggesting the additive value of EAT measurement for the risk stratification.

P911 | BEDSIDE
Low adiponectin and high NT-proBNP levels independently correlated with angiographic severity of coronary artery disease in non-diabetic patients: baseline data from the ANOX study

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Background: Biomarkers predicting the presence and severity of coronary artery disease (CAD) in non-diabetic patients with suspected CAD are unclear.
Methods: The ANOX study is a multicenter, prospective cohort study to determine the predictive value of possible novel biomarkers related to angiogenesis or oxidative stress for major adverse cardiovascular events among patients undergoing elective angiography. Between January 1, 2010 and November 1, 2013, a total of 2,513 patients were enrolled. After excluding 93 patients who were subsequently found ineligible or withdrew consent, and 1,088 patients with diabetes, the baseline data of 1,332 non-diabetic patients (47% with CAD, 25% with multivessel disease [MVD]) were analyzed. Blood samples were collected from the arterial catheter sheath at the beginning of coronary angiography. The presence of angiographic CAD (≥50% stenosis in ≥1 coronary artery) and its severity were assessed using the Gensini score. Serum levels of vascular endothelial growth factor (VEGF), VEGF-C, soluble VEGF receptor-2, adiponectin, leptin, and two oxidatively modified LDLs (the α1-antitrypsin/LDL complex and serum-amyloid-A/LDL complex), as well as N-terminal pro-brain natriuretic peptide (NT-proBNP), high-sensitivity troponin-I, and high-sensitivity C-reactive protein, were measured. We performed stepwise regression analyses including data on age, sex, systolic blood pressure, LDL-C, HDL-C, history of smoking habit, and these biomarkers.
Results: The presence of CAD was significantly correlated with age (OR, 1.6 per 10 year; 95% CI, 1.4–1.8), sex (OR, 2.1 for men; 95% CI, 1.6–2.7), HDL-C (OR, 0.87 per 10 mg/dL increase; 95% CI, 0.80–0.94), and natural log-transformed adiponectin (Ln-adiponectin) (OR, 0.77 per 1-SD increase; 95% CI, 0.67–0.87). The presence of MVD was also significantly correlated with age (OR, 1.4 per 10 year; 95% CI, 1.3–1.7), sex (OR, 2.7 for men; 95% CI, 2.0–3.8), HDL-C (OR, 0.89 per 10 mg/dL increase; 95% CI, 0.81–0.97), and Ln-adiponectin (OR, 0.76; 95% CI, 0.64–0.89), as well as LDL-C (OR, 1.05 per 10 mg/dL increase; 95% CI, 1.004–1.10) and Ln-NT-proBNP (OR, 1.3 per 1-SD increase; 95% CI, 1.1–1.5). After excluding 356 patients with normal coronary (Gensini score, 0) to attain normal distribution, independent determinants of Ln-Gensini score were age, sex, HDL-C, Ln-adiponectin, and Ln-NT-proBNP.
Conclusions: Low adiponectin and high NT-proBNP levels were independent predictors of the severity of CAD in non-diabetic patients with suspected CAD. The follow-up data of the ANOX study will provide evidence for the predictive values of these biomarkers independent of known risk factors and the severity of CAD at the baseline.
Acknowledgement/Funding: Grant-in-Aid for Clinical Research from the National Hospital Organization

P912 | BEDSIDE
Integration of stress MRI and CT CAC in suspected CAD - implication for risk stratification in diabetes

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Background: Stress testing for diagnosing ischemia is fundamental in the management of patients with suspected CAD and intermediate cardiovascular risk. Though, in patients with diabetes risk scores may under- as well as overestimate risk. Silent myocardial infarcts and ischemia affect frequently diabetics. Therefore, routine stress testing in diabetics is currently suggested. Cardiac MRI allows for accurate ischemia testing and detection of unrecognized myocardial scar (USCar).
Purpose: The aim of this study is to evaluate the impact of diabetes on MRI stress testing in patients with suspected CAD and to define the additional value of CT coronary calcium (CT CAC) in risk stratification.
Methods: Patients with suspected CAD who underwent CT CAC and Stress MRI were included. Stress MRI was analyzed regarding the presence of Wall motion abnormalities, perfusion deficits and the presence of delayed enhancement blinded to clinical and CT data in a random fashion. A MRI stress test was called pathologic if at least one of these three criteria was abnormal. Scar was defined as any hyperenhancement. For each patient, Framingham risk score (FRS) for prediction of 10-year general cardiovascular disease was calculated.
Results: 300 consecutive patients (20% female) were included in this study (mean age 53.1±9.7years). 23 (7.7%) MRI scans were pathologic. Mean Framingham risk score (FRS) was 16±12.6%. Patients with diabetes had higher FRS (38±21% vs. 15±11%), higher prevalence of CAC (83% vs. 54%, p:0.025, OR 4.16) and higher prevalence of pathologic MRI scans (11.1% vs. 7,4%, p=0.025). With increasing FRS, the prevalence and the extent of CAC increased (r=0.287, p<0.001). Similarly, the prevalence of a pathologic Stress MRI and unrecognized scars (Figure 1 a,b) increased with increasing CAC (p<0.001 for trend). Diabetics with zero CAC showed normal stress tests. Diabetes did not change the discriminative power of the FRS or CAC to predict pathologic MRI scans.

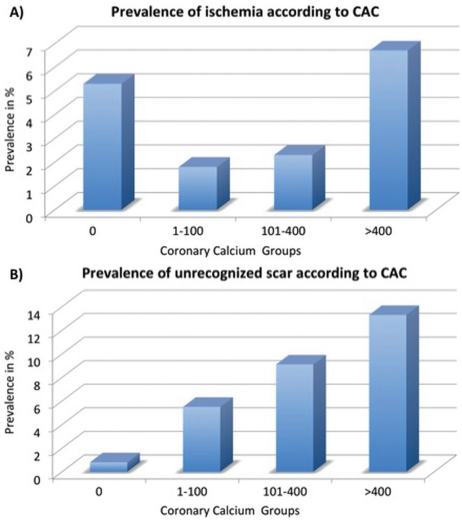

Figure 1

Conclusions: In this study of patients with suspected CAD and intermediate risk, diabetes was associated with higher Framingham risk scores and CAC scores, though, did not enhance prediction of pathologic MRI scans. Regardless of diabetic status, CT CAC changed risk stratification in patients with suspected CAD and can be used as a gatekeeper for further testing.This study suggests, that stress testing in diabetes without additional risk factors cannot be recommended.

P913 | BEDSIDE
Atypical presentation and comorbidities mutually influence management of ACS patients

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Background: Limited data are available on the association between comorbidities and acute myocardial ischemia with atypical presentation.
Purpose: The aim of this study was to investigate the impact of comorbidities on the management and outcomes of ACS patients with atypical presentation (i.e. ACS without chest pain).
Methods: Between 2010 and 2016, 11458 ACS patients were admitted at 57 hospitals included in the network of the ISACS-TC registry (ClinicalTrials.gov, NCT01218776). There were 1394 (12.2%) patients with unstable angina, 2855 (24.9%) with NSTEMI, and 7203 (62.9%) with STEMI.
Results: 995 (8.7%) ACS patients have atypical presentation at the initial evaluation, and the 40.2% of the overall study population have comorbidities (diabetes mellitus, heart failure, CKD, COPD, stroke, PAD, GERD or active cancer). Patients with comorbidities were not equally distributed: 38.7% were with typical presentation and 55.2% without typical presentation, (p<0.001). In-hospital mortality rate was much higher in patients with atypical presentation than in patients with the typical one (15.5% vs 6.3%, p<0.001). As well, mortality rate was lower for ACS patients with no-comorbidities than for ACS patients with comorbidities (5.1% versus 10.1%, p<0.001). Stratifying the population by the presence/absence of comorbiditis and the presence/absence typical presentation, we found a decreasing trend in use of evidence base treatment (aspirin, beta-blocker,

statin and reperfusion) and invasive procedure. Compare to patients with typical presentation and no-comorbidities (OR: 1, referent), patients with typical presentation and comorbidities (OR: 0.70), as well as those with atypical presentation and no-comorbidities (OR: 0.23), and those with atypical presentation and comorbidities (OR: 0.18) had a significant ($p<0.001$) lower probability to undergo in-hospital cardiac catheterization. On the opposite, there was an increasing trend ($p<0.001$) over subgroups in the risk of death (OR:1 referent, typical ACS presentation and no-comorbid; OR:2.00 typical ACS presentation and comordidities; OR: 2.52 atypical ACS presentation and no-comorbid; OR: 4.83 atypical ACS presentation and comordidities).

Conclusions: The presence of comorbidities and atypical ACS presentation dramatically influence the process of care. Patients with atypical presentation and comorbidities are those who receive the lowest treatment and those who have the highest risk of in-hospital death.

P914 | BEDSIDE

Usefulness of monocyte to HDL-cholesterol ratio to predict high SYNTAX score in patients with stable coronary artery disease

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Background: Recently, several studies has shown that monocyte to high density lipoprotein cholesterol ratio (MHR) are closely related with major adverse outcomes in various cardiovascular diseases.

Purpose: We aimed to investigate whether baseline MHR, an easily available inflammatory and oxidative stress marker, is associated with the severity and complexity of coronary atherosclerosis assessed by SYNTAX score.

Methods: In this cross-sectional study, a total of 1229 consecutive patients with coronary artery disease (CAD) who had undergone coronary angiography for stable angina pectoris were enrolled. The patients were classified two groups, those with low SYNTAX score ($\leq$22) and those with high SYNTAX score ($\geq$23). Multiple logistic regression analysis was used to identify the independent predictors of high SYNTAX score.

Results: Platelet, white blood cell (WBC), neutrophil, monocyte, MHR and CRP values were significantly higher in the high SYNTAX score group whereas HDL-C level was significantly lower in the high SYNTAX score group as compared with the low SYNTAX score group ($p<0.05$). Multi-vessel disease, chronic total occlusions, the left main coronary artery (LMCA) lesions and the left anterior descending coronary artery (LAD) lesions were more often present in the high SYNTAX score group. The rate of patients who underwent coronary artery bypass grafting (CABG) was also significantly higher in the high SYNTAX score group, whereas the rate of stent implantation for the coronary lesions was significantly higher in the low SYNTAX score group. In multivariate logistic regression analysis, MHR [odds ratio (OR): 1.083 (1.060–1.108), $p<0.001$] remained as independent predictor of high SYNTAX score as well as CRP [OR: 1.062 (1.043–1.080), $p<0.001$], LVEF [OR: 0.942 (0.929–0.954), $p<0.001$], hypertension [OR: 1.397 (1.056–1.847), p=0.019] and diabetes mellitus [OR: 1.464 (1.062–2.019), p=0.020]. Finally, in correlation analysis, MHR showed significant positive correlations with SYNTAX score (r=0.371, $p<0.001$) and CRP (r=0.336, $p<0.001$) [Figure 1].

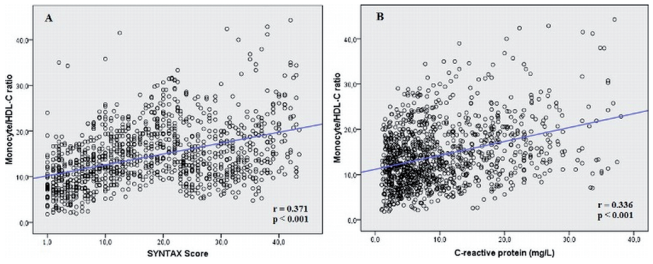

Figure 1.

Conclusions: Consequently, to the best of our knowledge, this is the first study showing MHR was independently associated with burden of coronary atherosclerosis assessed by SYNTAX score in patients with stable CAD.

P915 | BEDSIDE

Peripheral artery disease and non-st segment elevation acute coronary syndrome: impact on therapeutic management and in prognosis

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Introduction: Peripheral arterial disease (PAD) is an important comorbidity in non-ST elevation acute coronary syndromes (NSTEACS), and its presence could influence the therapeutic approach and prognosis of patients (pts).

Purpose: Evaluate the impact of PAD's comorbidity in the therapeutic management of pts with NSTEACS, in-hospital morbi-mortality and 1-year mortality.

Methods: We studied 7248 pts with NSTEACS enrolled in a Multicentric National Registry. We considered two groups: 1) Pts with PAD; 2) Pts without PAD. Recorded demographic variables, previous medical history, inpatient therapy, left ventricular function, coronary angiography and revascularization strategy performed. Defined the following in-hospital adverse events (IHAE): death, re-infarction, stroke, heart failure (HF), cardiogenic shock (CS), major bleeding (MB), need for blood transfusion (BT). Evaluated the in-hospital length of stay and mortality at 1 year. Multivariate analysis was performed to evaluate if the presence of PAD is a predictor of IHAE and/or 1-year mortality.

Results: The presence of PAD was documented in 7.3% (526 pts). These pts were older (70±11 vs 67±13 years, $p<0.001$), more likely to be males (82.1 vs 70.7%, $p<0.001$), to have history of hypertension (87.4 vs 74.1%, $p<0.001$), diabetes (55.3 vs 32.3%, $p<0.001$), dyslipidemia (76 vs 61.9%, $p<0.001$), previous MI (48.4 vs 24.6%, $p<0.001$), prior PCI (28.4 vs 17.5%, $p<0.001$), CABG (20 vs 6.5%, $p<0.001$), stroke (25.4 vs 7.5%, $p<0.001$) and chronic kidney disease (22.9 vs 6.3%, $p<0.001$).

Patients with PAD were more likely to evolve in Killip II-IV (26 vs 13.9%, $p<0.001$), with left ventricular (LV) dysfunction (Ejection fraction <50% – 42.7 vs 28.3%, $p<0.001$) and need for non-invasive ventilation (3 vs 1.7%, p=0.019); They were less often treated with beta-blockers (75 vs 87.5%, $p<0.001$) but more with diuretics (47.3 vs 26.6%, $p<0.001$); they were less likely to receive coronary angiography (69.8 vs 85.6%, $p<0.002$) but when performed, with larger femoral access rate (35.2 vs 21.4%, $p<0.001$); Pts with PAD had higher incidence of multivessel disease (76.7 vs. 52.4%, $p<0.001$) but more often was not planned any revascularization (25.4 vs 17.2%, $p<0.001$). Group 1 pts had higher duration of hospitalization (median 7 vs 5 days, $p<0.001$) and higher incidence of re-infarction (3.1 vs 1.4%, p=0.003), HF (26.7 vs 12.4%, p=0.002), CS (3.2 vs 1.8%, p=0.016), MB (2.3% vs 1.1, p=0.001) and BT (4.6 vs 1.6%, $p<0.001$), but not stroke (1.0 vs 0.7%, p=0.430). Patients with PAD had higher in-hospital mortality (4 vs 2%, p=0.003) and 1-year mortality (16.2 vs 6.2%, $p<0.001$). By multivariate analysis, PAD was established as an independent predictor of 1-year mortality (OR 1.57 [1.04–2.58] CI 95%, p=0.032), but not of IHAE.

Conclusions: In patients with NSTEACS, the presence of PAD affects therapy and revascularization strategy and is associated with higher in-hospital morbidity and mortality. This comorbidity is an independent predictor of death within 1 year.

P916 | BEDSIDE

Impact of smoking status on outcomes in stable coronary artery disease: an analysis of 32 499 patients from the CLARIFY registry

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Background: Tobacco smoking is the most important modifiable risk factor for cardiovascular morbidity and mortality. The excess cardiovascular risk of smoking in general populations is reduced to half after one year of smoking abstinence and has been reported to decrease to the level of never-smokers after prolonged cessation. We analyzed the impact of smoking status on outcomes in the large CLARIFY registry of outpatients with stable CAD.

Methods: CLARIFY is an ongoing international, prospective, observational, longitudinal registry of outpatients with stable CAD, defined as at least one of the following: prior myocardial infarction, coronary revascularization procedure, evidence of coronary stenosis >50%, or chest pain associated with proven myocardial ischemia. A total of 33,438 patients from 45 countries in Europe, the Americas, Africa, Middle East, and Asia/Pacific were enrolled between November 2009 and July 2010. Patients were followed for a maximum of 5 years until the end of December 2015. We conducted this analysis in 32 499 patients: 13 425 patients were never-smokers, 4061 current smokers, and 15013 former smokers at baseline.

Results: Overall, current smokers were younger than both never-smokers and former smokers (58.5 vs 66.2 and 63.8 years respectively, $p<0.0001$). There were more men among current or former smokers compared with never-smokers (87 and 90 vs 61%, $p<0.0001$). Never-smokers had less prevalence of asthma/COPD or peripheral arterial disease. Compared with never-smokers, both current and former smokers had increased risk of all outcomes (Table).

	Never smoker HR	Former smoker HR (95% CI)	Current smoker HR (95% CI)	P*
All-cause death	1.00	1.36 (1.24, 1.49)	1.93 (1.69, 2.21)	<0.001
Cardiovascular death	1.00	1.39 (1.20, 1.60)	1.72 (1.40, 2.13)	<0.001
Fatal or non-fatal MI	1.00	1.27 (1.10, 1.46)	1.66 (1.37, 2.00)	<0.001
Cardiovascular death/ MI	1.00	1.32 (1.18, 1.47)	1.73 (1.49, 2.02)	<0.001
Cardiovascular death/ MI/stroke	1.00	1.25 (1.13, 1.37)	1.62 (1.42, 1.86)	<0.001

*Adjusted for age, sex, geographic region, MI, PCI and CABG.

Conclusion: In contrast to the "smoker's paradox" reported after acute myocar-

dial infarction, current smokers with stable CAD have a greatly increased risk of future cardiovascular events compared to never-smokers, reinforcing the importance of smoking cessation. Cardiovascular risk remains elevated in former smokers with stable CAD, albeit at an intermediate level between current and never-smokers.

Acknowledgement/Funding: The CLARIFY Registry is sponsored by SERVIER

P917 | BEDSIDE
The impact of age in patients without co-morbidity disease on acetylcholine-induced coronary artery spasm

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Background: In previous studies, age was reported as a significant risk factor in coronary artery disease and endothelial dysfunction. However, there have been limited data regarding the impact of age in patients (Pts) without co-morbidity disease on the coronary artery spasm (CAS).

Method: A total of 2,245 pts who underwent intracoronary acetylcholine (Ach) provocation test were enrolled. Provocation test was performed by incremental doses (20, 50, 100ug) of Ach until get significant response (>70% narrowing). The pts without co-morbidity disease were previous coronary heart disease, hypertension, diabetes mellitus, dyslipidemia, peripheral vascular disease, cerebrovascular accidents and chronic kidney disease. The study population was classified into four groups; the Group 1 was 20 to 45 years old (n=698), the Group 2 was 46 to 55 years old (n=724), the Group 3 was 56 to 65 years old (n=544) and the Group 4 was over 65 years old (n=279). We investigated incidence of CAS and angiographic parameters among these groups.

Result: Baseline clinical characteristics were similar among the 4 different Age groups. During Ach provocation test, angiographic characteristics were different among groups; the response to Ach dose 50ug was the highest Group 4, the response to Ach dose 100ug was the highest Group 1, multi-vessel spasm and EKG change was the highest in Group 2. The incidence of CAS was highest in the Group 3. After the multivariate analysis, gender, myocardial bridge, and baseline spasm (>30% narrowing) were independent predictors of Ach induced CAS. The Group 3 was the highest independent predictor of CAS compared with other groups (Table).

Table. Risk factors associated with significant coronary artery spasm as assessed by Ach

Groups	Patients without co-morbidity diseases		
	Odd Ratio	95% Confidence Interval	*p*-Value
Age			
Group1 (20~45)	Reference		
Group2 (46~55)	1.866	1.498-2.324	<0.001
Group3 (56~65)	2.859	2.239-3.65	<0.001
Group4 (≥66)	2.596	1.923-3.504	<0.001
Gender	1.411	1.147-1.737	0.001
Current smoking	1.232	0.959-1.581	0.102
Current alcoholics	1.178	0.96-1.446	0.116
Myocardial bridge	2.470	1.939-3.147	<0.001
Baseline spasm (>30%)	1.811	1.449-2.264	<0.001

Conclusion: In this Study, we found that the increase of age in pts without co-morbidity disease predisposes towards a higher chances of significant CAS as assessed by intracoronary Ach provocation test.

P918 | BEDSIDE
Influence of age and gender on bleeding and late outcomes after PCI for ACS

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Background: Gender and age are non-modifiable factors influencing clinical outcomes in acute coronary syndromes (ACS). The pathophysiology of ACS may be different in women compared to men. Thus, we sought to evaluate the effect of age and gender on clinical outcomes in patients with ACS undergoing percutaneous coronary interventions (PCI).

Methods and results: Among 2728 (75% males) consecutive patients with ACS who underwent PCI at Liverpool Hospital, Sydney, Australia, from October 2003 to March 2010, we determined bleeding according to Bleeding Academic Research Consortium (BARC) criteria; also late clinical outcomes including mortality, myocardial infarction (MI), and target vessel revascularization (TVR) were examined. Patients were divided into 2 age groups (Group1<55 years=919, Group 2 ≥55 years=1809). Females were 9 years older (median 68 vs. 59 years; p=<0.001), more likely to have diabetes (29% vs. 20% p<0.001), hypertension (61% vs. 46%, p<0.001), anemia (24% vs. 13%, p<0.001), and renal impairment (39% vs. 17%, p<0.001); and less likely to be smokers (20% vs. 32%, p<0.001). With respect to angiographic/ procedural characteristic, females were less likely to have class B2/C lesions (62% vs. 67%, p=0.012), or lesions at bifurcations (17% vs. 21%, p=0.040), but had more calcified lesions (20% vs. 11%, p=<0.001), smaller stent diameter (2.75 [2.5–3] vs. 3 [2.75–3.5] mm, p<0.001),and less periprocedural intravenous glycoprotein IIb/IIIa inhibitors use (28% vs. 35%, P=<0.001), though similar DES use (25% vs. 24% p=0.655). Females had a higher incidence of type 2–5 BARC bleeding post-PCI (22% vs. 16% p=0.003) and at 3 year follow up, the mortality rate was higher among females (11% vs. 7% p=0.001). In Group 1, bleeding, mortality and MACE were higher in females, (27% vs. 14% p=0.002), (7% vs. 3% p=0.041) and (18% vs. 11%, p=0.042) respectively, with no significant difference in MI and TVR rates. In Group 2, TVR rates were less in females (7% vs. 10% p=0.026), while other clinical outcomes were similar. Using multivariable stepwise regression analysis modeling, female gender was not significant predictor of mortality, while it was significant predictor of bleeding (OR=1.69 [95% CI: 1.25–2.29], p=0.001).

