NORSKE ABSTRAKTER PÅ AHA 2016

288 Effects of Candesartan and Metoprolol on Myocardial Mass, Edema, and Fibrosis During Anthracycline Treatment in Early Breast Cancer: APRADA-CMR substudy

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Background: Anthracycline treatment may cause myocardial damage with myocyte death and expansion of the myocardial extracellular volume (ECV) fraction by edema and fibrosis. We tested the hypotheses that adjuvant treatment with the anthracycline epirubicin is associated with a dose dependent increase in myocardial ECV fraction and a reduction in total myocardial cellular volume and mass, and that these changes could be prevented by concomitant angiotensin or beta-adrenergic blockade.

Methods: The PRevention of cArdiac Dysfunction during Adjuvant breast cancer therapy (PRADA) trial was a 2x2 factorial, placebo-controlled, double-blind trial. 120 women with early breast cancer and no serious comorbidities were randomized to receive candesartan cilexetil, metoprolol succinate, or matching placebos concomitantly with adjuvant anticancer therapy. In 69 patients, ECV fraction, total ECV and cellular volume, and myocardial mass were measured by cardiovascular magnetic resonance before and at the completion of anthracycline therapy.

Results: Overall, ECV fraction increased from 27.5±2.7% to 28.7±2.9 % (p=0.001). There was a dose dependent association between cumulative anthracycline dose (400 mg/ m^2 vs. <400 mg/ m^2) and ECV fraction (mean change 3.2 % [95% confidence interval (CI) 1.0, 5.5] vs. 0.8% [95% CI 0.1, 1.5], p=0.009), as well as with increased total ECV (mean change 1.8 ml [95% CI 0.2, 3.5] vs. 0.2 ml [95% CI -0.5, 0.8], p=0.050). Candesartan treatment was associated with a decline in total cellular volume (mean change -3.5 ml [95% CI -4.7, -2.3]) and left ventricular mass (mean change -3.6 g [95% CI -5.2, -2.0]) (both p<0.001), and no change in total ECV; (mean change 0.1 ml [95% CI -0.9, 1.0], p=0.902). In contrast, in patients receiving no candesartan, total ECV increased (0.9 ml [95% CI 0.1, 1.7]; p=0.031) while total cellular volume (-0.7 ml [95% CI -2.2, 0.8]; p=0.366) and mass (0.2 g [95% CI -1.3, 1.7]; p=0.741) remained unchanged. There was no impact of metoprolol on ECV fraction, total ECV or cellular volume.

Conclusions

Anthracycline therapy is associated with a dose-dependent increase in ECV fraction and total ECV. Concomitant treatment with candesartan blunts the increase in total ECV and reduces left ventricular total cellular volume and mass.

412 Absence of the NLRP3 Inflammasome Improves Survival but Not Cardiac Remodeling Following Myocardial Infarction

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Introduction: Myocardial infarction (MI) causes a sterile inflammatory response through activation of the innate immune system. Upon activation of NLRP3, a cytosolic pattern recognition receptor, inflammasomes are formed together with scaffold protein ASC and caspase-1. This leads to maturation of the IL-1 family cytokines. While the inflammatory response is a prerequisite for healing of the infarction, a dysregulated response may have unbeneficial effects promoting cardiac remodeling. In this study we investigated whether absence of NLRP3 affects post-MI remodeling.

Methods and Results: C57Bl/6J (WT) and NLRP3 knock-out (NLRP3 KO) mice were subjected to an MI by coronary artery ligation. WT mice had a high mortality rate (43%) primarily due to ventricular rupture at day 4-6. The mortality rate was markedly reduced in NLRP3 KO mice (17%, $p<0.05$), despite comparable infarct sizes and heart function 1 day post-MI. Careful evaluation of cardiac dimensions by MRI and macrophage accumulation by histology did not reveal any differences in cardiac remodeling up to 21 days post-MI. However, NLRP3 KO mice showed a decreased expression of ANP, IL-6 and matrix metalloproteinases in the infarcted area. These observations point at a primary role of NLRP3 in infarction healing. To investigate this more closely, male WT and NLRP3 KO bone marrow chimeras were created and an MI was induced. Transplantation of NLRP3 KO bone marrow into WT mice greatly improved post-MI survival compared to WT to WT controls (100% vs. 53% survival, $p<0.001$). In addition, cardiac function measured by echocardiography was improved accordingly in NLRP3 KO chimeras ($p=0.06$).

Conclusions: NLRP3 activation in hematopoietic cells infiltrating in the myocardium disturbs infarction healing, thereby causing ventricular rupture. Ongoing studies aim at defining which specific cell type is mediating this effect.

M4001 Osteoprotegerin is Associated With Major Bleeding but Not With Cardiovascular Outcomes in Patients With Acute Coronary Syndromes - Insights From the PLATelet Inhibition and Patient Outcomes (PLATO) Trial

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Introduction: Elevated plasma levels of osteoprotegerin (OPG), a secreted cytokine receptor, might be associated with increased cardiovascular (CV) risk.