Conclusions: While bleeding and mortality were higher in younger females with ACS who underwent PCI, overall female gender was not predictor for late mortality after risk adjustment. However female gender predicted post-PCI bleeding. As PCI is now predominantly performed via radial access, whether similar factors still affect post-PCI outcomes needs clarification

P919 | BEDSIDE
Is elevated triglyceride related with clinical outcome in patient with AMI of KAMIR NIH study

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Introduction: Whether serum triglyceride level correlates with clinical outcomes of patients with acute myocardial infarction remains unclear.

Methods: From the Korea Acute Myocardial Infarction Registry, 8741 patients with acute myocardial infarction were enrolled between November 2011 and July 2015. The patients were divided into two groups according to fasting triglyceride levels: group I (lower TG ≤150mg/dl, n=6282) and group II (higher TG >150 mg/dl, n=2459). In hospital mortality rates and late clinical outcomes were compared between two groups.

Results: All-cause death and cardiovascular death, major adverse cardiac event (MACE) were significantly lower in higher TG group (hazard ratio [HR], 0.601; 95% confidence interval [CI], 0.489 to 0.739; P<0.001, HR, 0.622; 95% CI, 0.483–0.800, p=0.001, HR, 0.741, 95% CI, 0.630–0.871, p=0.005). However, after adjusted for clinical variables, the risk of all-cause death and cardiovascular death, MACEs was not significantly between higher TG group and lower TG group (p=0.880, p=0.600, p=0.728, respectively). Cox regression analysis confirmed serum triglyceride as a negative predictor for overall clinical outcomes.

Adjusted clinical outcomes in lower TG v

	HR (95% CI) for TG >150	P value
MACE	0.728 [0.776 to 1.194]	0.728
All cause death	1.027 [0.726 to 1.452]	0.880
Cardiovascular death	1.128 [0.719 to 1.771]	0.600
MI	1.085 [0.736 to 1.599]	0.680
TVR/TLR	0.876 [0.619 to 1.241]	0.457

Abbreviations: MACE, major adverse cardiac event; MI, myocardial infarction; TVR, target vessel revascularization; TLR, target lesion revascularization. Adjusted for age, sex, BMI, HTN, DM, dyslipidemia, smoking, pre-procedural TIMI flow, killip class, LVEF, DES ≥1, multivessel disease (1,2,3,LM), ACEi/ARB use, GPI use, statin intensity.

Conclusions: This study demonstrates that serum triglyceride level did not correlate with clinical outcomes in patients with STEMI treated who underwent primary PCI.

P920 | BEDSIDE
The predictive value of different equations for estimation of glomerular filtration rate in patients with coronary artery disease

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Background: Impaired renal function leads to dramatically increased risk for the development and progression of coronary artery disease (CAD). This association offers enormous potential for preventive therapies, particularly in early stages of chronic kidney disease (CKD).

Purpose: Cystatin c-based equations for estimated glomerular filtration rate (eGFR) perform more precisely to assess renal function than creatinine-based equations. Whether this is related with a better assessment of the patients' prognosis, a criterion for CKD-classification required by the guidelines, has not been answered for CAD-patients yet. Therefore, we aimed to analyze the predictive

value of the four most common eGFR-equations regarding CAD-severity and cardiovascular (CV) outcome.
Methods: From the AtheroGene study 2135 patients of the whole CAD spectrum were included and assessed regarding the combined outcome of CV death and non-fatal myocardial infarction. Further, we analyzed which of the eGFR-equations predicts complex CAD as assessed by the SYNTAX score with values ≥23 most precisely. The eGFR was calculated using serum creatinine (sCr) and the 4MDRD-equation, further with cystatin c (CysC) and sCr each alone and in combination (CysC/sCr) with the CKD-EPI-equation. Median follow-up was 4.3 years.
Results: Kaplan-Meier curve analysis and log-rank test for all four equations were significant (p for all <0.005). At early stages of CKD only the CKD-EPI-equation for CysC could differentiate the eGFR-categories regarding the risk for an endpoint event (log-rank test p=0.009 for eGFR >90 ml/min/1,73 m^2 vs. eGFR 60–90 ml/min/1,73 m^2). In the Cox regression analysis both eGFR calculated by CKD-EPI-equation for CysC and for CysC/sCr were predictive regarding the outcome in a fully adjusted model for all cardiovascular risk factors (CVRF) and Nt-proBNP (Hazard ratios (HR) per decline standard deviation (SD) for eGFR (CysC) 1.27 (1.07–1.50), p=0.007 and for eGFR (CysC/sCr) 1.22 (1.02–1.46), p=0.026). Furthermore, only eGFR calculated by CKD-EPI-equation for CysC and for CysC/sCr after adjustment for all CVRF were significantly associated with a SYNTAX score of ≥23 (Odds ratio per decline SD for eGFR (CysC) 1.57 (1.36–1.78), p<0.001 and for eGFR (CysC/sCr) 1.32 (1.13–1.53), p<0.001). Compared to the sCr-based equations areas under the curve (AUC) were higher for the CKD-EPI-equation using CysC (AUC endpoint 0.58/AUC SYNTAX Score ≥23 0.59) and CysC/sCr (0.58/0.58) to identify patients with an endpoint event or SYNTAX score of ≥23.
Conclusions: Of the four tested eGFR-equations the CKD-EPI-equation for CysC and for CysC/sCr provided a better predictive value regarding the severity of CAD and the outcome of patients compared to eGFR-equations using only sCr. These results may lead to a better identification of patients at increased cardiovascular risk due to renal dysfunction who benefit from intensive preventive therapies as endorsed by the guidelines.

P921 | BEDSIDE
Impact of serum level of uric acid on lipid component of coronary plaque in patients with coronary artery disease with optimal medical therapy

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Background: Elevated uric acid (UA) serum level is associated with increased cardiovascular events. However, little is known about the relationship between UA and coronary plaque under optimal medical therapy (OMT).
Purpose: We examined the association between serum levels of UA and coronary plaque using integrated backscatter intravascular ultrasound (IB-IVUS) in patients with coronary artery disease (CAD) who received OMT for low-density lipoprotein cholesterol (LDL-C) and blood pressure (BP) according to Japanese guidelines.
Methods: One hundred twenty-four CAD patients with OMT who underwent percutaneous coronary intervention under IB-IVUS guidance were included. IB-IVUS analysis was conducted on the non-culprit lesion to determine three-dimensional IVUS parameters including each plaque component. Fasting serum levels of UA were measured.
Results: In all of the patients, LDL-C level was 95±32 mg/dl (target LDL-C level: <100 mg/dl), and systolic and diastolic BP were 128±18 mmHg and 71±12 mmHg, respectively (target systolic BP: <140mmHg and target diastolic BP: <90mmHg). Serum UA levels were not related with plaque burden, but significantly related with the composition of plaque. Serum levels of UA were positively correlated with percent lipid volume (r=0.271, p=0.002) and negatively correlated with percent fibrous volume (r=-0.338, p=0.003). Logistic regression analysis indicated that the association between serum level of UA and percent lipid volume of plaque was significant after adjusting for conventional risk factors of CAD including age, gender, body mass index, hypertension, diabetes, dyslipidemia and smoking [odds ratio (95% confidence interval): 1.7 (1.1–2.8), p=0.017].
Conclusions: Elevated levels of UA were associated with greater lipid volume of coronary plaque in CAD patients with OMT. Serum level of UA may be an important therapeutic target to reduce “residual risk”.

P922 | BEDSIDE
Very high and very low risk patients: predictors of death - An exploratory analysis considering the baseline thrombotic and hemorrhagic risk

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Background: The GRACE and CRUSADE risk scores are useful risk stratification tools to identifie high-risk patients (pts) with Acute Coronary Syndrome (ACS) for whom more aggressive treatment is warranted.
Purpose: To search for independent predictors of death in pts with ACS categorized according to the thrombotic and bleeding risk at baseline.
Methods: From October 2010 to November 2014, 4445 consecutive pts with ACS (66±13 years; 73% male) included in a multicenter national registry were enrolled. Based on ROC curves, optimal cut-off points were created. Then, 4 groups were defined and compared: A) GRACE<160 and CRUSADE<33; B) GRACE≥160 and CRUSADE<33; C) GRACE<160 and CRUSADE≥33); D) GRACE≥160 and CRUSADE≥33. In order to determine predictors of risk of death at 12 months a Cox regression analysis was performed in the very high risk population (group D).
Results: Comparative analyses between A (n=2365; 53.2%), B (n=575; 12.9%), C (n=529; 11.9%) and D (n=976; 22.0%) groups revealed, respectively, progressive increasing age (58±11 vs 71±9 vs 71±11 vs 77±9, p<0.001), higher rates of previous cardiovascular diseases [stroke/TIA (4.9% vs 7.1% vs 12.3% vs 13.6%, p<0.001)], lower left ventricular ejection fraction (57±12 vs 53±12 vs 54±14 vs 49±14, p<0.001), more angina equivalents as clinical presentation (3.1% vs 5.4% vs 8.7% vs 21.8%, p<0.001) and higher Killip class (KK>1: 2.2% vs 12.0% vs 10.4% vs 46.6%, p<0.001). The myocardial revascularization was accomplished progressively in lower rates (87.6% vs 84.0% vs 83.1% vs 73.4%, p<0.001). In group D, 178 (18.2%) pts died during follow-up; ROC curves with optimal cut-off points were created and Cox regression identified independent predictors of endpoint death (Table).

	HR	95% CI	p-value
Age ≥79 years	2.02	1.40–2.91	<0.001
Hb ≤10.8g/dL	1.94	1.34–2.80	<0.001
Previous AMI	1.89	1.29–2.78	0.001
Coronary angiography	0.37	0.26–0.53	<0.001
Inotropic drugs*	1.76	1.07–2.89	0.025
Diuretics*	1.78	1.14–2.76	0.011

Hb: hemoglobin; AMI: acute myocardial infarction. *In hospital.

Conclusions: Age, atherosclerotic burden, and heart failure with inotropic drugs use all mark worse prognosis in pts with high GRACE and high CRUSADE scores. In spite of a clear benefit, an invasive revascularization strategy is paradoxically less frequently used in this higher risk population.

P923 | BEDSIDE
New-onset atrial fibrillation impacts in-hospital prognosis of patients with acute coronary syndromes

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Introduction: Atrial Fibrillation (AF) occurs in a percentage of patients with Acute Coronary Syndromes (ACS) and is linked with a poor prognosis
Purpose: This study intends to evaluate the impact of new-onset AF on the in-hospital prognosis of patients with ACS.
Methods: Prospective data of 1471 patients consecutively admitted between 1st October 2009 and 30th September 2015 diagnosed with an ACS. Patients with history of AF were excluded. The patients were divided into 2 groups: A) patients who developed AF during hospitalization (n=71; 4.8%; 59.2% male); B) patients who did not develop AF (n=1396; 95.2%; 71.1% male). The groups were compared according to the composite primary endpoint (CPE) (re-infarction, stroke, cardiovascular death) and secondary endpoints (re-infarction, stroke and cardiovascular death separately).
Results: Patients with new-onset AF displayed a higher incidence of EPC (A= 14.1% vs B= 7.1%, p=0.037), cardiovascular death (A=11.3% vs B= 5.5%, p=0.043) and cardiogenic shock (A=14.1% vs B=6.4%, p=0.025). Regarding re-infarction or stroke, no differences between groups were found.
Group A displayed a higher mean age (A= 72.6±13.0 vs B= 64.3±13.3, p<0.001), and a higher prevalence of previous stroke (A= 18.3% vs B= 6.9%, p=0.002), chronic heart failure (A=14.1% vs B= 4.6%, p=0.002) and hypertension (A= 78.9% vs B=64.5%, p=0.013). Patients with new-onset AF also exhibited a higher percentage of ST elevation myocardial Infarction (A= 70.4% vs B=57.0%, p=0.027) and Killip class >1 at admission (A=39.7% vs B=19.3%, p<0.001), but less patients were submitted to percutaneous coronary intervention (A=71.8% vs B= 90.1%, p<0.001). Upon release, no difference on double antiplatelet therapy prescription was found, and 11.3% of the patients with new-onset AF were anticoagulated.
Conclusion: New-onset FA is correlated with a worse in-hospital prognosis in patients with ACS.

P924 | BEDSIDE

Impact of hypertension on 5-year clinical outcomes in patients with coronary chronic total occlusion lesion

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Background: Hypertension (HTN) can worsen cardiovascular morbidity and mortality. However, there are limited data regarding the impact of HTN in patients (Pts) who have coronary chronic total occlusion (CTO) lesion on long-term clinical outcomes.

Methods: A total of 822 consecutive CTO pts who underwent coronary angiography, receiving either percutaneous coronary intervention (PCI) or optimal medical treatment (OMT) were enrolled. Pts were divided into two groups according to the presence of HTN; 1) the HTN group (n=536) and 2) Control group without HTN (n=286). To adjust for potential confounders, a propensity score matching (PSM) analysis was performed using the logistic regression model. Individual major clinical outcomes and major adverse cardiac events (MACE), the composite of total death, myocardial infarction, stroke and revascularization, were compared between the two groups up to 5 years.

Results: After PSM analysis, two propensity-matched groups (249 pairs, n=498, C-statistic=0.701) were generated and the baseline characteristics were well balanced. Up to 5 years, the HTN group showed higher incidence of stroke compared with the control group. However, there was no significant difference in the incidence of myocardial infarction, repeat revascularizations and MACE between the two groups up to 5 years.

Table. Cumulative Incidence of Clinical Outcomes Up to 5 Years

Variables, %	HTN (n=249)	Control (n=249)	p-Value
Total death	7.5 %	6.3 %	0.591
Cardiac death	3.6 %	4.0 %	0.807
Myocardial infarction	2.3 %	2.7 %	0.773
Stroke	2.2 %	0.0 %	0.025
Revascularization	15.3 %	17.6 %	0.676
Target lesion (CTO vessel)	6.9 %	8.7 %	0.501
Target vessel (CTO vessel)	8.6 %	11.5 %	0.361
Non-target vessel (Non-CTO vessel)	10.0%	12.1 %	0.602
Total MACE	21.6 %	22.4 %	0.960

Major adverse cardiac events (MACE) was defined as the composite of total death, myocardial infarction, stroke and revascularization.

Conclusions: In this study, hypertensive pts with CTO was associated with higher stroke incidence up to 5 years and thus should be given more careful management during clinical follow-up.

P925 | BEDSIDE

Incorporating hyperhomocysteinemia into hyperlipoprotein(a)emia predicts adverse cardiovascular outcome in patients with coronary artery disease

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Purpose: We sought to evaluate the incorporating prognostic value of hyperlipoprotein(a)emia and hyperhomocysteinemia in patients with coronary artery disease (CAD).

Methods: 5839 patients (60.4% male, mean age 61.3±11.2 years) with CAD were enrolled from 2000 to 2010. Laboratory values including lipoprotein(a) [Lp(a)] and homocysteine (Hcy) levels were obtained at the day of coronary angiography and analyses were done shortly after sampling. Patients were divided into four groups according to their Lp(a) and Hcy levels. Baseline risk factors, coronary angiographic findings, length of follow-up, and major adverse cardiovascular event (MACE) including cardiac death and non-fatal myocardial infarction (MI) were recorded.

Results: Over a mean follow-up period of 4.4±2.5 years, there were 132 MACEs (75 cardiac death and 57 non-fatal MI) with an event rate of 2.3%. Mean Lp(a) level and Hcy levels were 21.4±24.5 mg/dL and 9.9±4.3 mg/dL, respectively. Of the 5839 patients, 2624 patients (44.9%) were allocated in group 1 [normal Lp(a) and Hcy group]; 1262 patients (21.6%) in group 2 [elevated Lp(a), but normal Hcy group]; 1256 patients (21.5%) in group 3 [elevated Hcy, but normal Lp(a)] and 697 patients (11.9%) in group 4 [elevated Lp(a) and Hcy]. Composite MACE rates were 1.3% (33/2624), 2.1% (27/1262), 2.8% (35/1256), and 5.3% (37/697) for group 1, 2, 3 and 4, respectively. Kaplan-Meier survival analysis revealed that elevated Lp(a) and Hcy was associated with adverse cardiac outcome ($p<0.0001$). Furthermore, multi-variate Cox regression analysis after adjustment of age, gender, diabetes, hypertension, hypercholesterolemia, smoking and extent of CAD revealed that elevated Lp(a) and Hcy was associated with worse prognosis [HR 2.814, 95% CI 1.736–4.561 ($p<0.0001$)].

Table 1. Multivariate Cox regression analysis for predicting MACE (non-fatal MI and cardiac death)

	Multivariate		
	HR	95% CI	p-value
Age	1.053	1.033–1.074	<0.0001
Diabetes	1.935	1.356–2.761	<0.0001
Extent of CAD	1.534	1.286–1.828	<0.0001
Elevated Lp(a) & Hcy	2.814	1.736–4.561	<0.0001

Conclusions: Incorporating hyperhomocysteinemia into hyperlipoprotein(a)emia is associated with increased incidence of adverse cardiovascular events in patients with CAD.

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Clinical impacts of oral antihyperglycemic therapy including dipeptidyl peptidase-IV inhibitors in type 2 diabetic patients with acute myocardial infarction: from KAMIR-NIH

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Background: The cardiovascular effects of dipeptidyl peptidase-IV (DPP-4) inhibitors in type 2 diabetic patients after acute myocardial infarction (AMI) are not well-known.

Objectives: We assessed cardiovascular outcomes with DPP-4 inhibitor, as compared with metformin and sulfonylurea in patients type 2 diabetes who had a AMI.

Methods: We studied 955 type 2 diabetic patients with AMI, who received metformin, sulfonylurea or DPP4-inhibitor between January 2011 to May 2015 in the Korea Acute Myocardial Infarction Registry – National Institute of Heath (KAMIR-NIH). Patients were divided into 3 groups: 374 with metformin monotherapy (metformin group), 344 with metformin and sulfonyl urea (sulfonylurea group) and 238 with metformin and DPP-4 inhibitor (DPP-4 inhibitor group). The influence of oral antihyperglycemic therapy on a 3-year clinical outcome was examined and the primary endpoint was a composite of cardiovascular death, MI and cardiac revascularization.

Results: Baseline characteristics were not different except glucose and HbA1C. Sulfonylurea group and DPP4-inhibitor group had higher level of glucose and HbA1C than metformin group (glucose, 234.81 vs 229.62 vs 206.13 mg/dL, $p<0.001$; HbA1C, 8.034 vs 7.763 vs 7.337, $p<0.001$). The incidence of the composite primary endpoints at the 3-year clinical follow-up were not different (6.7% in metformin group; 9.7% in sulfonylurea group; 7.3% in DPP-4 inhibitor group, p=0.644). The 3-year composite endpoint free survival rate was not significantly different among groups (93.3% in metformin group; 90.3% in sulfonylurea group; 92.7% in DPP-4 inhibitor group, p=0.511). Compared with metformin group, DPP-4 inhibitor group showed no statistically significant excess risks of composite endpoint (hazard ratio, 1.174; 95% confidence interval, 0.574 - 2.403; p=0.660)

Conclusion: DPP-4 inhibitor group in type 2 diabetic patients with AMI may not be associated with cardiovascular outcomes.

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Gender difference in clinical characteristics of coronary artery spasm in patients with angina chest pain

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Background: Although vasospastic angina (VA) is more prevalent among Asian male in comparison with white populations, there is rare data concerning gender differences in patients with coronary spastic angina. We aimed to investigate the clinical characteristics between male and female patients with coronary artery spasm (CAS).

Methods: A total of 1535 consecutive patients without significant coronary artery disease (CAD) who underwent ergonovine provocation test between Jan. 2008 and Feb. 2015 were enrolled. Significant CAS was defined as $\geq$90% of narrowing accompanied by ischemic changes on electrocardiography by incremental intracoronary injection of 50, 100 and 200 μg. The clinical difference between male and female was compared according to the pattern of CAS.

Results: A total of 26.3% (404/1535) patients were diagnosed as VA documented by ergonovine provocation test with significant CAS, and more prevalent in male gender (35.7 vs. 17.9%, $p<0.001$). Compared with male patient female patients were older (55.6±9.7 vs. 51.9±11.4, $p<0.001$), less history of smoking (6.0 vs. 37.3%, $p<0.001$), had less organic stenosis (10 vs. 16.1%, $p<0.001$), less diffuse (66.2 vs. 64.6%, p=0.002) and fewer multi-vessel spasm (17.5 vs. 26.1%). Moreover, female patients showed more prevalence of intermediate grade (30–70%) of CAS (30.2 vs. 23.6%, $p<0.001$) and cardiac syndrome X defined as normal coronary artery with positive treadmill test (11.9 vs. 5.2%, p=0.021) compared with male patients.

Conclusion: The female VA prevalence was 35.8%, a half of male patients in Korean, with characteristics of diffuse provoked spasm, less organic stenosis, and less history of smoking. However, significant proportion of intermediate grade of CAS in female patients with angina chest pain might need further guideline for definition of VA and the gender-specific management.

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Incidence and predictive risk factors of acute coronary syndrome and death in end stage renal failure patients on renal replacement therapy

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Background: Cardiovascular morbidity and mortality in end stage renal failure (ESRF) patients is high. Studies in Asian patients, including the potential impact of different modalities of renal replacement therapy (RRT) and racial factors on outcomes are few. We aim to describe the incidence and predictive factors of death and acute coronary syndrome (ACS) in ESRF patients on different modalities of RRT in a multiracial Asian society.
Methods: In this retrospective cohort study, data was obtained from a nation-wide data base (National Registry Disease Offices) in Singapore. We included all adult patients with ESRF initiated on dialysis for at least 3 months, or who underwent renal transplant from 2007 to 2012 in Singapore. Outcomes were evaluated up till September 2014. Cox regression analysis was used to determine variables affecting death and ACS.
Results: Of 5425 patients, 4449 were on haemodialysis, 860 on peritoneal dialysis and 116 post renal transplant. Mean age was 60.3 (±13) years and 2389 (44%) were females. There were 3628 (67%) Chinese, 1313 (24%) Malays and 403 (7%) Indians. All cause mortality was 33% (n=1817), of which 35% (n=640) were cardiovascular related. Age more than 60 years (hazard ratio [HR] 2.43; 95% confidence interval [CI] 2.2 to 2.7; P<0.0001), ischaemic heart disease (IHD) (HR 1.97; 95% CI 1.79–2.16; P<0.0001), diabetes mellitus (HR 2.31; 95% CI 2.06–2.60; P<0.0001), cerebrovascular accident (HR 1.90; 95% CI 1.72–2.10; P<0.0001), peripheral vascular disease (HR 2.13; 95% CI 1.91–2.38; P<0.0001) and peritoneal dialysis, (HR 1.56; 95% CI 1.39–1.75; P<0.0001) were identified as independent risk factors for death via multivariate analysis.
There were 915 patients who developed ACS (5.6/100 person years). Predictive risk factors for ACS include an older age (HR 1.77; 95% CI 1.55–2.02; P<0.0001), IHD (HR 3.06; 95% CI 2.67–3.51; P<0.0001), diabetes mellitus (HR 2.78; 95% CI 2.34–3.31; P<0.0001), cerebrovascular accident (HR 1.76; 95% CI 1.53–2.04; P<0.0001), peripheral vascular disease (HR 2.17; 95% CI 1.86–2.54; P<0.0001) and Malay race (HR 1.17; 95% CI 1.01–1.36; P=0.04).
Conclusions: Mortality and ACS rates of ESRF patients on RRT are high in our cohort. Older patients, patients with known IHD and comorbidities had poorer outcome. Peritoneal dialysis and Malay race were found to be independent risk factors for death and ACS respectively. Further studies needs to be performed to elucidate the causes.

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Prevalence and short-term prognosis of familial hypercholesterolemia in patients with first acute coronary syndrome

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Purpose: Familial Hypercholesterolemia (FH) is a hereditary disorder predisposing to substantial increase of cholesterol levels and premature coronary heart disease (CHD). Its prevalence in patients with acute coronary syndromes (ACS) has not been fully studied. We sought to evaluate the prevalence and impact on short-term prognosis of probable/ possible FH in patients with first ACS and, in particular, with first premature ACS.
Methods: From Oct 2010 to Oct 2015, patients with ACS were included on a national multicentre registry. FH prevalence was evaluated based on cholesterol levels, familial history of premature CHD and premature index ACS, according with two validated sets of criteria: Dutch Lipid Clinic Network Criteria (DuC) and Simon Broome Criteria (SBC). Patients with possible confounding factors as prior coronary heart disease (age of diagnosis not included in the registry), previous statin therapy and without cholesterol levels analysis in the first 24 hours were excluded. Primary endpoint was defined as a composite of all-cause death, re-infarction and ischemic stroke during hospitalization.
Results: Among 3314 patients with first ACS, 496 (11.2%) had possible FH and 21 (1.4%) had probable FH according to DuC. The SBC identified 109 (2.5%) patients with probable FH. In a multivariate analysis, possible /probable FH was not an independent predictor of the composite endpoint (OR=0.27; CI 95% 0.06–1.16, p=0.079). At the time of hospital admission for premature first ACS, 412 (28%) patients had possible FH and 21 (1.4%) had probable FH according to DuC. Sixty-four (4,2%) patients achieved the SBC of probable FH. Except for dyslipidaemia and family history of premature CHD, the prevalence of cardiovascular risk factors was similar between patients with possible/probable FH and no FH (Hypertension: p=0.491; Diabetes: p=0.516; Smoking: p=0.485). There were no differences in the ACS type (ST-segment elevation ACS: possible/ probable FH 59.1% vs. no FH 60.4%, p=0.665) and in the incidence of the composite endpoint (0.4% vs. 1,8%, p=0,051). Patients with possible/probable FH had a higher prevalence of multivessel disease (37% vs. 29%, p=0.009)
Conclusions: FH is common among patients hospitalized with first ACS, especially in those with premature ACS. In premature ACS, this phenotypic diagnosis was associated with greater severity of CHD. Its identification with validated criteria may result in a more aggressive and targeted lipid lowering treatment.

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LDL cholesterol levels and 1-year hospitalization rate and mortality in patients with a previous ACS or coronary intervention

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Introduction: LDL cholesterol (LDL) levels have significant prognostic implications in patients with cardiovascular diseases. Nowadays, it's known that LDL levels are independently and directly related with coronary artery disease (CAD). Several studies have shown that achieving LDL levels below 70 mg/dL is beneficial in the secondary prevention of CAD.
Purpose: In this study we pretend to analyze a population of patients admitted to a Cardiology department with an acute coronary syndrome (ACS) and past medical history of percutaneous coronary transluminal angioplasty (PCTA), coronary artery bypass graft surgery (CABG) or previous acute myocardial infarction (AMI). In this subgroup of patients, we pretend to characterize the differences in baseline characteristics, as well as 1-year mortality and hospitalization rate between patients with fasting LDL levels higher than 70 mg/dL versus LDL levels equal or lower than 70 mg/dL measured during hospital admission.
Methods: We performed a retrospective, descriptive and correlational study with all patients admitted with an ACS in a Cardiology department between the 1st of October 2010 and 31st of August 2014. All patients with an ACS and past history of PCTA, CABG or AMI were included. We divided the patients in two groups: those with LDL equal or lower than 70 mg/dL and those with LDL higher than 70 mg/dL. We compared the baseline characteristics, admission data and therapy during hospitalization. The 1-year follow-up was done by phone call by a Cardiologist. We performed a univariate and multivariate statistical analysis of mortality and hospitalization at 1-year using SPSS.
Results: A total of 793 patients were included in this study, 628 (79,2%) of whom were male. During hospital admission, 105 (13,2%) of patients had LDL levels equal or lower than 70 mg/dL and 688 (86,8%) had LDL levels higher than 70 mg/dL. The following factors were significantly associated with LDL levels higher than 70 mg/dL: past history of smoking (p=0,015), PCTA (p=0,039), dementia (p=0,049), diabetes mellitus (p<0,01), CABG (p=0,017), stroke/transient ischemic attack (p=0,014) and coronary artery angioplasty during hospital admission (p=0.011). The absence of hypertension (p=0,043) and previous therapy with statin (p<0,01) were also significantly associated with LDL levels higher than 70 mg/dL.
There were no differences in mortality (p=0,076) or hospitalization rate (p=0,121) at 1-year follow-up between the two groups using a multivariate statistical analysis.
Conclusions: The vast majority of patients with an ACS and past history of PCTA, CABG or AMI have uncontrolled LDL levels according to current guidelines. Nevertheless, in this subgroup of patients, there were no differences in mortality and hospitalization rate at 1-year between those with a LDL equal or lower than 70 mg/dL compared to those with an LDL higher than 70 mg/dL measured during hospital admission.

STEMI TREATMENT AND OUTCOMES

P931 | BEDSIDE

Prevalence and outcomes of early vs. late stent thrombosis in patients presenting with ST- segment elevation myocardial infarction

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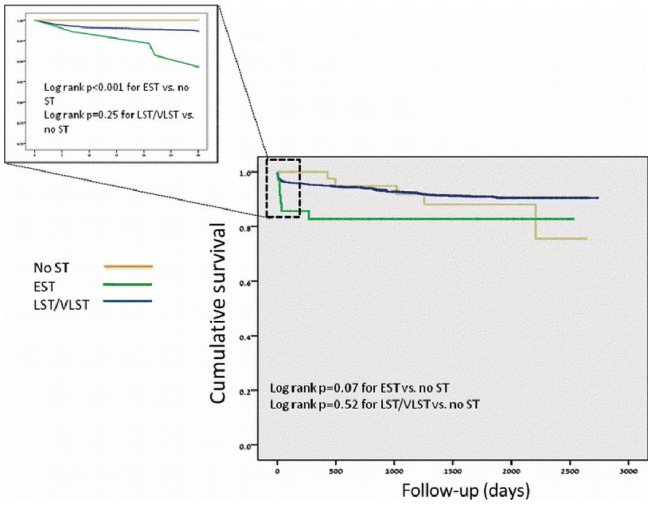
Background: Previous reports demonstrated inconsistencies regarding outcomes and prognosis of stent thrombosis (ST) when stratified to the time of occurrence. We evaluated the incidence and possible prognostic implications of early, late and very late ST presenting as ST elevation myocardial infarction (STEMI) in a large cohort of consecutive patients undergoing primary percutaneous coronary intervention (PCI).
Methods: We retrospectively studied 1722 STEMI patients treated by primary PCI.
The presence of ST was determined using the Academic Research Consortium definitions.
Patients were evaluated for the time of ST (early, late/very late), in-hospital outcomes as well as long term mortality.
Results: A total of 83/1722 (4.8%) patients demonstrated definite ST, 35 (42%) of whom had early ST, while 48 (58%) had late/very late ST. Patients with early ST had more adverse events during hospitalization, as well as higher 30 day mortality compared to patients with late/very late or no ST (11% vs. 0 vs. 2%, p<0.001). In

In hospital clinical outcomes

Variable	no ST (n=1639)	Early ST (n=35)	P*	Late or very late ST (n=48)	P†
Emergency CABG	31 (2%)	2 (5.5%)	0.15	2 (4%)	0.24
Mechanical ventilation	70 (4%)	4 (11%)	0.06	1 (2%)	0.71
Heart failure	133 (8%)	6 (17%)	0.06	6 (12%)	0.28
Ventricular arrhythmia	98 (6%)	4 (11%)	0.16	4 (8%)	0.53
Acute kidney injury	165 (10%)	10 (28%)	0.01	8 (17%)	0.13
Bradyarrhythmia	48 (3%)	1 (3%)	0.99	3 (6%)	0.17
30 days mortality	40 (2%)	4 (11%)	0.01	0 (0)	0.63

ST = stent thrombosis, CABG = coronary bypass artery graft. *P between early ST and no ST values. †P between late ST/VLST and no ST values.



Cumulative short and long term survival

a multivariate logistic regression model, early ST was an independent predictor of 30-day mortality (OR 6.6, 95% CI 1.1–38, P=0.033) No significant difference was observed in long term mortality between patients presenting with early, late/very late ST or no ST.
Conclusions: Among STEMI patients, the presence of early ST on PCI is independently associated with higher 30-day mortality

P932 | BEDSIDE
Diabetic vs. non-diabetic patients with ST-elevation myocardial infarction: comparison of cardiovascular risk profile, severity of infarction and mortality. Results from a STEMI-registry

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Introduction: Despite the importance of diabetes mellitus in the pathogenesis of coronary artery disease (CAD) its interaction with other cardiovascular risk factors has not been clarified. Aim of this study was to compare diabetic (Diab) vs. non-diabetic patients (nonDiab) admitted with ST-elevation myocardial infarction (STEMI) in term of their cardiovascular risk profile, severity of STEMI and prognosis.
Methods: Since 2006 all patients with STEMI from a large metropolitan region in northwest Germany (roughly 1 million inhabit.) are documented in a STEMI-registry. The comparative analysis of Diab vs. nonDiab was made in a multivariate logistic regression model.
Results: Of the 6909 pts. admitted between Jan. 2006 and Sep. 2015 with STEMI 1313 (19%) had overt diabetes while 5596 (81%) did not. Diabetics were older (67.1±12 vs. 63.1±13 years, p<0.01) and more likely to be female (33% vs. 27% in nonDiab, p<0.01). A multivariate analysis (adjusted to age and gender) revealed that diabetics showed a higher prevalence of obesity (BMI>30 kg/m^2) and hypertension. However they were less likely to smoke, suffer hypercholesterolemia or report a positive family history for CAD (table). CAD on admission was more severe in diabetic patients (2.1±0.8 vessels diseased vs. nonDiab 1.8±0.8, p<0.01). This remained significant after adjusting for confounders: 3-VD Diab vs. nonDiab OR 1.6, 95% CI 1.4–1.9, p<0.01. While early in-hospital mortality (<72h: Diab: 3.8% vs. 3.3% in nonDiab, p=0.3) was similar, diabetic pts. had elevated 30-days-(13.4% vs. 9.6%, p<0.01) and 1-yr. mortality rates (17.5% vs. 12.9%, p<0.01) and showed higher rates of reinfarction or target-lesion/vessel-revascularisations within 1 year (8.4% vs nonDiab. 5.6%, p<0.01). Adjustment in a COX-regression-analysis confirmed the higher MACCE-rates (death, myocard. reinfarction, cerebral events) for diabetic pts. within 1 year: HR 1.25, 95% CI 1.06–1.47 p<0.01.

Multivariate analysis of risk factors

	Obesity	Arterial hypertension	Positive FH for CAD	Smoking	Total cholesterol ≥240 mg/dl
OR (95% CI)*	2.4 (2–2.8)	1.8 (1.5–2.2)	0.74 (0.6–0.9)	0.73 (0.6–0.9)	0.66 (0.54–0.82)
P	<0.01	<0.01	<0.01	<0.01	<0.01

*OR >1 more likely in diabetics, OR<1 less likely in diabetics.

Conclusions: Diabetic patients admitted with STEMI showed higher rates of obesity and arterial hypertension while they were less likely to smoke, show hypercholesterolemia or report a positive family history for CAD. These results indicate that metabolic syndrome on the one hand and smoking, hypercholesteremia and genetic predisposition to CAD on the other might constitute two separate pathways leading to CAD. Diabetes was furthermore associated with a more advanced CAD at time of admission and higher MACCE-rates within 1 year.

P933 | BEDSIDE
Major bleeding in ST-segment elevation acute myocardial infarction: population characteristics, predictors and in-hospital prognostic impact

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Introduction: Major bleeding (MB) is a severe complication that can occur in ST-segment elevation acute myocardial infarction (STEMI) patients (pts) and its ocurrence could influence therapeutic management and prognosis.
Purpose: Characterization of pts with STEMI and MB (defined by the GUSTO criteria). Evaluation of MB's impact in therapeutic management of pts, in in-hospital mortality and major adverse events. Define potential predictors of MB ocurrence in STEMI pts.
Methods: We studied 4306 pts with STEMI from a National Multicentric Registry, and defined 2 groups: 1) Pts with MB; 2) Pts without MB. Data from pts demographics, previous medical history, anti-thrombotic medication, MI location, reperfusion strategy, coronariography/angioplasty was recorded. We defined the following in-hospital adverse events (IHAE): re-infarction, heart failure (HF), cardiogenic shock (CS), stroke, need for invasive mechanical ventilation (MV) and blood transfusion (BT). In-hospital mortality was compared and a multivariate analysis was perfomed to identify predictors of MB occurrence.
Results: In STEMI pts, MB was documented in 1.7% (75 pts). These pts were older (71±12 vs 64±14 years; p<0.001), more likely to be female (36.0 vs 25.3%; p=0.035) and with medical history of hypertension (78.1 vs 61.4%; p<0.004), chronic kidney disease (8.2 vs 3.4%; p=0.04), cancer (12.2 vs 4.2%, p=0.004), chronic obstructive pulmonary disease (COPD) (14.7 vs 3.9%, p<0.001) and previous bleeding (8.2 vs 1.3%, p<0.001). In group 1, pts were more likely to have an anterior MI (60.0 vs 47.6%, p=0.033), evolving in Killip II-IV (22.7 vs 13.0%, p=0.01). There were no diferences in the strategy of reperfusion, either primary percutaneous coronary intervention (94.9 vs 90.9%, p=0.287) or fibrinolysis (5.1 vs 9.1%, p=0.287). In hospital, pts with MB were more likely to receive Fondaparinux (16.0 vs 6.8%, p=0.002), without diferences regarding other anti-thrombotic agents, to receive >1 coronariographies (16.4 vs 8.2%, p=0.015) and by femoral access (54.4 vs 31.0%, p<0.001). There were no diferences regarding the presence of multivessel disease (54.7 vs 44.3%, p=0.096). Pts with MB were more likely to receive MV (5.3% vs 1.6%, p=0.001) and BT (40.0 vs 1.3%, p<0.001) but without diferences regarding the other IHAE. In-hospital mortality was higher in pts with MB (16.0 vs 4.6%, p<0.001). Using multivariate analysis, there were identified as predictors of MB the following: previous history of bleeding (OR 6.53 [2.41–17.64] CI 95%, p<0.001), hypertension (OR 2.2 [1.10–4.40] CI 95%, p=0.025), COPD (OR 3.90 [1.77–8.57] CI 95%, p=0.001), and use of Fondaparinux (OR 2.48 [1.22–5.07] CI 95%, p=0.013).
Conclusions: Major bleeding occured in 1.7% of pts with STEMI and was associated with higher in-hospital mortality and higher need for MV and BT. There were identified as predictors of MB in STEMI pts, the previous history of bleeding, hypertension, COPD and Fondaparinux administration during hospitalization.

P934 | BEDSIDE
LV remodeling and heart failure after anterior STEMI in women in the CIRCUS study

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Background: Previous studies report that women are more likely to develop heart failure after acute myocardial infarction. Whether this might be related to a worse adverse left ventricular (LV) remodeling after infarction remains unclear.
Objective: To examine whether gender might influence LV remodeling and incidence of subsequent heart failure after ST-elevation myocardial infarction (STEMI)
Methods: STEMI patients (included in the CIRCUS trial) presenting within 12 hrs of symptom onset with LAD coronary artery occlusion underwent PCI. Patients had echocardiography before discharge and at 1 year post-STEMI to assess LV remodeling. Infarct size was estimated by the creatine kinase peak (IU/L).
Results: 174 women and 796 men were included. Women were significantly older than men and had more hypertension. CK peak was significantly lower in women than in men. Both at baseline and at 1 year, women exhibited lower end-diastolic (LVEDV) and end-systolic (LVESV) volumes than men (Table). Increase in LV volumes within 1 year after MI was similar in both groups, however the incidence of heart failure was significantly higher in women compared to men (25% vs 17%, respectively; p=0.009), upon univariate analysis. After adjustment on several confounding factors, the association of female gender with heart failure events was not significant.

Echocardiographic measurements, CK peak

	Women	Men	p
LVEF at one year (%)	52±12	52±10	P=0.143
LVDV at one year (ml/m^2)	56±20	65±20	P<0.001
LVSV at one year (ml/m^2)	29±18	33±16	P<0.001
LVEF (%) variation from baseline to one year	4±10%	3±9%	P=0.247
% of LVDV variation from baseline to one year	12.8±26.9%	18.5±31.9%	P=0.107
CK peak (IU/L)	3637±2423	4325±2755	P=0.008

Conclusion: In anterior STEMI patients, despite smaller infarct size and comparable LV remodeling, women displayed an increased incidence of heart failure associated with their higher rate of comorbidities.

P935 | BENCH
Effect of the off-pump CABG on the outcome survival

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Background: If Coronary Artery Bypass Grafting (CABG) without cardiopulmonary bypass or cardioplegia (off-pump CABG, or OPCAB) is better than standard CABG is a subject under constant debate. The aim of our study was to assess the OPCAB survival outcome using Inverse Probability of Treatment Weighting (IPTW).
Methods: We used data on 823 patients undergoing coronary artery bypass (CABG) surgery. The treatment of interest was whether the patient had off-pump CABG (OPCAB). The main outcome was survival at follow up. IPTW was employed to create a synthetic sample and balance diagnostics was carried out using either quantitative or qualitative evaluations. The former employed the weighted standardized difference to compare means, prevalences, higher-order moments, and interactions. The latter used graphical methods to compare the distribution of continuous baseline covariates between treated and control subjects in the weighted sample. Adjusted Kaplan–Meier survival curves and log-rank test were used and the absolute difference in the probability of late death occurring within follow-up was assessed. Cox proportional hazards model was employed with robust sandwich-type variance estimator to estimate the statistical significance of the treatment effect.
Results: Standardized differences were used to compare the balance in measured baseline covariates between those who did and did not undergo OPCAB (Figure 1). The absolute reduction in the probability of late death within 51 months due OPCAB treatment was 0.005 for the weighted sample using average treatment effect (ATE) weights and 0.004 for weighted sample using average treatment effect for treated (ATT) weights and the number needed to treat were 197 and 239.The estimated hazards ratios were 0.811 (95% CI: 0.451–1.458) and 0.817 (95% CI: 0.437–1.528) for ATE and ATT, respectively. In our tutorial case, we estimated relative survival effects using IPTW: using ATE weights, moving an entire population from standard bypass to OPCAB it reduced the hazard of death by 18.9% whereas, employing ATT weights, among treated subjects OPCAB reduced the hazard of death by 18.3%.
Conclusions: Our result confirmed that OPCAB is a feasible and safe strategy of treatment having better results than standard CABG in the late FU.