Methods: We measured plasma OPG levels obtained on admission and at 1 month in a pre-defined subset of patients with acute coronary syndromes (ACS) randomized to 6 - 12 months treatment with ticagrelor or clopidogrel in the PLATelet inhibition and patient Outcomes (PLATO) trial *(NCT00391872)*. OPG was determined by enzyme immuno-assay. Rates of CV outcomes and major bleeding were presented by baseline OPG quartile groups. The multivariable associations of OPG levels (log transformed) with the composite endpoint of CV death, non-procedural spontaneous myocardial infarction (sMI) or stroke, and with non-CABG major bleeding were assessed with Cox proportional hazards models. Five adjusted models, with co-variates and incremental addition of log transformed biomarkers, were used: 1/ randomized treatment and clinical risk factors (including: age, gender and, hypertension e.g.) 2/ CRP and white blood cell count (WBC), 3/ cystatin C, 4/ hs-Troponin T and NT-proBNP and 5/ growth differentiation factor (GDF)-15.

Results: OPG levels were available in 5,135 (28%) patients at baseline, with a median (interquartile interval) of 2.7 (2.0 - 3.6) ng/mL. Event rates of the composite endpoint per increasing quartile

Association between admission OPG and outcomes (HRs per 50% increase in OPG level)

CV death / sMI / Stroke	N events / total	HR (95% CI)	P-value
Adjustment for rand. treat. and clin. risk factors	432 / 5123	1.18 (1.08-1.29)	0.0002
Above + addition of CRP and WBC	373 / 4431	1.11 (1.00-1.22)	0.0471
Above + addition of cystatin C	373 / 4430	1.10 (0.99-1.21)	0.0716
Above + addition of NT-proBNP and Troponin	371 / 4406	1.05 (0.95-1.16)	0.3710
Above + addition of GDF-15	371 / 4406	0.98 (0.88-1.09)	0.6706
Non-CABG major bleeding			
Adjustment for rand. treat. and clin. risk factors	198 / 5123	1.37 (1.21-1.55)	<.0001
Above + addition of CRP and WBC	167 / 4431	1.31 (1.14-1.51)	0.0002
Above + addition of cystatin C	167 / 4430	1.31 (1.14-1.51)	0.0002
Above + addition of NT-proBNP and Troponin	166 / 4406	1.32 (1.14-1.52)	0.0002
Above + addition of GDF-15	166 / 4406	1.26 (1.09-1.46)	0.0023

group were; 5.2%, 7.5%, 9.2% and 11.9%; and for non-CABG major bleeding: 2.4%, 2.2%, 3.8% and 7.2%. (Tabell).

OPG levels at 1 month (n= 3,668), in patients free from any outcome event, were likewise independently associated with bleeding during follow up (n=69); with an adjusted HR of 1.43 (1.04-1.96). There was no interaction between admission OPG levels and randomized treatment.

Conclusion: In multivariable analysis, osteoprotegerin was a strong and independent marker of major bleeding but not of ischemic CV events. Thus, OPG seems to provide important independent information on bleeding risk in patients with ACS.

T5213 Elevated Lp(a) Levels Strongly Increase the Risk for Cardiovascular Disease in Patients With Familial Hypercholesterolemia

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Introduction: Several studies have suggested that elevated levels of Lp(a) is a strong and independent risk factor for cardiovascular disease (CVD) in the general population. We and others have previously demonstrated that high Lp(a) levels is a CVD risk factor in familial hypercholesterolemia (FH) patients. This may suggest that high Lp(a) levels leads to a more aggressive phenotype in presence of a high LDL-cholesterol (LDL-C), which falls in line with clinical treatment of high Lp(a) often consisting of statin treatment to reduce the progression of atherosclerosis.

Hypothesis: In patients with FH, to investigate if CVD was more prevalent in patients with Lp(a) ≥ 900 mg/L than in those with Lp(a) levels < 900 mg/L despite otherwise similar cholesterol burden. Methods: Retrospective collection of data from medical charts of patients with FH followed at lipid clinics in Norway.

Results: All data are presented as mean (standard deviation) unless otherwise stated. In total, 614 adult FH patients with Lp(a) measurements were included in the study. FH patients with Lp(a) levels < 900 mg/L (n=515) was compared to FH patients with Lp(a) ≥ 900 mg/L (n=99). The two groups were otherwise similar in cholesterol burden in terms of age of FH diagnosis (30.2 [15.7] vs. 29.6 [15.2] years, P=0.748), age at start of lipid-lowering treatment (31.2 [12.4] vs. 33.2 [12.2] years, P=0.233), pretreatment LDL-C (6.8 [1.9] vs. 6.7 [1.9] mmol/L, P=0.726) and on-treatment LDL-C (3.4 [1.3] vs. 3.3 [1.2] mmol/L, P=0.716). The Lp(a) < 900 group had Lp(a) levels of median 196 (range 10-894) mg/L, and the Lp(a) > 900 group had levels of median 1200 (range 900-3180) mg/L, P<0.001. The Lp(a) ≥ 900 group had significantly higher prevalence of CVD (35.6 %) compared with the Lp(a) < 900 group (14.0 %), P<0.001. CVD was defined as cardiac bypass surgery (8.1% vs. 2.5%, P<0.05), clinical diagnosis of angina pectoris (9.1% vs. 4.1%; P< 0.05), percutaneous coronary intervention (3.0% vs. 1.4%, P>0.2) and myocardial infarction (12.1% vs. 6.0%; P<0.05), in the Lp(a) ≥ 900 and Lp(a) < 900 group, respectively.

Conclusions: Elevated Lp(a) levels severely aggravates the FH phenotype by increasing the prevalence of CVD. This may suggest that high Lp(a) is more important in presence of a high LDL-C.