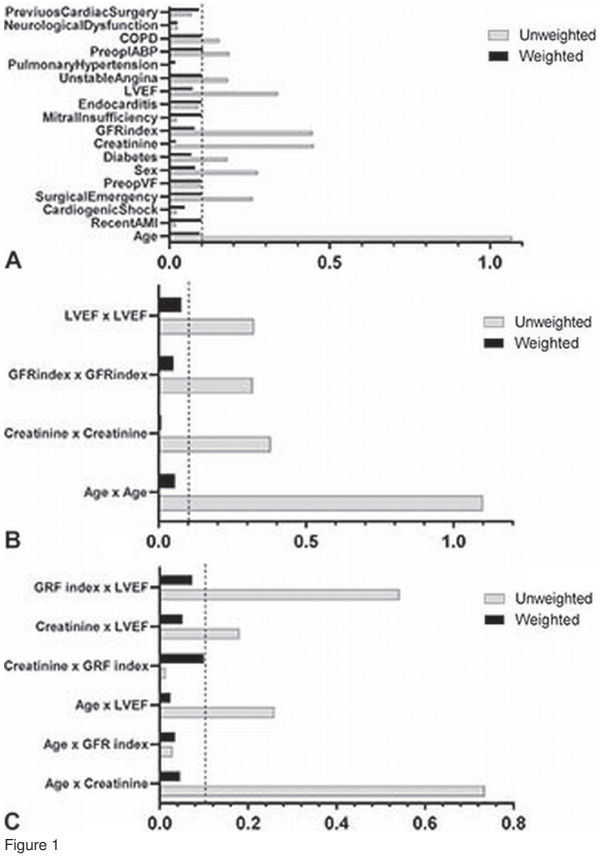

Figure 1

P936 | BEDSIDE
Intravenous Beta-blocker therapy for ST-Segment Elevation Myocardial Infarction could be associated with higher short-term mortality: a Swedish Nationwide Observational Study

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Background: Beta-blockers (BB) in the early phase of myocardial infarction have been shown to reduce infarct size, improve left ventricular ejection fraction (LVEF) and increase survival. However, the value of intravenous (IV) BB is unclear.
Methods: Using the national SWEDEHEART registry, we identified all patients with ST-segment elevation myocardial infarction (STEMI) undergoing percutaneous coronary intervention (PCI) with upstream dual antiplatelet therapy (DAPT) between 2006 and 2013. Patients with cardiogenic shock and cardiac arrest at presentation were excluded. Patients that received IV BB were compared to those that did not. The primary endpoint was all-cause mortality within 30 days. Secondary endpoints were in-hospital mortality, LVEF <40% at discharge and development of in-hospital cardiogenic shock. Instrumental variable analysis was performed as a secondary model with individual PCI-centers as a preference-based instrument to adjust for hidden confounders.
Results: Out of 16,909 patients, 2,876 (17.0%) were treated with IV BB. After adjusting for confounders, patients treated with IV BB had higher all-cause mortality within 30 days (table). Patients treated with IV BB were also more likely to develop cardiogenic shock and to be discharged with LVEF <40% and in-hospital. However, the instrumental variable analysis could not confirm an association between IV BB and mortality (table).
Conclusion: In this large nationwide Swedish observational study, we found no evidence for a benefit with IV BB in patients with STEMI treated with PCI and upstream DAPT. On the contrary, the use of IV BB was associated with higher short-term mortality, LVEF <40% at discharge and a higher risk of in-hospital cardiogenic shock incidence. However, instrumental variable analysis did not confirm the association between IV BB and higher mortality indicating possible confounding.
Acknowledgement/Funding: The Swedish Heart and Lung Foundation, Swedish Scientific Research Council, SSF (TOTAL-AMI), KAW, ALF, and Skåne University Hospital

P937 | BEDSIDE
Improvement of arterial stiffness and LV myocardial deformation in patients with coronary artery disease and diabetes mellitus type 2 after 6-month treatment with metformin and agonists of GLP-1R

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Agonists of Glucagon like peptide-1 receptors (GLP-1R) used in the treatment of diabetes mellitus (DM) type 2. Their action is based on the increase in glucose-dependent insulin secretion. The purpose of this study is to investigate in patients with coronary artery disease (CAD) and type 2 diabetes changes in arterial stiff-

Abstract P936 – Table 1. Results of primary and secondary endpoints

	IV BB (+)	IV BB (–)	Unadjusted HR (95% CI)	Multivariable adjusted HR (95% CI)	IV 2sls RR/100 patients (95% CI)
30 day mortality	103 (3.6%)	368 (2.6%)	1.37 (1.10–1.70)**	1.44 (1.14–1.83)**	–3.34 (–9.99–3.31)
In-hospital mortality	77 (2.7%)	272 (2.0%)	1.13 (0.88–1.46)	1.23 (0.93–1.61)	
			Unadjusted OR (95% CI)	Multivariable adjusted OR (95% CI)	
In-hospital re-infarction	30 (1.0%)	103 (0.7%)	1.43 (0.95–2.15)	1.65 (1.03–2.63)*	
LVEF at discharge ≤39%	743 (31.4%)	2138 (18.1%)	2.07 (1.88–2.29)***	1.70 (1.51–1.92)***	
Cardiogenic shock	56 (1.9%)	189 (1.3%)	1.45 (1.07–1.95)*	1.53 (1.09–2.16)*	

*p<0.05; **p<0.01; ***p<0.001HR, hazard ratio; OR, odds ratio; RR, risk reduction, 2sls, two-stage least square.

ness, LV myocardial deformation and glycocalyx thickness after 6-month treatment with metformin and agonist GLP-1R.
Methods: We examined 50 patients with type 2 diabetes and CAD (age:52±10 years) and 25 controls of similar age and sex and no atherosclerotic risk factors. Twenty five subjects received metformin and GLP-1R agonist and twenty five subjects received only metformin. In all subjects measured at baseline and after 6-month treatment: a) carotid-femoral pulse wave velocity (PWVc – Complior SP ALAM), central systolic blood pressure (cSBP), augmentation index (AI) of the aortic pulse wave (Arteriograph TensioMed); b) S', E' and E'/A' of mitral annulus by Tissue Doppler; c) LV longitudinal strain (GLS), systolic (LongSr) and diastolic (LongSrE) strain rate, peak twisting (pTw), peak twisting velocity (pTwVel) and peak untwisting velocity (pUtwVel) using speckle tracking echocardiography. The degree of LV untwisting was calculated as the percentage difference between peak twisting and untwisting at mitral valve opening (%dpTw – UtwMVO), at peak (%dpTw-UtwPEF) and end of early LV diastolic filling (%dpTw-UtwEDF); d) perfused boundary region (PBR) of the sublingual arterial microvessels (ranged from 5–25μm) using Sideview, Darkfield imaging (Microscan, Glycocheck). Increased PBR is considered an accurate index of reduced endothelial glucocalyx thickness because of a deeper RBC penetration in the glucocalyx; e) Flow mediated dilatation (FMD) of the brachial artery and percentage difference of FMD (FMD%).
Results: Compared to controls, diabetics with CAD had higher PWVa (10.3±2.2 vs. 8.1±1.9m/sec), AI (27.9±15 vs. 19.4±14.7%), PWVc (11.8±3.2 vs. 8.8±1.3m/sec), cSBP (136±20 vs. 119±18mmHg), PBR (2.1±0.2 vs 1.89±0.1μm) and lower GLS (–15±3 vs. –18±3%), LongSr (–0.78±0.1 vs. –0.96±0.2l/sec), LongSrE (0.77±0.29 vs. 1.2±0.3l/sec), S', E' and E/A ($p<0.05$ for all comparisons). Baseline FMD was related with %dpTw-UtwPEF ($r=0.65$, $p<0.05$). Six months later patients that received metformin and GLP-1R agonist achieved a reduction of PWVc (11.8±2.5 vs. 10.3±3.3m/sec, $p<0.05$) in parallel with an increase of pUtwVel (–97±49 vs. –112±52 deg, $p<0.05$), %dpTw-UtwMVO (31±10 vs. 40±14), %dpTw-UtwPEF (43±19 vs. 53±22) and FMD% (8.9±3 vs. 13.2±6, $p<0.01$). There were no statistically significant differences in patients that received only metformin. Reduced PWVc was related with reduced SBP ($r=0.62$), cSBP ($r=0.55$) and increased LongsrE ($r=–0.50$), %dpTw-UtwEDF ($r=–0.56$)respectively ($p<0.05$ for all associations).
Conclusion: Six-month treatment with metformin and agonist GLP-1R improves arterial stiffness, LV myocardial strain, twisting and untwisting velocity in patients with DM and CAD.

P938 | BEDSIDE

Is prehospital intravenous morphine administration associated with a lower infarct-related artery patency? Insight from a ST-segment elevation myocardial infarction prospective registry

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Background: About ST-Elevation Myocardial Infarction (STEMI), recent data suggested that morphine administration attenuate the antiplatelet agents efficacy.
Purpose: We aimed at determining the impact of pre hospitalization morphine intra venous administration on the infarct-related artery patency, defined as pre-primary percutaneous coronary intervention (PPCI) Thrombolysis In Myocardial Infarction (TIMI) flow grade 3.
Methods: This is a 5-years prospective multi-centric registry of patients referred by emergency medical service for a STEMI, with a coronary angiogram in the acute phase (<6 hours after admission). Patients treated by fibrinolysis were excluded. We compared the pre-PPCI TIMI flow (3 vs <3) in patients treated (group 1) vs untreated (group 2) with intra venous morphine before their admission in the hospital. A univariate analysis was performed, then all parameters with a p value <0.20 were included in a multivariate logistic regression.
Results: 553 patients were included (age 62±13; male: 445 (85%)): 168 patients in group 1, and 385 in group 2. Median delays were: from onset of symptoms to 1st call for medical assistance: 31 minutes, from 1st medical contact to arterial puncture: 77 minutes, from anti thrombotic treatment administration to arterial puncture: 51 minutes. The P2Y12 inhibitor associated with aspirin was clopidogrel in 234 patients (47%), prasugrel in 254 (51%), and ticagrelor in 8 (2%). Pre-PPCI TIMI flow grade was 3 in 23% of patients. Post-PPCI TIMI flow grade was 3 in 95% of patients. 42 patients (7%) died during the in-hospital follow-up. 11 patients (2%) presented major in-hospital bleeding complications (BARC 3 and 5). 11 patients (2%) presented acute/subacute stent thrombosis. Univariate analysis found no difference in the pre-PPCI TIMI flow in the 2 groups (21% in group 1, vs 23% in group 2, p=0.52). Furthermore, after adjustment for all the significantly different parameters in the 2 groups, we still didn't find any differences in pre-PPCI TIMI flow (Hazard Ratio: 0.9; 95% CI: 0.54–1.66; p=0.85), in post-PPCI TIMI flow (HR: 0.72; 95% CI: 0.26–2.02; p=0.53), or in in-hospital mortality (HR: 0.93; 95% CI: 0.40–2.20; p=0.85). Nevertheless, we found a trend to an increase of acute/subacute stent thrombosis in group 1 (HR: 2.82; 95% CI: 0.85–9.36; p=0.09).
Conclusions: In this registry, 30% of patients with STEMI referred by emergency medical system for a PPCI strategy received intra venous morphine before their admission. This doesn't seem to be associated with a lower rate of infarct-related artery patency.

P939 | BENCH

Characteristics, management, and long-term outcome of acute myocardial infarction type 2. The FAST-MI 2010 registry

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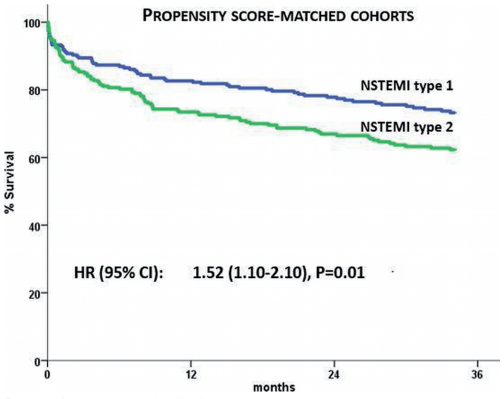
Background: Myocardial infarction type 2 (MIT2) is characterized by an ischemic imbalance, where a condition other than coronary artery disease contributes to myocardial necrosis documented by a dynamic increase in cardiac markers.
Methods: We evaluated the characteristics associated with MIT2 and 3-year mortality in the French FAST-MI 2010 registry, which collected information on all patients admitted for AMI in 76% of French institutions during a one-month period, with a possible extension up to one additional month, at the end of 2010. Cox multivariate analysis and matching on a propensity score for MIT2 were used to adjust for confounders.
Results: Of 4169 patients admitted to ICCU with AMI, 2364 (57%) had STEMI, 1567 (38%) NSTEMI type 1 and 238 (6%) MIT2. Compared with NSTEMIT1, those with MIT2 were older (76±12 vs 67±14 yrs), more often female (40 vs 29%), and had more frequent hypertension (77 vs 59%), diabetes (43 vs 24%), or non-CV comorbidity (41 vs 27%) (all P values <0.001). History of previous MI, PCI or CABG did not differ significantly. Initial presentation was characterized by heart failure (51 vs 10%), atrial fibrillation (18.5 vs 5%), cardiac arrest or syncope (17 vs 3%), and/or atypical chest pain (29 vs 9%). Early (<48 h) management differed markedly: aspirin (91 vs 98%), clopidogrel (85 vs 91%), prasugrel (5.5 vs 15%), GPIIbIIIa-i (12 vs 17.5%), LMWH (46 vs 60%), oral anticoagulant (7 vs 3%), coronary angiography (73.5 vs 94%), PCI (47 vs 68.5%). Triple vessel CAD was more frequent (33 vs 21%) and CABG used in 5% in both groups. LVEF was ≤40% in 32 vs 13%.
Three-year survival was 63% vs 87% (P<0.001). After Cox multivariate adjustment on baseline characteristics, HR for 3-yr death was 1.64, 1.27–2.13, P<0.001. Further adjustment on use of PCI and discharge medications attenuated but did not suppress the increased risk (HR 1.40, 1.04–1.89, P=0.03). In a population matched on a propensity score including demography, risk factors, history, and type of institution (238 pairs), 3-year survival was 63 vs 74% (P=0.01) (Figure).



Propensity score matched cohorts

Conclusion: NSTEMI type 2 patients are characterized by older age and more frequent non-CV comorbidity; their initial management is less in line with guidelines, and they have a higher 3-year mortality, even when adjusted on early myocardial revascularization. This entity should deserve specific attention from the cardiology community.
Acknowledgement/Funding: AstraZeneca, Daiichi Sankyo, Eli-Lilly, GSK, MSD, Novartis, Sanofi

P940 | BEDSIDE

STEMI in patients at advanced age (>80 years) compared to younger patients. Results of a 10-year follow up of a myocardial infarction registry (MIRLU)

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Background: Advanced age is known as a strong predictor for in-hospital mor-

tality of patients presenting with ST-elevation myocardial infarction (STEMI). Particularly octo- and nonagenerians with STEMI have shown increased in-hospital mortailty rates in clinical practice. However, to date only sparse data exist on this particular patient population. This data might help to improve the treatment and decrease mortality rates of this population in the future.
Methods: We retrospectively analysed data of the Myocardial Infarction Registry Ludwigshafen (MIRLU), which is an all-comers, real-world myocardial infarction registry. All patients with acute STEMI who were admitted to a hospital with an on site interventional cardiology between 2000 and 2009 were included in this analysis.
Results: Between 2000 and 2009 3143 patients with acute STEMI were admitted to hospital and enrolled into the registry. 391 (12.4%) of all patients were older than 80 years at time of enrollment.

	≥80 years (n=391)	<80 years (n=2752)	p-value
Age (years. median)	83.9	60.7	<0.001
Women	52.9%	25.6%	<0.001
Prior myocardial infarction	19.2%	13.4%	<0.01
Prior stroke/TIA	6.6%	4.8%	ns
Diabetes mellitus	37.6%	26.4%	<0.001
Renal impairment	20%	6.2%	<0.001
Atrial fibrillation	14.9%	5.4%	<0.001
Cardiogenic shock	18.9%	10.3%	<0.001
Left bundle branch block	8.6%	2.7%	<0.001
Coronary angiography	93.4%	98.7%	<0.001
PCI	78%	85.5%	<0.001
TIMI III – post PCI	93.2%	93.9%	ns
In-hospital mortality	18.7%	5.2%	<0.001
Mean in-hospital stay (days)	8.2	8.5	ns

Conclusion: In clinical practice every tenth patient presenting with STEMI is older than 80 years today. These patients in advanced age are more likely female, significantly show more comorbidities and present in a worse clinical condition compared to younger patients with STEMI. Invasive procedures, like coronary angiography and PCI, are performed significantly less often and in-hospital mortality is three times higher compared to younger patients.

P941 | BEDSIDE
The impact of elderly female on 30 days mortality in patients with ST elevation myocardial infarction

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Introduction: The number of elderly patients with ST elevation myocardial infarction (STEMI) has been increasing in Japan. Previous reports demonstrated that age or female gender was associated with poor outcomes. However, there are few reports discussing about the impact of elderly female on clinical outcomes in STEMI as compared to elderly male, young female, and young male.
Purpose: To determine the association of elderly female with 30 days mortality in patients suffering STEMI.
Methods: Data were collected from our cardiovascular workshop registry, a prospective multicenter cohort in an urban area of Japan, during May 2010 to June 2015. 1572 consecutive STEMI patients were enrolled. All patients carried by ambulance and underwent primary percutaneous coronary intervention after admission. Patients were divided into four groups according to age (>80 years old) and gender.
Results: Show in Table. Elderly female, elderly male, young female, systolic blood pressure <100 mmHg, Killip class, old myocardial infarction, symptom onset to balloon (SB) time <180 min, and final TIMI flow grade were entered in multivariate analysis. Elderly female (odds ratio (OR) 2.95, p=0.001), worse Killip class (OR 2.67, p<0.0001), and worse final TIMI flow grade (OR 0.29, p<0.0001) were the independent predictors of 30 days mortality in STEMI.

Results

	All n=1572	Elderly female n=135	Elderly male n=159	Young female n=210	Young male n=1068	p value
Age (yrs)	67.5±12.8	85.5±4.2	84.3±3.9	68.3±8.7	62.6±10.7	<0.0001
SBP (mmHg)	135±36.6	131±34.8	124±35.8	137±37.8	137±36.4	0.0002
Killip class 1 (%)	1121 (72.0)	74 (54.8)	90 (57.0)	156 (75.0)	801 (75.8)	<0.0001
LAD disease (%)	772 (49.6)	66 (50.8)	79 (49.7)	89 (42.8)	538 (50.9)	0.2
OMI (%)	128 (8.2)	16 (11.9)	21 (13.2)	9 (4.3)	82 (7.7)	0.006
SB time (min)	226±210	268±264	259±238	264±239	209±188	<0.0001
SB time <180 min (%)	964 (61.3)	74 (54.8)	86 (54.1)	106 (50.5)	698 (65.4)	<0.0001
Initial TIMI flow 0 (%)	1048 (66.8)	98 (73.1)	105 (66.0)	142 (67.6)	703 (66.1)	0.42
Final TIMI fow 3 (%)	1468 (93.7)	116 (86.6)	143 (89.9)	199 (94.8)	1010 (94.9)	0.0004
30 days mortality (%)	105 (6.7)	24 (17.8)	17 (10.7)	9 (4.3)	55 (5.2)	<0.0001

Continuous data are presented as mean ± standard deviation. Categorical variables are shown as percentages. SBP, systolic blood pressure; LAD, left anterior descending artery; OMI, old myocardial infarction; SB, symptom onset to balloon.

Conclusions: Elderly female itself was associated with higher mortality in patients with STEMI, rather than worse hemodynamics or longer SB time.

P942 | BEDSIDE
Acute myocardial infarction in patients presenting with pacemaker rhythm

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Objective: With increasing life expectancy, the number of pacemaker patients is growing. Correct diagnosis of acute myocardial infarction is challenging in these patients, with potential consequences for appropriate and timely treatment. Very little is known about patients admitted with acute myocardial infarction and pacemaker rhythm. This study aims to present characteristics, current management and outcome of patients admitted for acute myocardial infarction with pacemaker rhythm.
Methods: Patients with acute myocardial infarction enrolled in the Swiss national AMIS-Plus infarct-registry between January 2005 and December 2015 were analyzed. All patients with either paced ventricular rhythm or sinus rhythm with intrinsic conduction were included in this study. Outcomes were compared with patients with acute myocardial infarction and with sinus rhythm using propensity score matching. The primary endpoint was in-hospital death.
Results: Data from 300 patients with paced rhythm and 27595 with sinus rhythm were analyzed. Patients with pacemaker rhythm were older (78.2 vs. 65.4y; p<0.001), had more comorbidities (Charlson Comorbidity Index (CCI) >1: 54.0% vs. 21.1%; p<0.001) and a higher rate of heart failure upon presentation (Killip class>2 11.0% vs 5.9%; p<0.001) compared with patients in sinus rhythm. Door to balloon time in patients with paced rhythm is markedly delayed compared to patients with sinus rhythm (280min vs. 85 min; p<0.001).Consequently crude mortality in patients with pacemaker was high (11.3% vs. 4.6%; p<0.001). However, when adjusted for gender, age, CCI>1 and Killip>2 (used in propensity matching for), mortality was similar in both groups (11.2% vs 10.5%; p=0.70). 67% of paced patients upon admission were categorized as "Non-STEMI" irrespective of the diagnostic difficulties inherent with pacemaker rhythm.
Conclusions: Pacemaker patients with acute myocardial infarction represent a high risk group with doubled crude mortality compared to patients in sinus rhythm without ventricular paced rhythm due to higher age and higher Killip class. Diagnosis is difficult and results in delayed treatment. Treatment algorithms in all patients with myocardial infarction and paced rhythm should be adapted to STEMI patients or left bundle branch block.

P943 | BEDSIDE
Observational monocentric registry "CARDIO-STEMI SANREMO": effects of morphine administration in STEMI patients and its association with clinical in-hospital outcomes and long-term mortality

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Introduction: Patients with ST-elevation myocardial infarction (STEMI) benefit from morphine treatment for pain relief but that can lead to a delayed absorption of the oral antiplatelet therapies with potential decreased treatment efficacy.
Purpose: To assess the burden of morphine on reperfusion therapy success and its impact on in-hospital clinical outcome and on long term follow-up.
Methods: From February 2011 and December 2014, 533 pts enrolled in the monocentric registry "CARDIO-STEMI San Remo" underwent urgent PCI. Two groups were identified according to morphine use: morphine yes (My) and morphine no (Mn).
Results: Over the 533 pts analyzed, 281 (52.7%) received morphine before PCI. Pt in My group were younger (average age 63.8 vs 67.4, p<0.01), with a lower rate of hypertension (51.2% vs 61.5%, p=0.02) but more often smokers (47.7% vs 32.5%, p<0.01). The call to the emergency medical service instead of driving themselves to an emergency room, the onset of symptoms overnight and anterior STEMI were more frequent in the My group (all p<0.05). New oral P2Y12 receptor inhibitors (ticagrelor or prasugrel) were administrated in 65.8% of pts in My group versus 57.1% in Mn group (p=0.04). Morphine use was not associated with differences in pre-PCI TIMI flow of the culprit vessel, in administration of GP IIb/IIIa receptor inhibitors or in the use of manual aspiration thrombectomy. ST-segment resolution ≥50%, considered as a reperfusion endpoint, was similar in the two groups (77.0% vs 77.9%, p=0.81). In-hospital mortality (2.1% vs 4.4%), in-hospital MACE [death, reinfarction, stroke, stent thrombosis] (3.9% vs 1.6%) and BARC bleeding ≥2 (7.1% vs 7.9%) were not different between the two groups. After adjusting for propensity score, no significant differences in the endpoints between the two groups were found. At a median follow up of 1038 days, Kaplan-Meier curves were similar, with a survival rate of 89.7% in My group versus 88.6% in Mn group (Log Rank p=0.971). After propensity score matching, the risk for all-causes mortality was not increased according to morphine use (HR=1.142 [0.606–2.153]).

Conclusions: Although some studies point out pharmacokinetics interaction between morphine and P2Y12 receptor inhibitors, in our experience morphine use in STEMI patients is not associated with worse in-hospital outcome and long-term mortality. Our data conform to the recent published French Registry FAST-MI.

P944 | BEDSIDE
Impact of gender in patients admitted with ST-elevation myocardial infarction on cardiovascular risk profile, severity of infarction and prognosis- results from a STEMI-registry

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Introduction: Data about the impact of female gender on cardiovascular risk profile, infarction-severity and prognosis in patients with ST-elevation-myocardial infarction (STEMI) have been incoherent.
Methods: All pts. admitted at a large heart center in northwest Germany between 2006–2015 were documented in a STEMI-registry and entered analysis which was performed in a multivariate model and for subgroups prestratified by their initial TIMI-risk-score for STEMI.
Results: Of 6909 STEMI-pts. admitted between Jan. 2006 and Sep. 2015, 1915 (27%) were female while 4994 (73%) were male. The proportion of women remained constant between 2006–2015: p (for trend) = 0.5. Women were on average 8 years older than men (69.6±13 vs. 61.6±12 yrs, $p<0.01$). Age-adjusted data showed higher prevalences for hypercholesterolemia (total cholesterol ≥240 mg/dl, OR 1.68, 95% CI 1.4–2.0, $p<0.01$) and arterial hypertension (OR 1.36, 95% CI 1.2–1.6, $p<0.01$) in women, while smoking was less common (OR 0.83, 95% CI 0.7–0.98, p=0.03). Despite their older age women showed less extensive coronary artery disease (1.87±0.82 vessels diseased vs. 1.95±0.84 in men, $p<0.01$), while the size of the myocardial infarction (peak creatine kinase/body-surface-area) was similar: 894±1008 U/l/m^2 in women vs. 950±1008 U/l/m^2 in men, p=0.1. The TIMI-risk-score for STEMI at admission (scale 0–14) was higher for women: 3.9±2.3 vs. 2.8±2.3 in men, $p<0.01$. Accordingly women had higher 1-yr.-mortality (18% vs. 11%, $p<0.01$) and 1-yr.-MACCE-rates (death, reinfarction, cerebral events): 22% vs. 15%, $p<0.01$. This disadvantage for women remained significant after adjustment in a Cox-regression (table). When pre-stratifying data by their TIMI-risk-score women showed similar 1-yr.-mortality rates: low score (0–3): 3% for women vs. 2% for men; medium score (4–7): 16% vs. 15% for men, high TIMI-score (≥8): 56% vs. 55% for men.

Charact. of female vs. male STEMI-pts

	3-vessel disease	Peak CK >1000 U/L/m^2	Primary PCI	1-year mortality*	1-year MACCE*
OR/HR*(95% CI)					
women vs. men	0.73 (0.6–0.8)	1.1 (0.8–1.2)	0.89 (0.8–1.1)	1.36 (1.1–1.6)	1.38 (1.2–1.6)
p	<0.01	0.5	0.16	<0.01	<0.01

*OR/HR adjusted for age, diabetes, Killip class, first coronary event.

Conclusions: Women which constituted 27% of patients with STEMI in this analysis were on average 8 years older than men at time of infarction. While women showed higher rates of hypercholesteremia and arterial hypertension they were less likely to smoke. Despite coronary artery disease being less extensive in women and size of infarction being similar, women showed higher 1-yr.-mortality- and 1-yr.-MACCE-rates even after adjusting for confounders. This detrimental effect of female gender, reflected by the higher TIMI-risk-score at admission, requires further analysis.

P945 | BEDSIDE
effect of theoretic application of 2014 ESC guidelines on non-cardiac surgery in a population of end-stage liver disease patients candidates to transplantation

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Introduction: Orthotopic liver transplantation (OLT) is the only effective treatment in patients with end-stage liver disease (ESLD). Coronary artery disease (CAD) stongly increases peri-operative mortality, thus, identification of CAD is crucial. There is not a specific OLT widely accepted diagnostic algorithm for CAD detection. 2014 ESC guidelines on non-cardiac surgery consider OLT as a high-risk abdominal surgical intervention, thus, only patients with CAD history, suspected symptoms and/or low exercise capacity have indication to functional and/or morphologic exams such as stress-echo, coronary Computed Tomography (CCT), coronary angiogram (CGF).
Purpose of the study is to compare our cardiologic pre-OLT protocol, in which tests of myocardial ischemia and CCT are largely administered on the base of risk factors, and the ESC protocol, theoretically applied to the same population.
Methods: From 2012 to 2015, OLT candidates have been evaluated by cardiologic examination, electrocardiography and echocardiography. Dobutamine stress echo was systematically performed in all patients aged >35 years. Moreover coronary computerized tomography (CCT) was performed in subjects aged >50 years with diabetes and/or two or more of the following risk factors: active smoking, CAD family history, peripheral vascular disease and/or when stress-echo was not feasible. CGF was performed in patients with CAD history and/or suspected angina independently by results of stress-echo. We re-analyse our database in order to consider the clinical destination of each patient in case of application of ESC protocol. We calculate the potential differences in number of performed exams and in number of potentially missed CAD diagnosis.
Results: We evaluated 480 patients considered for OLT, 46 were excluded for pre-existent cardiac comorbidites, (9.5%). According to our protocol CAD was researched in 238 (49.5%). Stress Echo was performed in 146 (30.4%, 138 performed only for risk factors), positivity was found in 10 pz (2.1%), 19 (3.9%) underwent to CT. CGF was performed in 35 patients (7.2%), 16 (3.3%) for known CAD and/or symptoms, 12 (2.5%) for stress positivity, 2 (0.4%) for CCT positivity. Critical coronary lesions were found in 7 patients (1.4%), 3 with stress positivity. If ESC protocol had been applied in the same population, stress echo would be performed in 25 patients (5.2%, -83%), one positive; CT in 5 (1.0%, -74%); CGF in 13 (2.7%, -63%), 5 with coronary lesions (1.0%, -28%). Two of 7 patients with critical CAD would not have been identified by ESC protocol: they were asymptomatic, with good exercise capacity, but with high risk profile.
Conclusions:. 1) ESC protocol for pre-OLT evaluation is low resource-demanding, but it is not adequate to identify all CAD subjects. 2) CAD detection, despite low prevalence even in presence of risk factors, remains a challenge in candidates to OLT and the "gold" diagnostic algorithm remains still unclear.

P946 | BEDSIDE
Antiplatelet therapy in ACS patients with anemia

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Background: Advances in antithrombotic and antiplatelet therapies have led to a reduction in ischemic event rates in acute coronary syndromes (ACS), but have generally resulted in an increased risk of hemorrhagic complications. According to the World Health Organization, anemia was defined as serum hemoglobin levels <13 g/dl for men and <12 g/dl for women. The aim of this study was to identify the association of anemia with early and short-term outcomes in patients with ACS.
Methods: We consecutively recruited 1722 patients discharged with the diagnosis of ACS from 3 University Hospitals. We explored the association between the presence of anemia at admission with antiplatelet therapy, interventional versus conservative approach, and events during hospitalization and at 3 months follow-up.
Results: Of the total of 1722 patients enrolled, 445 patients showed anemia (25.8%). Anemia at admission was more frequent in females (30.6% vs 23.9%; $p<0.01$). Patients with anemia were elder (73.4±11.3 vs 63.7±12.9 years; $p<0.001$). The presence of arterial hypertension and dyslipemia was more prevelent in patients with anemia (81.6% vs 62.7% and 66.1% vs 33.9% respectively), while smoking was more frequent in non-anemic group (42.0% vs 22.1%; all comparisons $p<0.001$). The presence of other comorbidities, such as peripheral artery disease or renal impairment, were also higher in the anemic group (18.7% vs 5.7% and 49.7% vs 16.9% respectively; both $p<0.001$). If we compare antiplatelet treatment at discharge, 90 (20.2%) patients with anemia did not receive a second antiplatelet agent, 271 (60.9%) received clopidogrel, 65 (14.6%) ticagrelor and 19 (4.3%) prasugrel; While the number of patients without anemia who were not under double antiplatelet therapy was 175 (13.7%), 569 (44.6%) received clopidogrel, 365 (27.9%) ticagrelor and 175 (13.7%) parasugrel ($p<0.001$). Bleeding complications during hospitalization were higher in patientes with baseline anemia, with 6.8% of mirnor and 3.4% or major bleeding, compared with 3.7% of minor and 0.4% of major bleeding in those patients without anemia ($p<0.001$). At three months follow-up, patients with baseline anemia showed increased risk of minor and major bleeds. So, patients with anemia presented 5.3% of minor bleeding and 3.0% of major bleeding ($p<0.001$), compared with 3.9% of minor bleeding and 0.4% of major bleeding and those without anemia ($p<0.001$).
Conclusions: Anemia is a common condition in patients admitted for an ACS, and is associated with other comorbidities. Anemia gives a significant increase in bleeding morbidity both during hospitalization and three months follow-up.

P947 | BEDSIDE
Acute myocardial infarction mobilizes Muse cells into the peripheral circulation blood to attenuate cardiac remodeling

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Background: Multilineage-differentiating stress enduring (Muse) cells, pluripotent-like cells which are defined as SSEA3+ and CD105+ double-positive cells. Muse cells are able to differentiate into cells of all three germ layers from a single cell, self-renewable, and present in the bone marrow as ~0.03% of the mononu-

cleated fraction. We examined whether endogenous Muse cells are mobilized to improve the left ventricle (LV) function and attenuate LV remodeling.
Methods: The number of Muse cells in the peripheral circulating blood was measured by FACS in 66 patients with AMI (AMI group), 40 patients with coronary artery disease (CAD group), and 79 subjects with a healthy coronary artery (control group). In the AMI group, Muse cells were measured on days 0, 1, 7, 14, and 21 after AMI. Plasma sphingosine-1-phosphate (S1P) levels were measured by the LC-MS/MS system. Cardiac echocardiography was performed at the acute phase (within 7 days) and chronic (6 month) phases of AMI.
Results: The number of Muse cells in the peripheral circulating blood was greater in the AMI group (266±153 /100μL) than in the CAD group (168±86 /100μL) or the control group (172±137 /100μL). The number of Muse cells peaked on day 1 and gradually decreased and normalized on day 21 after AMI. The increase in Muse cells (ΔMuse cells) was positively correlated with peak creatinine kinase (CK) and ΣCK, indicators of MI size. The number of Muse cells was positively correlated with plasma S1P levels. The ΔMuse cells tended to be higher in patient with a positive ΔEF (ejection fraction) (EF at acute phase increased at chronic phase) than in patients with negative ΔEF (EF at acute phase increased at chronic phase), although there was no significance. However, ΔMuse cells was significantly greater in AMI patients whose LV diastolic dimension (LVDd) decreased or remained unchanged than in those whose LVDd increased at the chronic phase, suggesting that a greater number of Muse cells mobilized into the peripheral circulating blood attenuates LV remodeling.
Conclusion: AMI mobilizes Muse cells into the peripheral circulating blood after AMI, and these mobilized Muse cells attenuate LV remodeling in patients with AMI.

P948 | BENCH
Active cardiac-targeted delivery of sphingosine-1-phosphate attracts Muse cells to the infarcted region and replenishes cardiomyocytes to recover the cardiac function after myocardial infarction

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Background: Multilineage-differentiating stress-enduring (Muse) cells are pluripotent-like stem cells collectable from the bone marrow. We hypothesized that sphingosine-1-phosphate receptor 2 (S1PR2) agonist selectively delivered to the infarcted region attracts Muse cells to repair the infarcted myocardium after myocardial infarction (MI).
Methods: In rabbits, MI was induced by 30-min coronary occlusion and 2-weeks reperfusion. An S1PR2 agonist (SID46371153, 1 mg/kg) encapsulated with liposome with Sialyl Lewis X (SLX) (L-S1P group) or saline (control group) was intravenously administered 24 h after MI. We previously demonstrated the specific accumulation of liposomes with SLX in the infarcted myocardium. The number of endogenous Muse cells in the peripheral circulating blood was calculated at 36 h after MI by FACS as SSEA3+ and CD44+ double-positive cells. The MI size and LV function and remodeling were assessed. Other rabbits were intravenously injected with an allograft of 1x105 Muse cells labeled with GFP at 24 h after MI, and the homing of Muse cells to the infarcted heart and differentiation into cardiomyocytes and vessels were assessed. In vitro assessment of cell migration: Rabbit Muse and non-Muse cells were prepared by cell sorting, and the migration of Muse cells to the SIPR2 agonist was assessed using a matrigel invasion chamber.
Results: The number of endogenous Muse cells in the peripheral circulating blood at 36 hours after MI was higher in the L-S1P group (55±8 /100 mL) and in the control group (64±15 /100 mL) than in the sham group (42±12 /100 mL). There was no significant difference in the number of Muse cells between the L-S1P and control groups. The MI size as a percentage of the LV was significantly smaller in the L-S1P group (29.3±3.6%) than in the control groups (18.6±2.2%). The LV function was improved and LV remodeling was attenuated in the L-S1P group as compared with the control group. The GFP-positive Muse cells preferentially migrated to the border area of the infarct, and expressed ANP, troponin I, and a-actinin, and also expressed CD31 and smooth muscle actin, suggesting that Muse cells spontaneously differentiated into cardiomyocytes and vascular cells. On in vitro assessment, rabbit Muse cells migrated positively toward the S1PR2 agonist according to the concentration gradient, while non-Muse cells did not.
Conclusion: Cardiac-targeted delivery of sphingosine-1-phosphate after acute MI attracts endogenous Muse cells to the infarcted heart and replenishes cardiomyocytes to improve the cardiac function and remodeling.

P949 | BEDSIDE
Prognostic value of mitral regurgitation in patients with acute myocardial infarction treated by primary percutaneous coronary intervention

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Introduction: It is known that the presence of mitral regurgitation (MR) after myocardial infarction (MI) results to the poorer outcome. However, data regarding the prognostic role of different degrees of MR in MI patients treated by primary percutaneous coronary intervention (pPCI) remains scarce.
Purpose: 1. To compare clinical and echocardiographic parameters between different degrees of MR; 2. To examine long term prognostic value of MR in MI patients admitted to the pPCI.
Materials and methods: We analyzed, from a prospective electronic registry, 4113 MI patients (60±12 years, male 69%), admitted for pPCI from January 2009 – July 2013. All patients had echocardiographic examinations done before discharge. According to the mitral valve echocardiographic examination we defined two groups of patients; Group 1, with none or mild MR (3233 patients) and Group 2, with moderate or severe MR (880 patients). The primary outcome was all cause mortality at 3-years.
Results: Majority of patients had MI with ST segment elevation (92%). Group 2 compared to the Group 1 was older (65±12 vs. 59±11 years, $p<0.001$), had more often previous bypass operation (3% vs. 1.7%, p=0.013), previous MI (17.1% vs. 13.8%, p=0.015), hypertension (75.4% vs. 71.4, p=0.019), diabetes mellitus (29.2% vs. 21.4%, $p<0.001$), de novo atrial fibrillation (35.1% vs. 18.4%, $p<0.001$), Killip class 3 or 4 at the admission (5.8% vs. 1.8%, $p<0.001$), as well as lower ejection fraction (42%±12% vs. 49%±11%, $p<0.001$) and higher systolic pressure in right ventricle (40±10 vs. 33±8mmHg, $p<0.001$). Kaplan-Meier analysis demonstrated that death free survival at 3 years was significantly higher in Group 1 compared to the Group 2 (91% vs. 75.6%, $p<0.001$). After adjustment for relevant confounders, moderate or severe MR remained as an independent predictor of death (HR 1.87, 95% CI: 1.53–2.28, $p<0.001$).
Conclusion: Presence of moderate or severe MR was associated with poor long-term outcome of MI patients treated with pPCI. As such, it adds important information for risk stratification of post-MI patients that should be closely monitored and treated.

P950 | BEDSIDE
Mortality in younger patients with acute myocardial infarction presenting with or without chest pain

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Background: Chest pain/discomfort is the predominant symptom in patients with acute myocardial infarction (AMI), however some patients with AMI present without chest pain/ discomfort. It is has previously been shown that lack of chest pain in patients with AMI is associated with higher in-hospital mortality but whether the poorer outcome is sustained throughout the first year after onset has not been investigated.
Purpose: To investigate the long-term mortality in younger patients (<65 y) with a first AMI presenting with or without chest pain.
Methods: We used data from a Swedish quality of care register; the Register of Information and Knowledge about Swedish Heart Intensive Care Admissions (RIKS-HIA). In total we included 48,629 men (77%) and women (23%) aged 25–64 years, hospitalized with a first AMI between 1996 and 2010 in the study. Chest pain was defined as chest pain or discomfort.
Results: Overall, 92.9% of the younger patients (<65 y) with AMI presented with chest pain (men 93.7%, women 90.4%). Absence of chest pain was found in 6.3% and 9.6% of men and women. Smoking was common in both patients presenting with or without chest pain but more so in those presenting with chest pain (men 41.3 vs 37.7% and women 49.1 vs 43.0%). Men and women presenting without chest pain was slightly older, had more hypertension, diabetes or history of heart failure. Previous cardiac interventions were more common (PCI and CABG) in men without chest pain. In addition, patients presenting with no chest pain had more complications such as pre hospital cardiac arrest and cardiogenic shock and treatment with continuous positive airway pressure (CPAP).
In patients without chest pain the absolute 1-year mortality was markedly higher (men 14.5% and women 16.7%) compared to those presented with chest pain (men 2.9% and women 3.4%). Men and women presenting without chest pain also had a markedly higher 1-year mortality with a 5- fold higher 1–year mortality relative to those with chest pain (age-adjusted Hazard ratio (HR) in men 5.14, 95% CI:4.55–5.82 and women HR 4.96, 95% CI:4.14–5.94).
Conclusions: Younger patients without chest pain in had markedly higher relative risk of 1-year mortality compared to patients with chest pain. Also, patients without chest pain had more comorbidities and more complications.

P951 | BEDSIDE

Relationship between visit-to-visit variability of LDL cholesterol and clinical outcomes after primary percutaneous coronary intervention: a 7-year followup study

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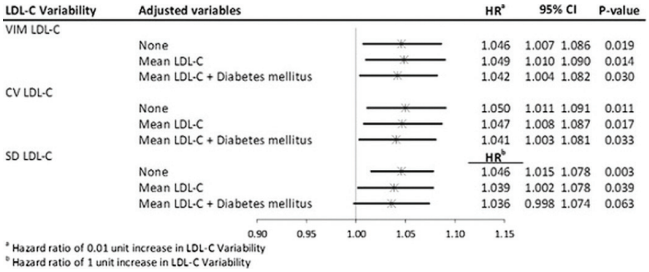
Background: Visit-to-visit variability in low-density lipoprotein cholesterol (LDL-C) levels was found to be a novel predictor of adverse events in patients with stable coronary heart disease. We aimed to evaluate the relationship between visit-to-visit LDL-C variability and 7-year clinical outcomes in patients who presented with ST-segment elevation myocardial infarction (STEMI).
Methods: A total of 105 patients who underwent successful primary percutaneous coronary intervention for STEMI were recruited to evaluate the prevalence of sleep apnea by polysomnography (without subsequent treatment) from 2007–2008. The patients were followed up prospectively in the outpatient setting. Visit-to-visit LDL-C variability was evaluated from 2 months after discharge (LDL-C level stabilization period) through the use of various measurements of LDL-C variability: Variation independent of mean (VIM, primary measure), coefficient of variation (CV) and standard deviation (SD). VIM is a statistical tool rather than a clinical measure, and is a transformation of the standard deviation that is designed to be uncorrelated with mean follow-up LDL-C levels. Major adverse cardiac event (MACE) was defined as a composite of death, myocardial infarction, stroke, unplanned revascularization and heart failure admission. After excluding 3 patients who were lost to follow-up and 9 patients with less than 3 valid LDL-C measurements, 93 patients were analyzed for the present study. Lipid-lowering regimen on discharge included Simvastatin 10 mg (n=5), 20 mg (n=37), 40 mg (n=43), others (n=4), and none (n=4).
Results: After an average of 87.6±11.9 months follow-up, 31 patients (33.3%) developed MACE. Visit-to-visit LDL-C variability was recorded during a mean of 10.6±4.4 outpatient clinic visits. Compared with the non-MACE group, the MACE group had a higher visit-to-visit LDL-C variability (VIM: 0.23±0.10 vs. 0.19±0.08; p=0.031; SD: 0.60±0.30 vs. 0.44±0.23; p=0.014; CV: 0.24±0.10 vs. 0.19±0.08; p=0.02) and a higher prevalence of diabetes mellitus (p=0.028). There were no significant differences between the MACE and non-MACE groups with regard to other clinical and angiographic characteristics including sleep apnea status, infarct location, ECG ST-segment resolution, and left ventricular ejection fraction. The baseline LDL-C levels were similar between the MACE and non-MACE groups (130.4±39.2 mg/dL vs. 130.2±28.1 mg/dL, p=0.987). There was a trend towards higher mean LDL-C levels in the MACE group compared with the non-MACE group (98.9±26.3 vs. 89.2±18.5, p=0.068). The results after adjusting for mean LDL-C and diabetes mellitus are shown in the Figure.



LDL-C variability and clinical outcomes

Conclusion: This is the first report showing an independent association between visit-to-visit variability in LDL-C and long-term MACE in patients successfully treated with primary percutaneous coronary intervention for STEMI.