M4184 Diastolic Dysfunction in the Ischemic Pig Heart is Partially Restored by Dobutamine-Ivabradine Combination, but Not by Omecamtiv Mecarbil, Due to Increasing Lusitropy and Filling Time

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Introduction: Acute diastolic failure in post-ischemic cardiogenic shock is associated with a grave prognosis. We assessed the impact of two novel inotropic strategies on the diastolic properties in a clinically relevant swine model of post-ischemic acute heart failure.

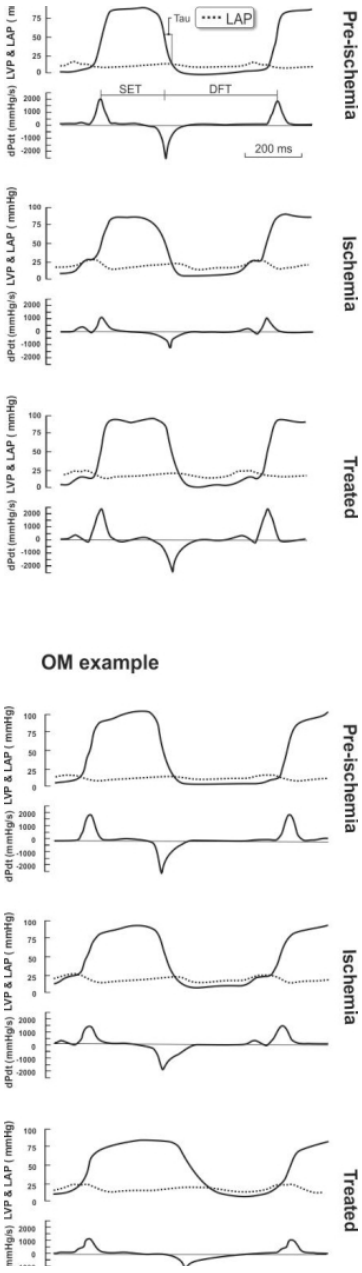
Hypothesis: Dobutamine-ivabradine and omecamtiv mecarbil treatments exert different lusitropic effects on early diastole in acute heart failure.

Methods: Anesthetized pigs were subjected to left ventricular ischemia through the injection of polystyrene microspheres into the coronary main stem (n=12). The animals were then randomized to receive omecamtiv (OM) (bolus 0.75 mg/kg plus 0.5 mg/kg/h) (n=6) or a combination of dobutamine (5 µg/kg/min) and ivabradine (0.29 ±0.16 mg/kg) (D+I) (n=6).

Results: Ischemia reduces stroke volume, despite an increase in left atrial pressure. This decrease in stroke volume is associated with impaired early relaxation, systolic dilatation and an increase in late diastolic stiffness. Both treatments reversed systolic dilatation, but only D+I was able partially to restore the stroke volume from 26 ± 5 to 33 ± 5 mL. D+I enhanced early relaxation (Tau decreased from 45 ± 11 to 29 ± 4 ms) and prolonged the diastolic filling time

(DFT, increased from 338 ± 60 to 352 ± 40 ms), whereas OM prolonged Tau (42 ± 5 to 62 ± 10 ms) and shortened the DFT (from 326 ± 68 to 248 ± 84 ms).

Conclusions: Our data suggest that the lusitropic effect of dobutamine-ivabradine treatment, an effect not observed with omecamtiv, is necessary for the restoration of post-ischemic early diastolic function and thus restoration of stroke volumes in severe acute heart failure.



M4268 Lower Systemic Arterial Compliance is Associated With Increased Cardiovascular Morbidity and Mortality in Aortic Valve Stenosis

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Introduction: Systemic arterial compliance (SAC) significantly influences cardiovascular morbidity and mortality in hypertension, but this has not been assessed in a prospective study in aortic stenosis (AS).

Hypothesis: Lower SAC is associated with reduced outcome in AS.

Methods: Data from 1471 patients (38% women) with initially asymptomatic mild-moderate AS enrolled in the Simvastatin and Ezetimibe in Aortic Stenosis study was used. Median follow-up was 4.3 years. SAC was assessed as the ratio of stroke volume index to central pulse pressure.

Results: In multivariable linear regression analysis, lower SAC at baseline was associated with older age, hypertension, obesity, presence of a small aortic root and more severe AS (all $p<0.001$). In Cox regression analysis, lower SAC (per 1 ml/m²/mmHg) was associated with higher hazard rates for major cardiovascular events, aortic valve events, ischemic cardiovascular events and total mortality (all $p<0.05$), also after adjusting for hypertension, left ventricular mass, AS severity, presence of a small aortic root, randomized study treatment and aortic valve replacement (Table).

Events	*HR (95% CI)*	*p-value*
Major cardiovascular event (n=497)	*2.38 (1.64-3.45)*	*<0.001*
Aortic valve event (n=458)	*2.33 (1.56-3.45)*	*<0.001*
Ischemic cardiovascular event (n=243)	*2.08 (1.22-3.57)*	*0.007*
Non-haemorrhagic stroke (n=50)	*5.26 (1.43-20.00)*	*0.013*
Cardiovascular death (n=75)	*6.67 (2.17-20.00)*	*0.001*
Total mortality (n=148)	*5.56 (2.56-11.11)*	*<0.001*

Conclusion: In AS patients without known cardiovascular disease, but a high prevalence of hypertension, lower SAC is associated with higher morbidity and mortality independent of other well-known prognosticators. Table. The association of lower SAC with cardiovascular events in asymptomatic AS in multivariable Cox analyses.

S4045 Regional Myocardial Work by Magnetic Resonance Imaging and Noninvasive Left Ventricular Pressure: A Feasibility Study in Left Bundle Branch Block

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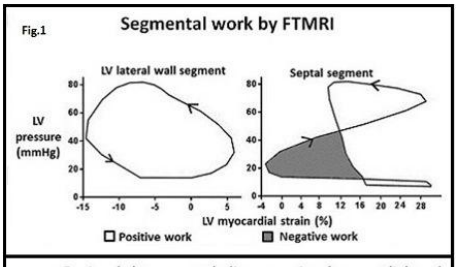
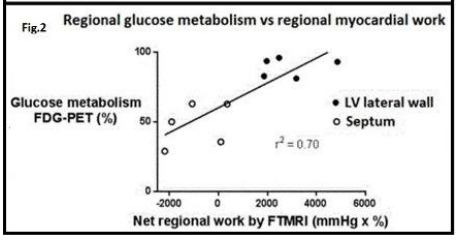
Introduction: We have recently innovated and validated a noninvasive estimate of the left ventricular (LV) pressure curve. This study investigates the feasibility of calculating regional myocardial work from strain by feature tracking magnetic resonance imaging (FTMRI) and noninvasive LV pressure.

Purpose: To determine if regional myocardial work can be measured clinically by MRI and noninvasive LV pressure, and to test the feasibility of this approach in left bundle branch block (LBBB).
Method: In 17 patients with heart failure (9 non-ischemic and 8 ischemic), ejection fraction ≤ 35% and LBBB, circumferential strain was measured by FTMRI in a midventricular short axis cine view. By definition, work during myocardial shortening is positive and work during lengthening is negative. Net work is the sum of positive and negative work. Five non-ischemic patients also underwent 18F-fluorodeoxyglucose (FDG) Positron Emission Tomography (PET). Segmental values were reported as percentages of the segment with maximum myocardium FDG uptake.

Results: Net septal work was -972±1805 (mean±SD), whereas net LV lateral wall work was 2824±1489 mmHg×% (p=0.001). Negative work in the septum implies that energy is absorbed due to work done in the LV lateral wall (Figure 1). A similar pattern was observed in FDG uptake, with septal uptake of 48.1±13.6% and LV lateral wall uptake of 89.3±6.1%. Regional FDG uptake correlated with regional myocardial work (Figure 2).





Conclusions: FTMRI in combination with noninvasive LV pressure demonstrated markedly different workloads on the septum and LV lateral wall in patients with LBBB. Work distribution corresponded well with regional glucose metabolism. These results suggest that FTMRI in combination with noninvasive LV pressure is feasible as a clinical tool to measure regional myocardial work.

S4048 Plasma Notch Ligand Dll1 is Associated With Symptom Severity and Diastolic Dysfunction in Dilated Cardiomyopathy

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Introduction: In idiopathic dilated cardiomyopathy (IDC), left ventricular dilation is caused by myocardial remodeling, to which inflammation, fibrosis and changes in the extracellular matrix composition contribute. The subprocesses may involve Notch signaling. Circulating Notch ligand Delta-like-1 (DLL1) is elevated in chronic heart failure (HF).

Hypothesis: We hypothesized that in IDC, circulating DLL1 would correlate to clinical and hemodynamic variables.

Methods: We measured plasma DLL1 in a prospectively recruited cohort of 102 patients with IDC, left ventricular end diastolic internal diameter ≥6.5 cm and ejection fraction ≤40% and in 32 age- and sex-matched healthy controls.

Results: The study population had a median DLL1 of 11.3 ng/mL (interquartile range 9.7, 13.2). DLL1 was higher in patients in NYHA class III/IV compared to controls and NYHA class I/II (Figure 1A). Survival was poorer in patients with high DLL1 plasma levels (Figure 1B). DLL1 correlated with N-terminal pro-B-type natriuretic peptide (NT-proBNP), C-reactive protein (CRP), White blood cell count (WBC) and Troponin T (TnT), and modestly with echocardiographic indicators of diastolic dysfunction (DD) (Table 1). Particularly high DLL1 levels were observed in patients with severe HF (i.e. NYHAIII/IV) and high E/e' or E/A ratios (Figure 1C).

Conclusions: Plasma DLL1 is elevated in IDC and correlates with neurohormonal activation, inflammation and adverse outcome. Levels are particularly high in patients with severe HF and DD. Notch signaling may have a role in severe HF caused by IDC.

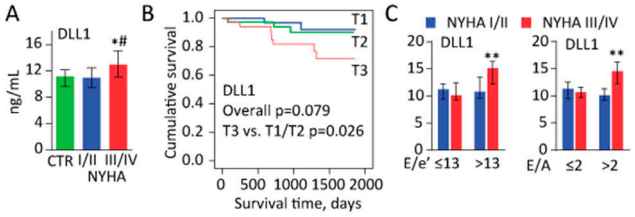

Figure 1. A Plasma levels of DLL1 in IDC patients with NYHA functional class I/II and III/IVand healthy controls (CTR). *p<0.05 vs. CTR, #p<0.01 *vs.* NYHA I/II. **B** Kaplan-Meier plot for the association between lower T1(blue), middle T2(green) and upper T3 (red) tertiles of DLL1 and all-cause/anticipated mortality. **C** Plasma levels of DLL1 according to diastolic dysfunction as assessed by echocardiography. **p<0.01 vs. other groups.