P952 | BEDSIDE

Grouping patients with prior myocardial infarction with benign and serious prognosis by non-invasive coronary flow velocity reserve values during exercise echo. 3-year follow-up

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Patients with previous myocardial infarctions (MI) are considered very high risk for subsequent cardiac events. However, the coronary flow velocity reserve values (CFVR) could potentially identify patients with different prognoses. The aim of the study was to define the prognostic value of CFVR during exercise echocardiography in patients with prior MI.
Methods: Inclusion criteria for the study were 1) history of MI; 2) need of exercise echocardiography for diagnostic or stratification aims; 3) good visualization of left anterior descending artery (LAD) during the exercise test; 4) opportunity for follow-up. 279 patients (212 men, 56±8 years old) were included in the study. All patients performed a supine bicycle test with a conventional visual assessment of wall motion abnormalities, with additional coronary flow velocity measurements in LAD before and during exercise. During a median follow-up of 36.6 months, there were 114 patients with major adverse cardiac events (MACE). There were 5 cardiac deaths, 9 non-fatal MI and 107 revascularizations (coronary stenting and/or coronary artery bypass grafting). Some patients had more than one event.
Results: The group with the most severe MACE – cardiac death or non-fatal MI - had a higher velocity in LAD at rest (50±22 vs. 35±16 cm/s, p<0.002), a lower difference between peak and rest velocities (3±28 vs. 25±24 cm/s, p<0.007), and CFVR values (1.1±0.4 vs. 1.8±0.7, p<0.006) compared to other patients. The cut-off value of CFVR>2.0 divided the study population into two subgroups with different levels of cardiac risk: a subgroup with benign prognoses and a subgroup with a very high risk for subsequent cardiac events. Among the subgroup with CFVR>2.0, 0% patients had MI or death, and 0.42% patients per year had coronary artery bypass grafting. Whereas, within the subgroup with CFVR≤2.0, 11.3% patients per year had the most severe MACE (death, myocardial infarction, and coronary artery bypass grafting). Thirty-four percent of patients in this subgroup had MACE within 3 years.
Conclusion: Whenever suitable, performing exercise stress echocardiography with coronary flow velocity analysis in LAD during the same tests can be recommended for prognostic purposes in patients with a prior MI. CFVR≤2.0 is a predictor of adverse events in such patients within 3 years.

MICROCIRCULATION AND INFLAMMATION

P953 | BEDSIDE

Uncovered plaque ruptures in patients with ST elevation myocardial infarction assessed by optical coherence tomography and intravascular ultrasound

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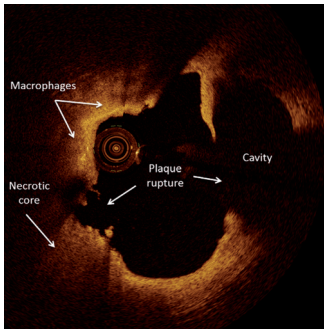
Background: In patients with ST segment elevation myocardial infarction (STEMI) the infarct-related occlusion is frequently located at the site of the maximum thrombus burden, whereas the origin of the plaque rupture (the true culprit) may be situated proximal or distal to it.
Purpose: To examine stent coverage of true culprit lesions in 86 STEMI patients who underwent primary percutaneous coronary intervention.
Methods: Images of lesions were obtained using optical coherence tomography (OCT) and intravascular ultrasound IVUS) with iMap within 48 hours after stent implantation and after 12 months. The relative distribution of necrotic core (NC), fibrotic tissue (FT), lipidic tissue (LT), and calcific tissue (CT) was determined for the 5 mm stent reference segments.
Results: The overall incidence of post-procedure OCT-detected uncovered plaque ruptures was 11 in 86 patients (12.8%), and 8 (9.3% of patients) of these plaque ruptures were identified as the culprit lesion by OCT. None of these plaque ruptures were angiographically visualizable, while 7 (87.5%) were visible on concomitant IVUS-analysis. All uncovered culprit plaque ruptures were located at the proximal stent edge (0.15 (0.0, 3.1) mm from the stent edge). The mean cavity area was 1.9 mm^2 (0.6 to 2.7 mm^2), mean cavity length was 2.0 mm (1.5 to 4.9 mm) and minimum lumen area 7.5 mm^2 (4.8 to 9.3 mm^2) after 12 months, 3 (37.5%) culprit related uncovered plaque ruptures were healed insufficiently with cavity and fibrous cap remnants. One patient had the uncovered plaque rupture treated after 100 days due to stable angina pectoris. The median lumen area at the plaque rupture site was reduced from 7.5 (4.8, 9.3) mm^2 to 3.6 (2.8, 8.0) mm^2 (p=0.012). In reference segments with uncovered culprit plaque rupture, the plaque volume (65.6±15.8 mm^3 vs 34.4±9.2 mm^3, p<0.001), vessel volume (111.8±19.6 mm^3 vs 75.2±21.2 mm^3, p<0.001), and percentage NC (34.9±9.9% vs 18.3±11.3%, p<0.001) were significantly higher compared to reference segments without plaque ruptures. Peri-stent plaque volume did not differ significantly between the two groups (198.6±56.2 mm^3 vs 181.9±75.2 mm^3, p=ns). Percentage of FT was lower in reference segments with uncovered plaque ruptures (40.4±10.2% vs 58.8±14.2% (p=0.001)), while no difference was found for LT and CT.



Culprit plaque rupture

Conclusions: Uncovered culprit plaque rupture was not an uncommon finding in patients treated with PPCI and located proximally to the implanted stent. Uncovered plaque ruptures were associated with significantly lumen reduction during the spontaneous healing process.
Acknowledgement/Funding: The danish heart foundation

P954 | BEDSIDE
Comparison of anti-inflammatory effects of rivaroxaban versus dabigatran in patients with non-valvular atrial fibrillation (RIVAL-AF study) - multicenter randomized study

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Background: Some experimental studies showed that direct oral anticoagulants (DOAC) have the anti-inflammatory effects. However, serial changes of inflammatory markers in patients receiving DOAC remain unknown.
Methods: In this multicenter randomized study, 117 patients with non-valvular atrial fibrillation were randomly assigned to rivaroxaban (n=55) or dabigatran (n=62) treatment. We evaluated between-group differences in the levels of inflammatory markers including high sensitivity C-reactive protein (hsCRP), pentraxin-3 (PTX-3), interleukin (IL)-1β, IL-6, IL-18, tumor necrosis factor-α (TNF-α), monocyte chemotactic protein-1 (MCP-1), growth and differentiation factor-15 (GDF-15), and thrombomodulin (TM) as a marker of endothelial dysfunction at baseline and 12 months after randomization.
Results: Baseline characteristics were similar across treatment groups. Main results are shown in Table. There were no significant differences in the interval changes of all inflammatory markers between the groups. Compared with rivaroxaban group, the interval change of the TM levels in dabigatran group significantly increased from baseline to 12 months (0.28±0.63 vs 0.58±0.80 FU/ml, $p<0.05$).

The interval change between the groups

	Rivaroxaban group		Dabigatran group		p value*
	baseline	12 months	baseline	12 months	
hsCRP, ng/ml	667 (345–1530)	668 (425–1855)	723 (386–2170)	558 (320–1260)	0.65
PTX-3, ng/ml	2.0 (1.5–2.6)	1.8 (1.3–2.5)	1.9 (1.5–2.8)	1.8 (1.3–3.1)	0.49
IL-1β, pg/ml	10 (10–12)	10 (10–13)	10 (10–12)	10 (10–13)	0.64
IL-6, pg/ml	2.6 (1.6–3.6)	1.9 (1.4–3.2)	2.6 (1.8–3.7)	2.2 (1.6–3.1)	0.49
IL-18, pg/ml	198 (159–263)	197 (157–261)	209 (183–251)	197 (167–247)	0.41
TNF-α, pg/ml	1.1 (0.8–1.3)	1.1 (0.8–1.6)	1.2 (0.8–1.5)	1.1 (0.8–1.5)	0.39
MCP-1, pg/ml	282 (237–351)	304 (242–360)	256 (220–292)	256 (215–315)	0.28
GDF-15, pg/ml	1270 (934–1673)	1350 (980–1850)	1220 (955–1650)	1345 (931–1913)	0.40
TM, FU/ml	2.8 (2.3–3.5)	3.1 (2.6–3.8)	2.8 (2.5–3.2)	3.3 (2.6–4.0)	<0.05

Data given as medians (25th–75th percentiles). *p value of the interval change between the groups.

Conclusions: There were no significant differences in the interval changes of all inflammatory markers from baseline to 12 months between rivaroxaban and dabigatran groups. Patients in dabigatran group had the increased change in TM levels more than those in rivaroxaban group, which may lead to the damage of endothelial cells.
Acknowledgement/Funding: Bayer Yakuhin, Ltd

P955 | BEDSIDE
Ischemic postconditioning attenuates positive effects of remote ischemic conditioning on endothelial function in patients with STEMI

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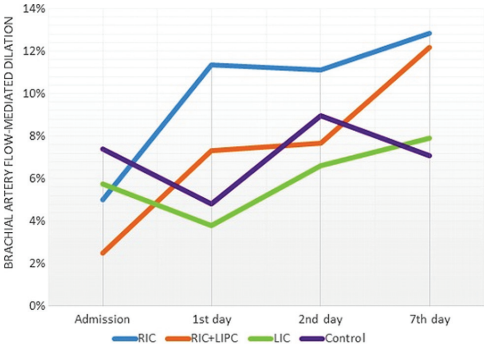
Background: Remote ischemic conditioning (RIC) and local ischemic postconditioning (LIPC) are among the most commonly investigated methods of cardioprotection in patients with STEMI. Despite this interest, few studies have addressed the issue of combined application of RIC and LIPC.
Purpose: The aim of our research is to study the effects of separate and combined applications of RIC and LIPC on endothelial function in patients with STEMI.
Methods: Patients with STEMI (n=116) were randomly allocated to one of the following groups: (1) the RIC group (n=42), primary PCI (pPCI) combined with RIC, consisting of four cycles of 5-min inflation and 5-min deflation of an upper-arm blood pressure cuff initiated before pPCI; (2) the RIC+LIPC group (n=24), pPCI combined with RIC and LIPC, consisting of four cycles of 1-min inflation and 1-min deflation of the angioplasty balloon; (3) the LIPC group (n=17), pPCI combined with LIPC, and (4) the control group (n=33), pPCI alone. We assessed endothelial function using the brachial artery flow-mediated dilation (FMD) test at admission, and then on the 1st, 2nd, and 7th days after pPCI.
Results: According to the brachial artery FMD test results, an endothelial dysfunction was observed in patients in all groups at admission. In the RIC group, on the first day after PCI, the median value of the brachial artery FMD-test result increased from 5% to 11,3% (p=0,0008), and normal levels of brachial artery FMD remained in this group on the 2nd and 7th days after PCI. In the RIC+LIPC group, normalization of endothelial function was noted only on the 7th day after PCI: the median value of brachial artery FMD-test results in this group increased from 7,7% to 12,9% (p=0,004). In the LIPC and control groups, endothelial function remained depressed on the 2nd and 7th days after PCI.



Dynamics of the FMD-test results

Conclusions: RIC significantly improves endothelial function in patients with STEMI, as assessed from the brachial artery FMD-test. We have demonstrated for the first time that LIPC attenuates positive effects of RIC on endothelial function in patients with STEMI when used in combination with RIC. LIC alone has not shown significant impact on endothelial function in patients with STEMI.
Acknowledgement/Funding: This work was supported by the Russian Federation Government grant #14.B25.31.0016

P956 | BEDSIDE
Thrombectomy does not influence the infarct size and microvascular obstruction assessed by cardiac magnetic resonance in patients with STEMI treated with primary coronary intervention

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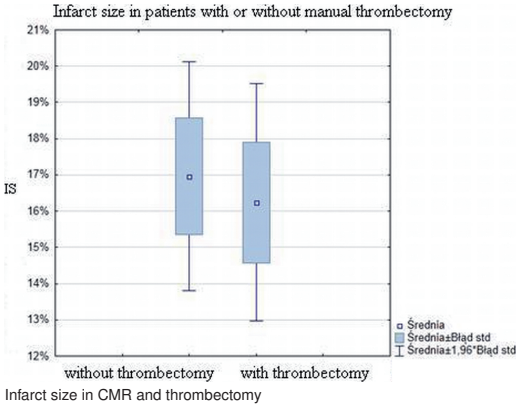
Background: Infarct size and microvascular obstruction evaluated by cardiac magnetic resonance (CMR) have a prognostic value in patients with ST-segment elevation myocardial infarction (STEMI) treated with primary percutaneous coronary intervention (pPCI). Time to treatment and successful reperfusion are essential in those patients. Some trials have shown that thrombectomy improves surrogate and clinical outcome. Lastly thrombectomy is questioned to be effective in patients with STEMI.
Aim of the study: The aim of the study was to evaluate the influence of manual thrombectomy, time-to-treatment and successful reperfusion on infarct size (IS) and microvascular obstruction (MVO) assessed by CMR in patients with STEMI.
Material and methods: We examined 85 patients (mean age 59±11 years; 59 males and 26 females) with first STEMI treated with pPCI within 12 hours from symptoms onset. Infarct related artery TIMI flow and MBG were evaluated after pPCI. CMR was performed on the 1.5T system within 96 hours after pPCI. Morphology and function of myocardium was estimated by steady-state free precession (SSFP) sequence. To evaluate the infarct size and MVO, a late gadolinium enhancement (LGE) sequence was performed (10–15 min after administration of gadobutrol). Infarct size was defined as area above 50% of the maximal signal intensity within LGE (FWMH – full-width half maximum), MVO was described as the area of absence or hyperenhancement of myocardium surrounded by LGE. IS and MVO were determined by planimetry and summation of discs method.
Results: The mean infarct size in study group was 16.52±10.54% of LV myocardial mass. The presence of MVO was observed in 28 patients (32.94%) with a mean size of 8±6% of infarct size. Manual thrombectomy during pPCI was per-



Infarct size in CMR and thrombectomy

formed in 37 patients (43.53%) and these patients had mean ejection fraction 54.36±8.8% with IS estimated on CMR 16.96±9.8% of myocardial mass and MVO 3.85% of infarct size. The patients treated by pPCI alone, without thrombectomy, had similar EF (54.8±10.7%; p=ns) and CMR findings: IS = 16.25±10.05% of LV myocardial mass (p=ns) and MVO = 4.84% of infarct size (p=ns). Patients treated in 90 minutes from the symptoms onset had lower infarct size than patients treated after 360 minutes from the beginning of chest pain (p=0.048). Revascularization was successful in 41 patients (MBG 3 and TIMI 3) and these patients had IS estimated on CMR 13,31±8,3% of LV mass and MVO 2,46±4,97% of IS. 44 patients with impaired reperfusion (TIMI<3 and/or MBG<3), had much worse CMR outcomes: IS = 17.43±10.12% of LV mass and MVO = 3.41±5.71% of IS (p<0.001).

Conclusion: Manual thrombectomy during pPCI does not improve CMR outcomes in STEMI patients. Rapid treatment and successful reperfusion in patients with STEMI results in smaller infarct size and microvascular obstruction assessed by CMR.

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Adipocyte size distribution and depot-specific modulation of pro- and anti-atherosclerotic adipocytokines and innate immune molecules in human adipose tissue

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Background/Introduction: Obesity is closely associated with a low-grade inflammation, which may predispose individuals to metabolic disturbance and subsequent atherosclerotic cardiovascular diseases (ASCVD). Adipose tissue releases a number of pro- and anti-inflammatory molecules (adipocytokine) and those closely interacts with the innate immune molecules. However, depot- and gender-dependent variations in adipocyte size and adipocytokines/innate immune molecules have not been studied.

Purpose: We evaluated depot- and gender-specific regulation of anti-atherosclerotic adiponectin and pro-atherosclerotic innate immune molecules in human adipose tissues.

Methods: Pair samples were obtained from subcutaneous (SAT) and visceral adipose tissue (VAT) during elective surgery (Male: 35; Female: 27). Expressions of adipocytokines and innate immune molecules were evaluated by semi-quantitative qPCR. Adipose cell-size distribution was obtained from tissue samples fixed in osmium tetroxide and analyzed by Beckman Coulter Multisizer. The subcutaneous fat area (SFA) and intra-abdominal visceral fat area (VFA) were measured at the level of the umbilicus, using a standardized method with computed tomography (CT) scans.

Results: In female, there was a correlation between SFA vs HOMA-IR (r=0.420, p=0.037) and between the mean sizes of SAT adipocytes vs HOMA-IR (r=0.233, p=0.309). On the contrary, in male, there was neither a significant correlation between SFA vs HOMA-IR (r=0.207, p=0.247) nor between the mean sizes of SAT adipocytes vs HOMA-IR (r=0.149, p=0.497). There was a correlation tendency between VFA vs HOMA-IR (r=0.432, p=0.074) and between size of VAT adipocytes vs HOMA-IR (r=0.456, p=0.050) in female, but there was no correlation between VFA vs HOMA-IR (r=0.111, p=0.730) and between size of VAT adipocytes vs HOMA-IR, (r=0.166, p=0.753) in male. Levels of adiponectin were higher in SAT and VAT of female than those of male (p<0.001 and p=0.011, respectively). NLRP3, IL1β, IL18, TLR2 were comparable in SAT and VAT between genders. However, TLR4 and TLR9 were increased in female SAT and VAT and HMGB1 in female VAT. Levels of adiponectin were not correlated with mean diameter of adipocyte (φ, μm) in SAT and VAT of male, but negatively well correlated in those of female (r= –0.392 and r= –0.616). Such negative correlations were also observed between levels of TLR2, TLR4 and HMGB1 and φ in female. Levels of NLRP3 and IL1β were positively correlated with φ in male, but not in female.

Conclusions: Adiponectin and innate immune molecules were differentially expressed in male and female adipose tissues, suggesting that the depot- and gender-specific signals could serve as ASCVD via chronic inflammation.

Acknowledgement/Funding: MEXT, Japan #23591314, #24591338, #24591063; MHLW, Japan, #201315008A, #201315011A.

P958 | BENCH

Rosuvastatin improved cardiac dysfunction after coronary microembolization via alleviating TNF-alpha induced oxidative stress

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Background: It has been demonstrated that statins plays a critical role on primary prevention of myocardial infarction. However, it is unclear about the effect of statins on cardiac dysfunction caused by coronary microembolization (CME).

Objectives: This study was designed to evaluate the impact of rosuvastatin on cardiac dysfunction caused by CME.

Methods: In vivo study, mice CME models were developed by injecting a total of 500,000 polyethylene micro-particles (average 9–12 diameters) into the left ventricle when transiently obstructed the ascending aorta. There were three groups: sham-operation group (n=8), CME group (n=9) and rosuvastatin therapy group (n=8, oral received 40mg/kg per day one week before CME). Cardiac function was evaluated by echocardiography. Serum and myocardial expression of tumor necrosis factor-α (TNF-α) were detected. In vitro study, cardiomyocytes isolated from adult Sprague–Dawley rats were exposed to TNF-α (40 ng/mL) for 48 hours. Rosuvastatin was pretreated before adding TNF-α, while antioxidant N-Acety-L-Cysteine (NAC) was used as positive control. Then, reactive oxygen species (ROS) and necrosis/apoptosis were detected by flow cytometry, and NADPH Oxidase-2 (NOX-2) detected by western blot.

Results: Compared with CME group, rosuvastatin significantly improved cardiac function after CME (LVEF: 3 days later: 54.6±5.8% vs. 63.2±6.2%, P<0.01; 10 days later: 56.8±7.1% vs. 64.6±6.7%, P<0.05). We also found that pre-treatment with oral rosuvastatin not only decreased the average area of microinfarctions (7.2±5.7% vs. 2.9±2.2%, P<0.05), but also decreased serum and myocardial expression of TNF-α. Meanwhile, myocardial NOX-2 expression was inhibited by rosuvastatin, which was increased significantly on CME group. In vitro study, ROS generation and cardiomyocytes apoptosis were increased after TNF-α exposure. Compared with positive control therapy (NAC, 1nM for 1 hour), rosuvastatin had the similar protective effect on the reduction of ROS and apoptosis. Western blot demonstrated that NOX-2 expression was significantly reduced after rosuvastatin therapy.

Conclusions: TNF-α induced oxidative stress could be involved in cardiac dysfunction after coronary microembolization. Rosuvastatin improve heart function by alleviating TNF-α-NOX-2 induced ROS generation.

Acknowledgement/Funding: National Natural Science Foundation of China (Grant No: 81200146, 81570314 and 81370322)

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Late sodium channel inhibition (ranolazine) improves angina and myocardial perfusion in patients with severe microvascular coronary dysfunction

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Background: In a prior pharmacologic probe trial of late Na channel inhibition (ranolazine) in symptomatic subjects without obstructive coronary artery disease (CAD) with a wide range of perfusion reserve defined by cardiac MRI, we found no improvement in angina or myocardial perfusion reserve (MPRI) overall. However, severe coronary microvascular MCD, (e.g. coronary flow reserve (CFR) <2.5) is associated with adverse prognosis and responsive to certain pharmacologic agents. We explored clinical characteristics and myocardial perfusion responses in a pre-specified subgroup that had invasively determined CFR from the trial.

Methods: Symptomatic subjects (majority female 98%) with non obstructive CAD and invasively determined CFR (adenosine or regadenoson) enrolled in a randomized, double-blind, cross-over trial of ranolazine (500–1,000 mg bid for 2 weeks) vs placebo were analyzed. Symptomatic outcomes were assessed by Seattle Angina Questionnaire (SAQ) and perfusion by cardiac MRI derived MPRI. Coronary angiographic, CFR, and CMRI data were analyzed by core laboratories.