Table 1. DLL1 levels at baseline (n=102) and correlation (Spearman) with clinical, biochemical and echocardiographic measures

	Total population	DLL1 correlation
Clinical characteristics		
Age (years)	51±14	-0.14
Men – %	73	0.09
NYHA I/II/III/IV – %	15 /60/20/6	0.26**
Biochemistry		
WBC (10^9/L)	7.7 (6.2, 9.4)	0.33**
CRP (mg/L)	3.0 (1.1, 7.6)	0.51**
NT-proBNP (pg/ml)	1332 (583, 2903)	0.31**
TnT (ng/L)	13 (10, 20)	0.28**
Echocardiography		
LVEF (%)	26±10	-0.24*
E/e' ratio (%)	12.3 (9.8, 18.1)	0.23*
E/A ratio (%)	1.3 (0.8, 2.1)	0.15

Values are presented as mean± standard deviation, median (interquartile range) or percent as appropriate. E/e' ratio, Pulse wave Doppler peak early mitral filling (E-wave) to tissue Doppler mitral annular e' velocity; E/A ratio, Pulse Wave Doppler peak early mitral filling (E-wave) to peak late mitral filling (A-wave) velocity.

M5008 Ventricular Shape in TGA Patients Differs Significantly From Controls

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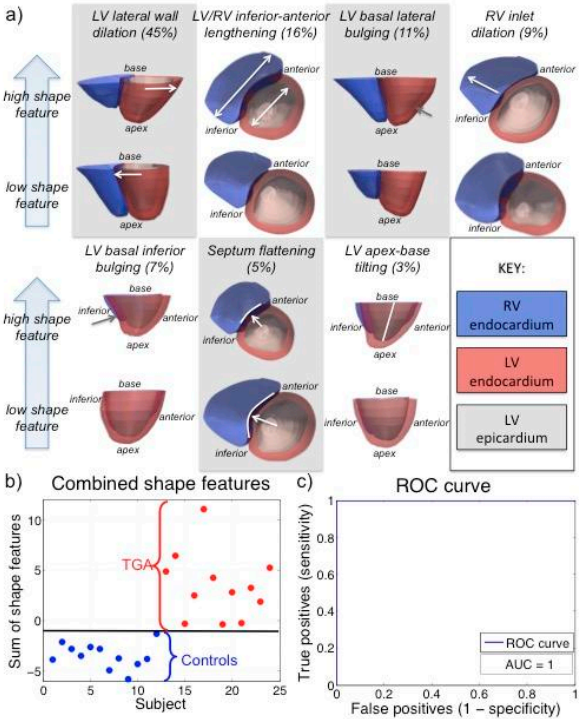
Introduction: In classic transposition of the great arteries (TGA), little is known about how the condition impacts ventricular structure, and if/how remodeling occurs as a consequence of the original condition and after the arterial switch operation (ASO) in the early neonatal period. We hypothesized that structural differences may be present in ASO TGA patients compared to controls, and sought to quantify these differences to determine if subjects can be defined as healthy or TGA based on ventricular shape information alone.

Methods: We studied population of 12 TGA patients (6 male, age 12±1.5 years) and 12 age-matched controls (4 male, age 13±1.7 years). Ventricular shape was segmented from short-axis CMR images at the end-diastole (ED) phase of the cardiac cycle and ED volume (EDV) was computed from the segmentation. Statistical shape analysis was applied to compute the most common ventricular shape features in the TGA population, after indexing for BSA. Each subject was characterized quantitatively as a combination of these shape features for the control- and TGA-populations. The sum of these values was used as a shape measure. A statistical classification method was applied to this measure to predict the patient group.

Results: Seven shape features captured 95% of the variance of shape in the TGA population and are summarized in the figure (a) with the % of variance of each shape feature given in brackets. The sum of the shape features for both populations is shown in the figure (b), as well as the line that divides the groups (in black). The classification yielded 100% accuracy (i.e. subjects were correctly classified). The resulting receiver operating characteristic curve is shown in the figure (c). There were no EDV differences between groups.



Conclusions: We found significant shape differences between the TGA patients and the healthy controls from the quantified measures of ventricular shape, which was highly accurate in discriminating between the two groups.

M5014 Ventricular Shape Correlates to Arrhythmic Events in ARVC Patients

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Introduction

Arrhythmogenic Right Ventricular Cardiomyopathy (ARVC) patients undergo ventricular shape remodeling as the disease progresses. Since this remodeling may be indicative of arrhythmic risk, we investigated the relationship between computationally calculated shape features in ARVC patients and history of arrhythmias.

Methods

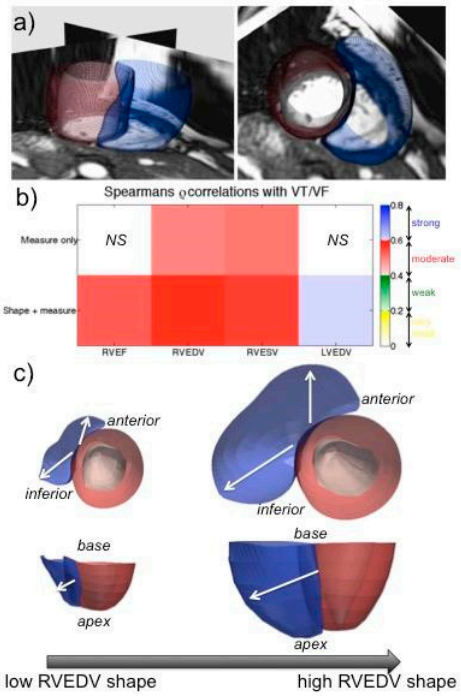
A population of 27 ARVC patients was studied (13 male, age 38 ± 14 years, 12 with a history of VT or VF). Three-dimensional (3D) models of the LV endocardium and epicardium, as well as the RV endocardium, were created at ES and ED from CMR recordings (Figure a). Partial least squares analysis was applied to the 3D ES geometry together with measures of RVEDV, RVESV, RVEF, LVEDV, or LVEF, to compute common shapes features in the population. For visualization purposes, each shape feature was plotted in 3D from low to high values of the feature. Correlations for volume/EF measures alone and these measures supplemented with the computed common shape features were calculated against history of arrhythmias.

Results

A strong correlation was found between VT/VF and the combination of LVEDV with shape, while volumes alone did not correlate with VT/VF (Figure b). Similarly, moderate correlation was found when RVEF was combined with shape, while not for RVEF alone. Shape also improved the correlation with VT/VF for RVEDV and RVESV. Visualization of the RVEDV shape feature showed RV inlet and RV outlet dilation, and RV freewall bulging (Figure c).

Conclusions

Supplementing traditional measures of structural remodeling with advanced shape analysis provides better clinical correlation to VT/VF than traditional measures alone. Shape analysis methods could be important tools to better predict arrhythmias in patients and provide visualization of ARVC ventricular remodelling.



T4075 What is a Realistically Low Mortality in Cardiogenic Shock?

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Background: In geographic areas with abundant revascularization options, both the incidence and mortality of cardiogenic shock (CS) seem to be decreasing. However, an aggressive revascularization strategy for ischemic heart disease seems to bring acute CS-mortality only to a sub 40% level and therefore a need for improvement still exists. We have established a "cardiogenic shock-team" with the intent to institute ECMO-treatment early in patients deemed insufficiently supported with medical treatment and acute revascularization.

Methods: We evaluated 1497 patients diagnosed with cardiac failure admitted to the University Hospital of Northern Norway 2013 and 2014, after the systematic ECMO-algorithm was established, to find cases of cardiogenic shock and postcardiotomia heart failure. These patients were compared to an earlier study in our institution during the years 2003 and 2004.

Results: Our pre-ECMO results demonstrated a 30 day mortality of 38% in 126 patients with cardiogenic shock and postcardiotomia heartfailure treated in a 2 year periode. Twelve % (n=15) of

the diseased patients were deemed to be potential candidates for ECMO-treatment.

In the two year period since establishing the ECMO-team model we treated 73 patients using identical criteria for CS. 12 patients (16%) were treated with ECMO. CS hospital mortality during the last period was 28%, . Among the nonsurvivors ECMO was declined because of age in 32%, preexisting co morbidity in 9%, uncontrolled bleeding in 5% and multi organ failure in 27%. Hospital mortality among the ECMO patients was 25% and 30-day mortality was 33%. Kaplan-Meier curves comparing ECMO vs non ECMO patients show no difference in long term survival.

We identified 5 nonsurviving non-ECMO patients who potentially could have been selected for ECMO-treatment by our contemporary ECMO-protocol.

Conclusion: Establishing a cardiogenic shock-team has improved the survival of these patients. Our retrospective analysis indicates that the triage of these patients can be even more refined. However, given some of these patients age and comorbidity, a close to zero mortality does not seem clinically realistic.

T4081 Increased Heart Rate Aggravates Diastolic Dysfunction in Left Bundle Branch Block

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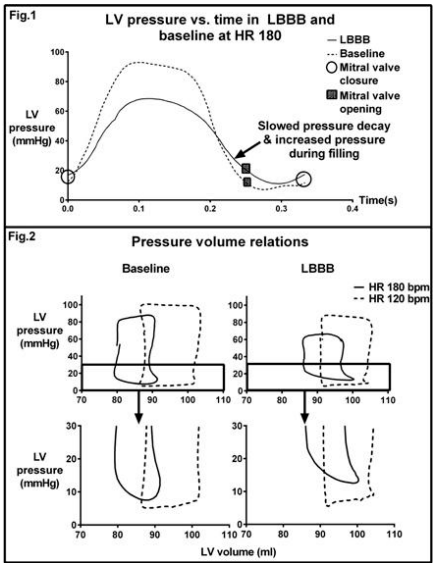
Introduction: In left bundle branch block (LBBB) left ventricular (LV) pressure decay is slowed due to dyssynchronous relaxation. At low heart rates (HR) this may not substantially affect diastolic pressure as there is still sufficient time for complete relaxation and filling.

Hypothesis: The slowed pressure decay and abbreviated diastole in LBBB will increase LV filling pressure and increase diastolic stiffness due to incomplete relaxation at high HR.