Results: A total of 81 patients had invasively determined CFR (range 1.4–5.5). Subjects with severe MCD (CFR<2.5, n=35) had similar demographic and symptomatic findings vs. those with less severe MCD (CFR ≥2.5, n=46) but improved angina (SAQ 7 5.76±11.51 vs -0.86±13.54, p=0.04), and mid-ventricular myocardial perfusion reserve (MPRI, 2.17±0.56 vs 1.90±0.41, p=0.03) with ranolazine vs

Baseline characteristics by CFR

Mean ± SD, Frequency (%)	CFR <2.5 (n=35)	CFR ≥2.5 (n=46)	p-value
Age (years)	54.43±10.80	55.02±9.82	0.80
Typical angina	10 (28.57%)	16 (34.78%)	0.63
Angina frequency (baseline SAQ angina)	62.29±27.66	57.83±26.66	0.43*
ACH response (%) (n=58)	–2.01±16.19	–2.68±22.60	0.69*
ACE/ARB	10 (28.6%)	21 (47.8%)	0.17
Statins	17 (48.57%)	31 (67.39%)	0.11

T tests and Fisher's Exact test for categorical variables, *Wilcoxon rank sum. MI, myocardial infarction; LVEDP, left ventricular end diastolic pressure; ACH, acetylcholine; ACE, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker.

placebo. A lower end-diastolic volume predicted beneficial SAQ angina response (p=0.03) among patients with CFR<2.5.
Conclusions: Among symptomatic subjects with invasively determined CFR, those with more severe MCD (CFR <2.5) had improved angina and CMRI MPRI with ranolazine. These findings support the hypothesis that the late Na channel is important in this syndrome and its inhibition may provide a therapeutic opportunity for management in this difficult to manage population.
Acknowledgement/Funding: Gillead

P960 | BEDSIDE
Cystatin C: a marker of angiographic coronary collateralization in stable angina patients with chronic total occlusion

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Objective: Cystatin C, an endogenous anti-angiogenic factor, was considered as an emerging biomarker in cardiovascular disease and proved to be an important predictor for adverse outcomes among patients with coronary artery disease. We investigated whether and to what extent cystatin C was associated with angiographic coronary collateralization in patients with stable coronary artery disease and chronic total occlusion.
Methods: Serum levels of cystatin C and high-sensitive C-reactive protein (hsCRP) and glomerular filtration rate (GFR) were determined in 866 patients with stable angina and angiographic total occlusion of at least one major coronary artery. The degree of collaterals supplying the distal aspect of a total occlusion from the contra-lateral vessel was graded as poor (Rentrop score of 0 or 1) or good coronary collateralization (Rentrop score of 2 or 3).
Results: In total, serum cystatin C was higher in patients with poor collateralization than in those with good collateralization (1.08±0.32 mg/L vs. 0.90±0.34 mg/L, P<0.001), and correlated inversely with Rentrop score (adjusted Spearmen's r=–0.145, P<0.001). The prevalence of poor coronary collateralization increased stepwise with increasing cystatin C quartiles (P for trend <0.001). Odds ratio for poor collateralization increased to 6.300 (95% confidence interval [CI] 4.065–9.764) in the highest compared with those in the lowest quartile of cystatin C level (P<0.001). These associations remained significant after adjusting for multiple variables (OR: 7.021, 95% CI 4.261–11.570, P<0.001). ROC curve analysis showed that AUC was 0.687 (95% CI 0.652–0.722, P<0.001) and the optimal cut-point of serum cystatin C was 0.97 mg/L, with a diagnostic sensitivity and specificity of 61.3% and 67.2% for the presence of poor coronary collateralization. After adjusting for age, gender, risk factors for coronary artery disease, GFR and hsCRP, serum cystatin C ≥0.97 mg/L remained independently associated with poor collateralization (OR 2.374, 95% CI 1.660–3.396, P<0.001). The diagnostic value of cystatin C levels for detecting poor coronary collateralization persisted regardless of age, gender, presence or absence of diabetes, hypertension or renal dysfunction.
Conclusions: Serum cystatin C reflects angiographic coronary collateralization in patients with stable coronary artery disease, and cystatin C ≥0.97 mg/L indicates a great risk of poor coronary collaterals.

P961 | BEDSIDE
Automated calculation of coronary zero flow pressure and microcirculatory diastolic conductance from intracoronary pressure and flow velocity measurements

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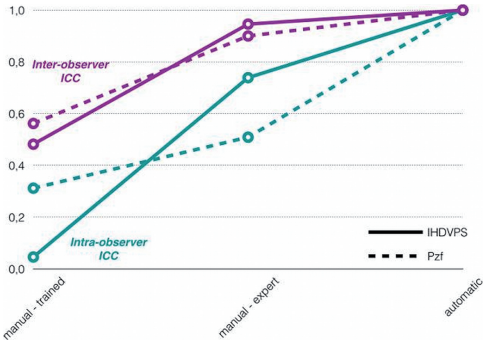
Background: Microcirculatory diastolic conductance (Instantaneous Hyperaemic Diastolic Velocity-Pressure Slope, IHDVPS) and coronary zero-flow pressure (Pzf) are two physiological indices that provide valuable information about the presence of remodelling and compression of the coronary microcirculation. Recently, Pzf has been proposed as the best predictor of microvascular injury in STEMI. The applicability of both indices is hampered by the difficulties in its calculation, that is based on manual post-processing of pressure and flow velocity signals. Specifically, some of the issues are (i) selection of the cycles to be included in the analysis, (ii) selection of the diastolic interval to generate the pressure-flow velocity relationship (DI); and (ii) inference of a global estimation from the individual indices per cardiac cycle, which usually ignore inter-cycle variability. To overcome these limitations, we developed and validated a new method automated approach to estimate IHDVPS and Pzf.
Methods: The proposed automated method restricts the analysis to those cycles with a good linear relationship between pressure and flow during mid-to-late diastole. A mixed-effect model was applied to obtain a final estimate of both indices. Physiological data, obtained with intracoronary pressure and Doppler guidewires in 20 subjects with stable angina, was used for validation purposes. IHDVPS and Pzf were calculated independently by 2 expert analysers, 2 ad hoc trained analysers, and automatically by the developed software. Measurements were repeated to estimate both intra- and inter-observer variability.
Results: Correlation between automatic and manual measurements was higher for experts (IHDVPS: 0.927; Pzf: 0.862) than for non-experts (IHDVPS: 0.652; Pzf: 0.745). Automated measurement were equivalent to those obtained by expert analysers (IHDVPS 2.44±1.33 and 2.34±1.33 respectively, p=NS; Pzf 41.7±13.8 and 36.3±14.7, p=NS), but significantly different to those obtained by trained analysers (IHDVPS 3.34±2.51, p<0.05; Pzf 43.1±14.6, p=NS). The coefficient of variation was lower for automatic (0.18) than for manual analysers (expert: 0.36; trained: 0.42). The automated analysis required 0.38 minutes per patient, 2 to 5 minutes for expert analysers, and 6 to 11 minutes for trained analysers. Intra- and inter-observer variability was significantly higher for trained analysers than for expert analysers (Figure 1).



Intra- and inter-observer ICC of methods

Conclusion: The developed software allowed calculation of IHDVPS and Pzf with the same degree of accuracy as an expert operator, and significantly better accuracy than an ad hoc trained physician. Of note, compared with an expert analyser, automated calculations are performed 5 to 13 times faster with a variability reduced by 50%. This automated approach might facilitate the adoption of IHDVPS and Pzf in research and clinical practice to perform a more comprehensive assessment of coronary microcirculation.

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Intracoronary ECG monitoring during provocative acetylcholine test in chest pain patients with normal coronary angiography: results from AChPOL Registry

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Introduction: A significant proportion of patients undergoing coronary angiography due to chest pain has normal or near normal coronary arteries.
Purpose: The aim of this study was to assess the changes detected with intracoronary electrocardiography (icECG) during provocative test with acetylcholine in mid-European patients population and its influence on further diagnosis and treatment.
Methods: Between January 2011 and December 2012 we selected patients with normal or insignificant changes in coronary arteries and a history suggesting Prinzmetal disease or microvasculature impairment. The full history of these patients included the nature of their chest pain (typical or atypical, exertional, at rest, nocturnal) and coronary risk factors. Nitrates and calcium channel blockers were stopped 48 hours before the test. Acetylcholine (ACh) was injected through the Judkin's catheter after performing the angiographic procedure. Acetylcholine was injected in incremental doses of 25, 50 and 75 mg into the right coronary artery and 25, 50 and 100 mg into the left coronary artery. Test was defined as positive when asymptomatic >70% coronary spasm was induced or when the reduction in lumen diameter was more than 50% together with present chest pain and/or changes in ECG. Unipolar intracoronary ECG (icECG) was recorded before, during and after ACh administration. The coronary wire was placed in all vessels at the border of mid and distal segments.
Results: In the abovementioned period of time we performed 156 provocative tests with ACh, in which 54 were performed with the additional use of icECG. The spasm was observed in 35 patients (64.8%, Prinzmetal disease; group I), in 13 (24.1%) patients during ACh administration chest pain and ST depression in standard ECG appeared (microcirculation dysfunction, group II) and in 6 (11.1%) there were no signs and symptoms (group III).
When analyzing baseline icECG recordings we observed more pronounced ST depression in the group II (microcirculation dysfunction) than in the group I (Prinzmetal disease, p=0.003) or the group III (negative ACh test, p=0.001). During ACh administration there was no difference between the group I and the group II regarding ST-elevation in icECG. Moreover, after the procedure in the group II again ST depression was more pronounced comparing with two other groups (p=0.005). There was difference between groups I and III.
When observing these patients during 3-year follow-up we disclosed that in group II there was the lowest rate of completely or nearly asymptomatic patients (after introduction of proper medical treatment). This rate was 62.9%, 23.1% and 83.3% in group I, group II and group III, respectively.
Conclusions: icECG monitoring during provocative test with acetylcholine proved the presence of baseline ischemia in patients with microcirculation dysfunction. And this group proved to be the poorest responder to the given treatment.

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Coronary microvascular alterations in patients presenting with myocarditis: histopathological data and clinical correlations

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Background: Coronary microvascular dysfunction (CMD) has been associated with a number of cardiac diseases despite normal epicardial arteries. In particular, in patients with structural heart disease, type B CMD is sustained by adverse remodelling of intramural arterioles, which produces an impairment in coronary flow reserve and bears an independent prognostic value.
Purpose: Based on histological data, we aimed to define the prevalence of CMD in patients with myocarditis and to find possible relationship with clinical, laboratory, ECG and imaging data.
Methods: We analysed 33 consecutive patients (23 males; mean age 41.8±7.3 y) with a histopathological diagnosis of myocarditis in the absence of any known structural heart disease. They all presented to ER with symptoms and underwent coronary angiography showing normal epicardial arteries. Endomyocardial biopsy (EMB) was performed, and histological specimen analysed. CMD was defined as the presence of any structural alterations of small vessels, including media hypertrophy, perivascular fibrosis and intraluminal thrombosis. Baseline ECG, echocardiogram, cardiac magnetic resonance (CMR) and lab values were recorded.
Results: 13 patients (39.4%) had evidence of CMD at EMB. Patients with CMD were females in 7/20 cases vs. 3/20 without CMD (p=0.03), while age was similar between groups (44.3±7.9 vs. 40.3±6.8 y, p=ns). Also family history and cardiovascular risk factors were similar (all p=ns). Angina was the symptom of presentation in 7/13 patients with CMD vs. 10/20 patients without (p=ns. ECG showed ST-T abnormalities in 4/13 vs. 10/20 patients respectively (p=ns). Lab values showed differences in troponin T and NT-proBNP levels: 4.4±2.8 vs. 1.6±1.3 ng/mL ($p<0.01$) and 8.9±2.3 vs. 12.4±3.6$\times 10^2$ pg/mL ($p<0.01$). Left ventricle EDV and EF were 128±14 mL vs. 132±16 mL and 50±5% vs. 50±6% (both p=ns); regional wall-motion abnormalities were seen in 6/13 vs. 14/20 patients (p=ns). CMR with STIR and LGE showed oedema and fibrosis in 1/13 vs. 9/20 (p=0.05) and 10/13 vs. 17/20 patients respectively (p=ns). Interstitial fibrosis was confirmed by EMB in 13/13 vs. 14/20 patients (p=0.06). Cardiac myocytes dimensions were similar between groups: 18±3 vs. 18±4 μm (p=ns). Myocarditis was found to be acute in 9 patients (3/13 vs. 6/20, p=ns) with a viral aetiology in 8 (3/13 vs. 5/20, p=ns). Viruses with known endothelial tropism (PVB19 and HHV6) caused 1/3 vs. 3/5 cases (p=ns).
Conclusion: In patients with biopsy-proved myocarditis, CMD was common, especially in females, and correlated with higher levels of troponin T and lower levels of NT-proBNP. Patients with CMD had less oedema but not significantly more fibrosis at CMR; however, all of them had interstitial fibrosis at EMB. CMD resulted unrelated to myocytes dimensions, aetiology of myocarditis, cardiovascular risk factors, symptoms at presentation, ECG and echocardiographic features.

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Chronic inhibition of lipoprotein-associated phospholipase A2 is not associated with improvement in coronary endothelial function

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Background: Lipoprotein-associated phospholipase A2 (Lp-PLA2) is a novel circulating biomarker for vascular wall inflammation, which is bound to low density and high density lipoproteins, promoting vascular inflammation. Lp-PLA2 is associated with coronary endothelial dysfunction and is an independent risk factor for cardiovascular events. The current study tested the hypothesis that administration of darapladib, an Lp-PLA2 inhibitor, would improve coronary endothelial function.
Methods: We conducted a double-blind trial in 51 patients with coronary endothelial dysfunction who were randomized to receive oral darapladib, 160 mg orally daily, or placebo. Coronary angiography was performed at baseline and after 6 months of treatment to assess the primary endpoints of change in endothelial function, including coronary responses of blood flow and coronary artery diameter to graded intracoronary acetylcholine injections.
Results: A total of 51 patients were randomized to placebo (n=29) or darapladib (22), and showed no significant difference in baseline characteristics between the groups. Their average age was 55±10.8 years. Hypertension was present in 57% and hyperlipidemia in 38%. On follow-up, there was no significant difference in the degree of response to acetylcholine of coronary artery diameter (+5.3±21.2% vs. +5.6±24.4% in the placebo group, p=0.96) or coronary blood flow (+6.5±85.3% vs. +32.7±101.8% p=0.33) (Figure 1).
Discussion: Our findings suggest that a 6-month Lp-PLA2 inhibition with darapladib is not associated with improvement in coronary endothelial function. These observations may shed light on the failure of recent studies to achieve reduction in cardiovascular events using treatment with darapladib.

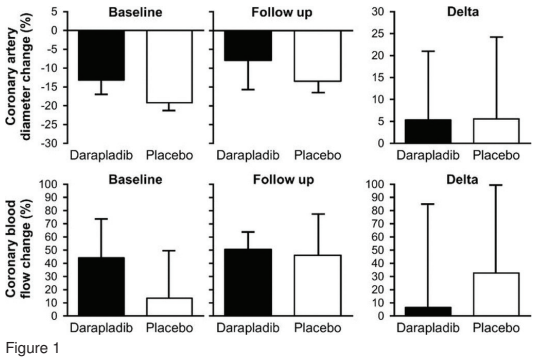

Figure 1

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Saline-induced coronary hyperemia mechanisms and effects on left ventricular function

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Background: During thermodilution-based assessment of volumetric coronary blood flow we observed that intracoronary infusion of saline increased coronary flow. This study aims to quantify the extent and unraveling the mechanisms of saline-induced hyperemia.
Methods: A total of 32 patients were studied. In 24 patients intracoronary Doppler flow velocity measurements were performed at rest, after an intracoronary bolus of adenosine and during increasing infusion rates of saline at room temperature through a dedicated catheter with 4 lateral side-holes. In 8 patients, global longitudinal strain and annular early diastolic velocities were assessed by transthoracic echocardiography during a prolonged saline infusion.
Results: As compared to the increase in flow obtained by adenosine, flow increased by 6%, 46%, 111%, and 112% during infusion of saline at rates of 5, 10, 15 and 20 mL/min, respectively. Maximal saline-induced and adenosine-induced increase in flow velocity correlated closely (R2=0.95 $P<0.001$). The same infusion rates given through one end-hole (n=6) or in the contralateral artery (n=6) did not induce a significant increase in flow velocity. Intracoronary saline given on top of an intravenous infusion of adenosine did not further increase flow. Intracoronary saline infusion did not produce significant changes in blood pressure or in left ventricular function. Heart rate decreased by 15% during saline infusion (P=0.021).

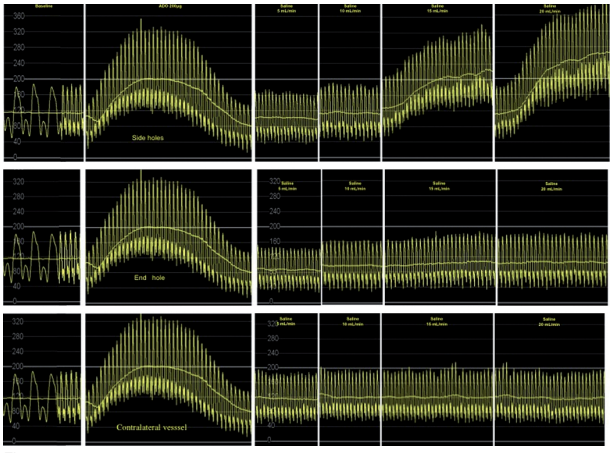

Figure 1

Conclusion: Intracoronary infusion of saline at room temperature through a dedicated catheter for coronary thermodilution induces steady state maximal hyperemia at a flow rate≥15 mL/min. These findings facilitate the measurements of absolute coronary blood flow and microcirculatory resistance.

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Obstructive vs. nonobstructive coronary artery disease in women and men with myocardial infarction

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Background: Information on sex differences in clinical presentation, risk factors and prognostic significance of myocardial infarction (MI) with obstructive vs. nonobstructive coronary artery disease (CAD) is missing as previous studies on nonobstructive CAD have focused on women with the exclusion or underrepresentation of men.
Purpose: This study aimed to identify sex-based differences in risk factors related to obstructive vs. nonobstructive CAD in MI patients.
Methods: Data were derived from 9098 acute coronary syndrome patients who underwent coronary angiography. They were admitted to 57 hospitals included in the network of the ISACS-TC registry (ClinicalTrials.gov, NCT01218776) between January 2010 and January 2016. The primary end-points were ST-elevation myocardial infarction (STEMI) as index event and the composite endpoint of all cause 30-day mortality or severe left ventricular dysfunction at discharge (LVD; ejection fraction at echocardiography <40%). Multivariate logistic regression methods were used to identify baseline risk factors that were independent predictors of obstructive vs. nonobstructive CAD. Patients were categorized as having significant CAD (any stenosis≥50%) and nonobstructive CAD (any stenosis 0% to<50%). Patients with unstable angina (n=819) were excluded, giving a final study population of 8279 patients
Results: Of the 8279 patients, 91.6% had significant CAD and 8.4% had nonobstructive CAD. Men exhibited less often nonobstructive CAD than women (7.7% vs 10.3%, P<0.001). In nonobstructive CAD, significantly more men than women presented with STEMI (49.9% vs. 36.2%, P=0.001). Smoking (OR 1.55, 95% CI: 1.10–2.18) and male sex (OR: 1.52, 95% CI: 1.08–2.15) were independent determinants for clinical presentation with STEMI. The frequency of the composite endpoint of death or severe LVD was not significantly different between men and women (14.5% vs 11.9%, P=0.34). Sex-specific regression models of obstructive versus non obstructive CAD showed that hypercholesterolemia predicts significant CAD in men (OR: 1.44, 95% CI: 1.17–1.77) and in women (OR: 1.42, 95% CI: 1.04–1.92). However, the predictive risk factors varied considerably for women. The effects of older age (OR: 1.02, 95% CI: 1.01–1.04), diabetes (OR: 2.01, 95% CI: 1.41–2.86) and current/ former smoking (OR 1.95, 95% CI: 1.41–2.69), were stronger in women. The OR for obstructive CAD in men versus women among diabetes and/or smokers was 1.12 (95% CI: 0.90–1.39).
Conclusions: Male patients with myocardial infarction are less frequently found to have nonobstructive CAD, but those with nonobstructive CAD have a greater risk of STEMI compared with women. Women are less likely to develop obstructive CAD in the absence of diabetes and smoking. The presence of diabetes or smoking equalizes the odds by sex. These results suggest aggressive life style changes and CAD prevention strategies in women with diabetes and smoking.

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Typical angina is associated with greater coronary endothelial dysfunction but not abnormal coronary flow reserve: results from ranolazine in coronary microvascular dysfunction (RWISE)

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Background: Prior results of the anti-anginal therapy ranolazine in subjects with no obstructive coronary artery disease (CAD) and coronary microvascular dysfunction (CMD) suggested benefit in subjects with adenosine-mediated low coronary flow reserve (CFR). However, our recent RWISE trial failed to demonstrate this benefit in the pre-specified typical angina (TA) subgroup.
Purpose: We performed subgroup analysis comparing subjects who presented with TA vs non-typical angina (NTA) in the RWISE study.
Methods: We conducted a randomized, double-blinded, placebo- controlled, cross-over trial of ranolazine for 2 weeks in 128 subjects with signs and symptoms of myocardial ischemia and no obstructive CAD. TA was defined as sub-sternal chest pain precipitated by physical exertion or emotional stress and relieved with rest or nitroglycerin. NTA was defined as symptoms that did not meet criteria for TA. Coronary reactivity testing measured responses to adenosine, acetylcholine, and nitroglycerin, and cardiac magnetic resonance determined myocardial perfusion reserve index (CMR MPRI) were evaluated by core laboratories.
Results: 31% of the subjects had TA, and the mean age (55.2±9.8 yrs), ethnicity, sex, traditional risk factors and cardiac medications did not differ between the TA and NTA groups. Compared to NTA, invasively assessed baseline acetylcholine-mediated coronary endothelial function, cold pressor and nitroglycerine responses were worse in the TA group (all p<0.05), while adenosine-mediated CFR and MPRI were similar (Table).

	Typical Angina (n=40)	Non-Typical Angina (n=88)	p-value
Baseline CMR MPRI	1.8±0.54	1.77±0.48	0.81
Acetylcholine (36.4 mcg) response (%)	–8.74±17.92	1.62±20	0.03
CFR	2.72±0.54	2.67±0.7	0.79
NTG response (200 mcg)	3.97±18.24	13.47±20.66	0.05
Forearm COP response (%)	–9.87±17.85	2.79±20.21	0.01

COP: cold pressor test; NTG: intra-coronary nitroglycerine.