Methods: In 7 canines we performed atrial pacing at high (166± 17 (SD)) and low (120± 1 bpm) HR before and after induction of LBBB. LV volume and pressure and pericardial pressure were measured. Mean diastolic pressure was calculated as average LV pressure between mitral valve opening and closure. The time constant of LV pressure decay (*tau*), and minimum dP/dt were calculated. LV diastolic stiffness was assessed using end diastolic transmural LV pressure-volume (PV) relations.

Results: *Tau* was increased, minimum dP/dt lower, and duration of diastole shorter at both HRs in LBBB compared to baseline ($p< 0.05$). At low HR there was no difference in mean diastolic pressure between LBBB (6.4±2.2 mmHg) and baseline (6.2±1.7 mmHg). At high HR however, mean diastolic pressure was significantly higher, 11.2±4.6 mmHg in LBBB vs. 7.2±2.3 mmHg at baseline ($p< 0.01$) (Fig.1). Increasing HR resulted in an upward shift of the LV diastolic transmural PV relation of 4.0±1.8 mmHg in LBBB, whereas no upward shift (-0.1± 2.0 mmHg) was seen prior to induction of LBBB ($p< 0.001$) (Fig. 2).

Conclusions: Increased HR in LBBB increased diastolic stiffness and increased LV diastolic pressure. This mechanism may lead to dyspnoea and exercise intolerance in LBBB patients.



T5027 Impaired Subendocardial Contractility and Longitudinal Shortening With Aging, Reduce Midwall Fiber Stress, Increasing Circumferential Shortening and Preserving Ejection Fraction

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Introduction: Left ventricular (LV) longitudinal function declines with age, potentially due to subclinical pathological development of fibrosis and reduced perfusion in the subendocardial region. On the other hand, radial function is increased, thus preserving ejection fraction (EF). The mechanism of compensatory increased radial function is not fully understood.

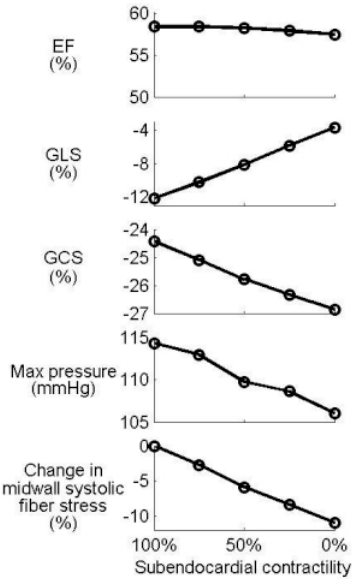
Hypothesis: Impaired contractility in the subendocardium with predominantly longitudinal fibers, reduces longitudinal shortening but also reduces systolic midwall fiber stress. This

reduced "afterload" of the predominantly circumferentially oriented midwall fibers, increases circumferential shortening which preserves EF.

Methods: We applied a finite element model of the LV which included nonlinear, transversely isotropic passive elastic myocardial properties, active fiber tension prescribed as a function of time and fiber length, and the anatomical transmural change in fiber orientation from endocardium to epicardium. Simulations of the cardiac cycle were performed; first with homogenous contractility and then with reduced contractility in the subendocardial region. We assessed changes in EF, peak systolic pressure, global longitudinal strain (GLS), global circumferential strain (GCS), and fiber stress.

Results: Reduced subendocardial contractility decreased longitudinal shortening (Figure), while circumferential shortening increased. There was practically no change in EF. Peak systolic pressure was moderately reduced. In the midwall, systolic fiber stress was reduced.

Conclusions: Reduced contractility in the subendocardium, reduces longitudinal shortening, but also reduces midwall circumferential fiber stress which seems to promote compensatory increased circumferential shortening that maintains EF. This mechanism may be one explanation for the observed changes in myocardial strains during aging.



S5100 The Impact of Aortic Valve Replacement on the Intermediate Survival of Patients With Severe Aortic Stenosis

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Introduction Recently more comorbid, elderly and frail patients with severe aortic stenosis are being eligible for aortic valve replacement (AVR) due to emerging new techniques. However, there is a lack of real life studies presenting impact of AVR in this population.

Hypothesis AVR is of prognostic significance vs. medical treatment in patients with severe aortic stenosis (AS) adjusted for significant confounders and effect modifiers.

Methods A prospective observational study of consenting patients >18 years of age under consideration for AVR at our tertiary teaching hospital. We used an explanatory strategy to investigate the relationship between AVR and survival. All other variables were of interest only as possible confounders or effect modifiers of this association. Maentel-Haenszel stratification analysis was performed to quantify confounders and to pinpoint effect modifiers using the Breslow and Day test of heterogeneity. Confounding was quantified by comparing the crude incidence rate ratio (IRR) with the adjusted Maentel-Haenszel IRR. Adjustment for multiple confounders was performed using the Cox proportional hazard regression model with a manual backward stepwise elimination procedure. The follow-up period was defined as time from AVR or from initial consultation (for non-operated patients) to date of death or study closing.