Conclusions: Among subjects with CMD and no obstructive CAD, the subset of subjects with TA had greater acetylcholine-mediated endothelial dysfunction but not adenosine-mediated CFR compared to NTA. The lack of association of TA with abnormal adenosine-mediated CFR may have contributed to the lack of benefit of ranolazine in the RWISE TA subjects.
Acknowledgement/Funding: Gilead Sciences

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Serum mimecan reflects angiographic coronary collateralization in patients with stable coronary artery disease and chronic total occlusion

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Objective: Mimecan/osteoglycin is an emerging biomarker of coronary atherosclerosis and has significant impact on cardiovascular outcomes. This study aimed to assess whether and to what extent serum mimecan reflects angiographic coronary collateralization in patients with stable coronary artery disease and chronic total occlusion.
Methods: Serum levels of mimecan were determined in 559 consecutive patients with stable angina and angiographic total occlusion of at least one major coronary artery. The degree of collaterals supplying the distal aspect of a total occlusion from the contra-lateral vessel was graded as poor (Rentrop score of 0 or 1) or good coronary collateralization (Rentrop score of 2 or 3).
Results: Serum mimecan was significantly elevated in 209 patients with poor collateralization than in 350 those with good collateralization (31.9 ng/mL vs. 19.9 ng/mL, P<0.001), and correlated inversely with Rentrop score (Spearmen's r = -0.444, P<0.001). The prevalence of poor coronary collaterals increased stepwise from the lowest to the highest quartile of serum mimecan (P for tread <0.001). ROC curve analysis showed that the area under the curve was 0.749 (95% CI, 0.707–0.791, P<0.001) for serum mimecan in prediction of poorly developed coronary collateralization with an optimal cutoff point of 26.4 ng/mL (sensitivity = 71.8% and specificity = 74.6%). After adjusting for age, gender, traditional risk factors for coronary artery disease, multivessel disease, glomerular filtration rate and C-reactive protein, serum mimecan (per SD) remained an independent determinant for poor collateralization (OR, 2.718; 95% CI, 2.081–3.551; P<0.001). The result patterns were similar when the patients were specified by gender, age, body mass index, presence or absence of hypertension and diabetes, and status of renal function.
Conclusions: Serum mimecan is significantly and positively associated with angiographic poor coronary collateralization in patients with chronic total occlusion.

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Association of increased chromogranin A, decreased vasostatin-2 and catestatin levels in serum, and their ratios with poor coronary collateralization

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Purpose: We investigated whether serum levels of chromogranin A, vasostatin-2, and catestatin were related to coronary collateralization status in coronary artery disease (CAD) patients with chronic total occlusion. The biological effects of vasostatin-2 and catestatin on angiogenesis were evaluated with in vitro and in vivo experiments.
Methods: Serum levels of chromogranin A, vasostatin-2 and catestatin were determined in 452 consecutive patients with angiographic total occlusion of at least one major coronary artery. The degree of collaterals was graded according to the Rentrop scoring system. To evaluate the effects of vasostatin-2 and catestatin on post-hindlimb ischemia angiogenesis, we injected intra-peritoneally saline, vasostatin-2 or catestatin everyday for 1 month after ligation of left femoral artery in C57Bl/6 mice. The animals were sacrificed at 2 weeks and 4 weeks.
Results: Low (Rentrop score of 0 or 1) and high (Rentrop score of 2 or 3) coronary collateralization occurred in 179 and 273 patients, respectively. Notably, serum chromogranin A levels were higher (56.13 [21.64–122.69] ng/ml vs. 18.18 [7.34–43.61] ng/ml), but vasostatin-2 (2.87 [2.18–3.54] ng/ml vs. 3.67 [2.97–4.71] ng/ml) and catestatin levels (2.18 [1.20–3.15] ng/ml vs. 3.14 [1.92–5.17 ng/ml])

were lower in patients with poor collateralization than in those with good collateralization (all P<0.001). Multivariable logistic regression analysis suggested that increased chromogranin A, decreased vasostatin-2 and catestatin, and reduced chromogranin A/vasostatin and chromograninA/catestatin ratios were independently associated with poor collateralization in patients with CAD, besides conventional factors (age, female gender, smoking, hypertension, diabetes, renal impairment and CRP). Histological analysis and molecular approaches showed that vasostatin-2 or catestatin administration significantly improved post-ischemia angiogenesis as compared with saline, with inhibition of ACE expression by the former and up-regulation of ACE2 expression by the latter in mRNA microarray analysis. Stimulation of HUVECs with vasostatin-2 or catestatin also promoted tube formation in matrigel consistently. Combination of these two peptides exhibited synergistic improvement of angiogenesis in vivo and in vitro. Moreover, when vasostatin-2 was injected in hindlimb ischemia mice with adenovirus-mediated over-expression of ACE, or when catestatin was injected in the same mouse models with adenovirus-shRNA-mediated knockdown of ACE2, the phenomenon of angiogenesis improvement was significantly attenuated.
Conclusion: Increased serum chromogranin A, decreased serum vasostatin-2 and catestatin levels, and their ratios are associated with poor collateralization in CAD patients with chronic total occlusion. Vasostatin-2 and catestatin promote angiogenesis in mice with hindlimb ischemia mainly through inhibiting ACE expression and increasing ACE2 expression, respectively.

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Characterization of vascular phenotype in patients with coronary artery ectasia: a case-control study

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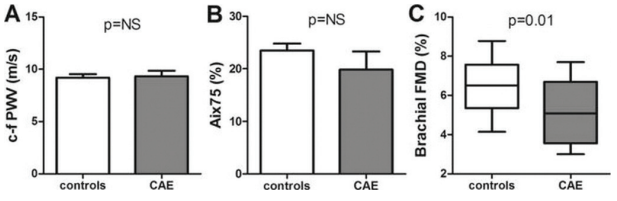
Background: Coronary artery ectasia (CAE) is a common finding in subjects undergoing coronary catheterization but the pathophysiology of this entity remains poorly understood. Systemic impairment of vascular function in these patients may be associated with CAE development but this has not been explored yet.
Purpose: To study the vascular phenotype of patients with CAE.
Methods: Forty (n=40) patients with CAE and 40 age- and sex-matched control subjects with first diagnosis of coronary artery disease were enrolled in this study. Before coronary catheterization patients underwent assessment of endothelial function by using brachial artery flow-mediated dilatation (FMD). Carotid-femoral pulse wave velocity (PWV) and augmentation index (AIx) were measured as an index of arterial stiffness.
Results: There were no significant differences in prevalence of risk factors (i.e. arterial hypertension, diabetes mellitus, dyslipidemia & smoking) between CAE and no CAE patients (p=NS for all). Positive family history for CAD was more frequent among subjects with CAE (χ^2=13.673, p<0.001). There were no significant differences in PWV (A) or AIx (B) between the two groups (p=ns for both). Interestingly, brachial FMD was significantly lower in CAE patients (C).



Conclusions: Our findings suggest that coronary artery ectasia is strongly associated with an adverse vascular phenotype characterised by systemic endothelial dysfunction. Moreover genetic variants increasing susceptibility to CAD may also have a role in the pathogenesis of coronary ectasias development.

P971 | BEDSIDE
Impact of exercise training on the ischemic threshold- Results of the Leipzig EXerCIse Training versus mEdical management in patients with stable coronary artery disease (EXCITE) trial

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Background: Exercise training leads to an improvement of the coronary collateral circulation. However, clinical relevance of coronary collaterals is still controversial with the association between collateral growth and ischemic threshold still unclear.
Purpose: We aimed to investigate in the impact of exercise training on the ischemic threshold. In addition, we elucidated the association between the change in coronary collateral growth and ischemic threshold.
Methods: We randomized 60 patients with significant CAD (FFR≤0.75) to high-intensity exercise (group A, 20 patients) or moderate-intensity exercise (group B, 20 patients) for 4 weeks or to a control group (group C, 20 patients). At baseline and after 4 weeks, the coronary collateral flow index (CFI) was measured invasively and the ischemic threshold was assessed in ergospirometry expressed in heart rate and watt.
Results: Four weeks of exercise training resulted in a significant increase in ischemic threshold as compared to usual care with no difference between the high- and moderate-intensities. Spearman rank correlation revealed a significant association between the change in CFI and change in ischemic threshold after 4 weeks (Spearman correlation coefficient 0.425, p=0.006). Mean heart rate at ischemic threshold assessed in ergospirometry at baseline was 113±18 bpm with no statistical differences between groups (P=0.30). At 4 weeks, we observed a significant increase in heart rate at ischemic threshold in patients who underwent exercise training compared to the control group (group A compared to group C: P=0.015; group B compared to group C: P=0.001) with no difference between high- and moderate intensities (P=1.0). In detail, after 4 weeks, mean heart rate at ischemic threshold increased from 118±19 bpm to 132±20 bpm in group A and from 107±22 bpm to 132±21 bpm in group B. We noted no change in mean heart rate at ischemic threshold after 4 weeks in group C (from 116±13 bpm to 117±13 bpm).
Conclusion: High- and moderate-intensity exercise training for 4 weeks resulted in a significant increase in ischemic threshold. In addition, we observed a significant correlation between change in CFI and change in ischemic threshold after 4 weeks (P=0.034, correlation coefficient 0.336).

P972 | BEDSIDE
Inflammation, atrial fibrillation and ventricular arrhythmias in acute coronary syndrome patients

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Introduction: Inflammation increases the risk of arrhythmias and is associated with worse prognosis of patients with acute coronary syndrome (ACS). C-reactive protein (CRP) is the most frequently used inflammatory marker, whereas white blood count (WBC) and neutrophils/lymphocytes ratio (N/L) are cheaper to obtain and widely available, but far less studied. The objective of this study was to assess the relation between CRP, LC and N/L, and the development of atrial fibrillation (AF) or ventricular arrhythmias (VA) in patients with ACS.
Methods: Data were collected within a cohort study of 939 consecutive patients with a discharge diagnosis of ACS in two hospitals. Patients with infection, primary hematological diseases or under immunosuppressive drugs were excluded. 44 (5.6%) patients had previous history of AF and were therefore excluded from the de novo AF analysis.
Sociodemographic data, previous medical history, including previous AF, type of ACS (ST elevation myocardial infarction (STEMI) and non-ST elevation ACS (NSTEACS) and occurrence of arrhythmias during hospitalization (de novo AF and VA-ventricular tachycardia or ventricular fibrillation) were obtained by face-to-face interviews and medical records review. Inflammatory markers were obtained from complete blood count results at admission.
Results: In our sample of 786 patients (mean age 64±13 years; 77.1% men) 36.4% had STEMI and 63.4% NSTEACS.
De novo AF developed in 61 (7.8%) patients, in whom WBC median levels on admission were significantly higher (10.2×10^9 vs 9.0×10^9/L; p<0.01), as were levels of neutrophils (7.4×10^9 vs 6.0×10^9/L; p<0.01) and N/L (4.4 vs 3.1; p<0.01). Mean CRP levels were also higher among patients with de novo AF (0.8 vs 0.4 mg/dL; p<0.01). After multivariate analysis (age, sex, ACS type, HF history and smoking status) these results remained statistically significant.
VA were observed in 255 (32.4%) patients. In this group, median WBC levels were higher (10.1×10^9 vs 8.6×10^9/L; p<0.01), as were levels of neutrophils (7.1×10^9 vs 5.6×10^9/L; p<0.01) and N/L (4.1 vs 3.0; p<0.01); these differences were similar after adjustment. No differences in median CRP levels were found between patients with or without VA during hospitalization (0.41 vs 0.40 mg/dL, respectively; p=0.50).
Conclusion: Higher inflammatory markers, namely WBC, neutrophils and N/L at admission were associated with an increased risk of AF or VA during hospitalization in ACS patients.

P973 | BEDSIDE
Detection of dynamic change in levels of plasma oxidized low density lipoprotein during coronary artery bypass grafting using a natural monoclonal antibody

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Background: We used a naturally occurring antibody (mAb LO1) against oxidised low density lipoprotein (oxLDL) to develop a new assay that measures levels of oxLDL in plasma. We characterised the assay with enzyme-linked immunosor-

bent assay (ELISA), Western Blotting as well as immune precipitation and mass spectrometry then the tested the ability of the assay to detect dynamic changes during conventional coronary artery bypass grafting (CABG).
Purpose: To develop a new assay to measure levels of oxLDL in plasma and demonstrate its ability to reflect dynamic oxidative stress.
Methods: We developed a sensitive and specific ELISA capture for oxLDL using a well characterised anti MDA-LDL antibody isolated in our laboratory (termed mAb LO1). We then characterised the assay using immunoprecipitation of patient plasma, western blotting, mass spectrometry as well as ELISA. We tested the assay on plasma samples from ten patients (age 65.1±8.2 years) undergoing conventional CABG, taken at four different time points: baseline, 60, 120, and 300 minutes.
Results: We established that mAb LO1 can immunoprecipitate malonaldehyde modified LDL (MDA-LDL) prepared in the laboratory, but not unmanipulated LDL, as detected by western blotting for Apolipoprotein B (ApoB). We then used this approach to determine whether mAb LO1 recognises antigen in human plasma, and were able to isolate a clear band in the ~200kD range. This was confirmed by mass spectrometry to be ApoB (77% peptide match), and to contain oxidation products. We then optimised a capture ELISA using immobilised mAb LO1 and HRP or biotin tagged polyclonal anti-ApoB for detection. We demonstrated variability amongst patient, stability on freeze, thaw cycles as well as ability dynamically detect changes in oxLDL content in plasma subjected to bench-top oxidation. Furthermore, we demonstrated lack of correlation of the new assay with an established Lp(a) assay in a cohort of patients undergoing coronary angiography.
In patients undergoing CABG using conventional bypass studied longitudinally over 5 hours, we found that despite the reduction in ApoB levels between baseline and 60 minutes, likely secondary to haemodilution on bypass, there was an increase in MDA-LDL levels with a significant increase in the MDA-LDL/ApoB ratio at 60 minutes (% change 33.0 ± SD185.2, $p<0.05$) followed by significant reduction and renormalization of the ratio during recovery by the 120 minute time point with little difference from baseline (-14.0% ± 32.6, $p>0.05$).
Conclusion: We characterised a novel assay that utilises mAb LO1 to recognised oxidised LDL in plasma and can be used in a capture ELISA to detect temporal changes in patients undergoing CABG surgery. This assay may have several applications including determining oxidative injury and response to treatment.
Acknowledgement/Funding: National Institute of Health Research Imperial Biomedical Research Centre

P974 | BEDSIDE
Associations of hs-CRP and NT-proBNP levels with reperfusion success of primary PCI in STEMI patients

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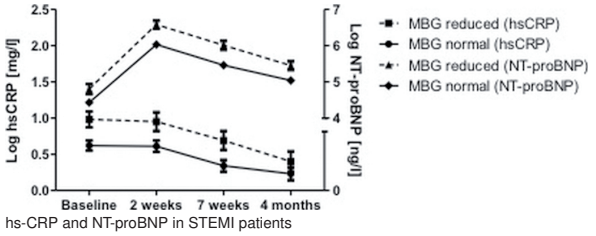
Background: Reperfusion success of primary percutaneous coronary intervention (PCI) predicts clinical outcome but its association with well established plasma markers of inflammation and myocardial dysfunction remains to be determined. The aim of this study was to determine the association of high sensitivity C-reactive protein (hs-CRP) and N terminal probrain natriuretic peptide (NT-proBNP) levels with reperfusion success of PCI in patients presenting with a first ST-elevation myocardial infarction (STEMI).
Methods: We examined hs-CRP and NT-proBNP levels in 376 consecutive patients presenting with a first STEMI. Hs-CRP levels were measured at baseline, 2 weeks, 7 weeks and 4 months after intervention. Myocardial blush grade (MBG) after PCI was used as measure of myocardial reperfusion. In multivariate analysis, we adjusted for sex, age, time between symptom onset and catheterization, heart rate, and TIMI flow (pre- and postintervention).
Results: Reduced reperfusion was associated with increased hs-CRP and NT-proBNP levels at baseline and also during 4 months follow-up (hs-CRP levels: 2.0 vs 2.2 mg/l (baseline), 1.7 vs. 2.2 mg/l (2 weeks), 1.5 vs. 1.9 mg/l (7 weeks); NT-proBNP levels: 115 ng/l vs. 75 ng/l (baseline); 887 ng/l vs. 468 ng/l (2 weeks); 423 ng/l vs. 236 ng/l (7 weeks); 235 ng/l vs. 153 ng/l (4 months)) (Figure). After multivariate analysis baseline hs-CRP remained independent associated with reduced reperfusion (HR 1.36 per doubling of hs-CRP level), p=0.043), while NT-proBNP was not significant (HR 1.18 per doubling of NT-proBNP level, p=0.203).



hs-CRP and NT-proBNP in STEMI patients

Conclusion: hs-CRP levels at presentation are associated with reperfusion success. Decreased reperfusion success is associated with long-term increased hs-CRP. Although it is difficult to unravel the exact mechanism, this phenomenon could be a consequence of the degree of myocardial necrosis patients have at presentation and the association of inflammation and myocardial necrosis. Due to the decreased reperfusion (and myocardial damage), hs-CRP levels remain increased for a longer time.

P975 | BEDSIDE
A novel echocardiographic method for predicting subclinical atherosclerosis in patients with familial mediterranean fever: a pilot study

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Introduction: Systemic inflammation has an important role in the initiation of atherosclerosis, which is well-known associated with arterial stiffness. Aortic flow propagation velocity (APV) is a new echocardiographic parameter of aortic stiffness. The relationship between systemic inflammation and arterial stiffness has not been well-described in patients with familial Mediterranean fever (FMF).
Purpose: In this study, we aimed to investigate the relationship between arterial stiffness and APV in FMF patients.
Methods: Sixty-one FMF patients without cardiovascular involvement in an attack-free period and 57 age- and sex-matched healthy individuals were included into the study. Flow propagation velocity of the descending aorta (Figure 1) and carotid intima-media thickness (CIMT) were measured to assess arterial stiffness.

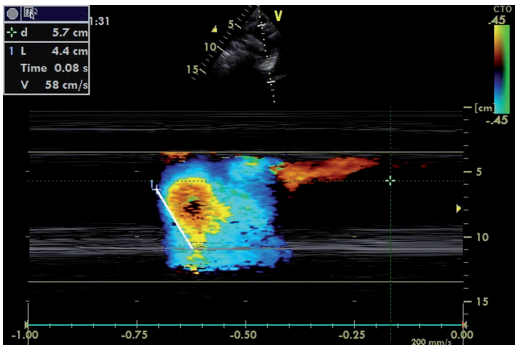

Figure 1

Results: APV was significantly lower and, CIMT was significantly higher in the FMF group than control group. There were significant correlations between APV and mean CIMT (r=–0.424, $p<0.001$), erythrocyte sedimentation rate (ESR) (r=–0.198, p=0.032), left ventricle ejection fraction (r=0.201, p=0.029). In addition, APV (beta=–0.486, $p<0.001$), age (beta=0.323, $p<0.001$) and ESR (beta=0.207, p=0.009) were independent predictors of subclinical atherosclerosis – CIMT – in multiple regression analysis.

Table 1. Demographic, biochemical and echocardiographic properties in patients with FMF and controls.

	FMF patients (n=61)	Controls (n=57)	P value
Age, years	27.3±6.7	28.8±7.1	0.251
Female, n (%)	43 (70.5)	36 (63.2)	0.397
Systolic blood pressure, mmHg	109.6±11.2	111.5±9.4	0.330
Diastolic blood pressure, mmHg	70 (70–80)	70 (65–80)	0.839
LDL cholesterol, mg/dL	101.9±26.6	102.8±35.6	0.877
CRP, mg/L	3.45 (3.40–9.65)	3.45 (3.30–4.43)	0.110
ESR, mm/h	9 (4–21)	5 (2–8)	<0.001
NLR	1.78 (1.41–2.53)	1.82 (1.39–2.05)	0.190
WBC count, $\times 10^9$/L	7.21±1.92	7.54±1.82	0.346
Mean CIMT, mm	0.49±0.09	0.40±0.10	<0.001
APV, cm/sec	60.2±16.5	89.5±11.6	<0.001

Conclusions: Our results revealed that APV may be used to identify the early atherosclerosis in FMF patients. APV is one of the independent predictors of subclinical atherosclerosis in FMF patients.

P976 | BENCH
The relation between the volume and the localization of epicardial adipose tissue and the presence and the extension of coronary artery disease

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Aim: Type 2 Diabetes Mellitus (DM) is an important risk factor for cardiovascular disease (CVD). Clinical studies keep on searching for the possibility of having epicardial adipose tissue (EAT) as an independent risk factor for CAD, and as a marker for evaluation for the presence, severity and activity of CAD and the determination of the theraphy modalities. Also, because of asymetrical distrubition of EAT, there is a question mark in minds about in which localization of EAT mea-

surment is more capable to predict CAD and several studies have been done on this issue. In our study we aimed to evaluate the relation between the volume and the localization of EAT and the presence and the extension of CAD which was detected by coronary computed tomography angiography (CCTA) in Type 2 DM patients without known CAD.

Material and method: A total of 157 consecutive patients with DM underwent CCTA were included retrospectively for the present study. After an evaluation of the CCTA images, the study population was divided into two groups (a CAD(+) group and a CAD(–) group) on the basis of the presence of coronary atherosclerosis. In these two groups of patients, total and left atrioventricular groove EAT volumes were measured. Blood samples were taken from all patients for evaluation of cholesterol panel, biochemistry parameters and markers of inflammation.

Results: In our study age, male sex, smoking, hemoglobin A1c (HbA1c), creatinine, total cholesterol, C-reactive protein (CRP), total and left atrioventricular groove EAT volumes were found significantly associated with coronary atherosclerosis. Total and left atrioventricular groove EAT volumes were found significantly high in patients with CAD than patients without CAD. Although, in univariate analysis both total and left atrioventricular groove EAT volumes were found significantly associated with coronary atherosclerosis, in multivariate analysis only left atrioventricular groove EAT volumes were found as an independent predictor for CAD. (The area under ROC (Receiver Operator Characteristic) curve 0.718; 95% CI: 0.641–0.787). Additionally, total and left atrioventricular groove EAT volumes were positively correlated with CRP values (p=0.0001/p=0.0001) and coronary atherosclerosis detected segment numbers (p=0.0001/p=0.0001).

Conclusion: In our study, left atrioventricular groove EAT volumes were determined as an independent predictor for CAD in Type 2 DM patients without known CAD. It was also found that, although, total EYD volume is associated with CAD, it is not an independent predictor. Also, both total and left atrioventricular groove EAT volumes are associated with coronary atherosclerosis extension.