Results Among 480 evaluated patients with severe AS, 389 had AVR and 91 were declined operative treatment. One-, three-, and five-year cumulative survival rates, respectively, were 95%, 87%, and 73% among operated patients, and 82%, 47%, and 27% among non-operated patients. Median survival time was 1604 days (95% CI, 1554-1655) in operated patients vs. 1090 days (95% CI, 954-1226) in non-operated patients ($p<0.001$). The effect of operation on mortality depended on the interaction with diabetes, when adjusted for significant confounders (i.e. age, atrial fibrillation, NT-proBNP, hs-Troponin T, and NYHA classification). We found an effect of AVR on mortality in patients without diabetes (HR, 0.29; 95% CI, 0.19-0.468; $p<0.001$), but not among patients with diabetes.

Conclusions AVR shows great prognostic effect in patients without diabetes.

M2052 Alirocumab Dosing in a Real World Setting: Data From an Open-label Treatment Extension to the ODYSSEY Program for Patients With Heterozygous Familial Hypercholesterolemia

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Introduction: ODYSSEY OLE (NCT01954394) is an open-label extension (OLE) study of four Phase 3 clinical trials (FH I, FH II, LONG TERM [LTS] and HIGH FH) evaluating long-term efficacy and safety of alirocumab (ALI) in patients with heterozygous familial hypercholesterolemia (HeFH) over up to 3.5 years of treatment.

Objective: ALI can be administered as 75 or 150 mg Q2W, but how this dosing strategy is applied in daily practice is largely unknown. We assessed dosing strategies used during OLE.

Methods: Patients were on maximally tolerated statin +/- other lipid-lowering therapy. Patients started on ALI 75 mg Q2W (patients enrolled from HIGH FH started OLE with 150 mg Q2W and were not analyzed here). Physicians could adjust the ALI dose based on clinical judgment and LDL-C level; if further LDL-C reduction was required the ALI dose could be increased to 150 mg Q2W.

Results: 909 patients (mean age 54.6 years, 56.1% male) with HeFH were analyzed. At OLE entry, HeFH patients from LTS (n=318) had a higher mean baseline LDL-C (161.7 mg/dL) than those from FH I (n=392; 106.7 mg/dL) and FH II (n=199; 87.0 mg/dL). These values reflect both patients receiving placebo during the parent studies as well as 8 weeks off-treatment for those enrolled from LTS (those from FH I/II began OLE on completing double-blind treatment). 868 patients (95.5%) completed ≥1 year of treatment. At time of analysis, 50/909 (5.5%) had discontinued treatment (20 [2.2%] due to adverse events).

During OLE, 59.1% of patients remained on ALI 75 mg Q2W and in 40.9% the dose was increased to 150 mg Q2W. Median time to first dose increase was 12.6 weeks and in nearly all cases was due to LDL-C level being deemed too high. Mean LDL-C in patients maintained on 75 mg Q2W during OLE was 67.6 mg/dL. For those who received a dose increase to 150 mg Q2W, mean LDL-C was 128.7 mg/dL prior to dose adjustment.

Overall, 77.8% of patients reported any TEAE, a rate similar to the ALI and placebo arms in the parent studies. Injection site reactions were reported by 5.4%, neurological TEAEs by 2.0% and neurocognitive TEAEs by 1.1% of patients.

Conclusions: In this real world setting, ALI 75 mg Q2W provided sufficient control of LDL-C level in a majority of HeFH patients, with dose increase to 150 mg Q2W used for those requiring greater LDL-C reduction.

M2178 Empagliflozin Reduces Markers of Arterial Stiffness, Vascular Resistance and Cardiac Workload in EMPA-REG OUTCOME

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Introduction: In EMPA-REG OUTCOME®, empagliflozin added to standard of care in patients with type 2 diabetes and established vascular disease, significantly reduced the primary composite outcome of CV death, non-fatal myocardial infarction or non-fatal stroke, a result driven mainly by a 38% reduction in CV death. We aimed to assess the vascular effects of empagliflozin in the trial, beyond its recognized effects in reducing systolic blood pressure (SBP) and diastolic BP (DBP).

Hypothesis: We hypothesized that empagliflozin reduced 1) pulse pressure (PP), a vascular marker of arterial stiffness determined by the cardiac output, the stiffness of elastic central arteries and wave reflection (PP = SBP - DBP), 2) mean arterial pressure (MAP), a measure reflecting the cardiac cycle determined by the cardiac output, systemic vascular resistance, and central venous pressure (MAP = ([2 x diastolic BP]+ systolic BP)/3), and 3) the double product (DP), a marker of cardiac workload and an indirect measure of myocardial oxygen demand (DP = heart rate x SBP).

Methods: Patients with type 2 diabetes and high CV risk were randomised to receive placebo, empagliflozin 10 mg, or empagliflozin 25 mg in addition to standard of care. We analysed changes from baseline to week 164 for SBP, DBP, HR, PP, MAP and DP, between treatment and placebo groups using a mixed model repeated measures analysis.

Results: In total, 2333, 2345 and 2342 patients received placebo, empagliflozin 10 mg and empagliflozin 25 mg, respectively and followed for a median period of 3.1 years. There were nominal significantly greater reductions in PP, MAP and DP with empagliflozin treatment as compared with placebo (Table), without increases in mean HR (Table).

Table. Effects of empagliflozin on blood pressure, heart rate and markers of arterial stiffness, vascular resistance and cardiac workload in EMPA-REG OUTCOME

		Placebo	Empagliflozin 10 mg	Empagliflozin 25 mg
Systolic BP (SBP) (mmHg)	N analysed at baseline/week 164	2322/981	2322/1034	2323/1070
	Mean (SE) SBP at baseline	135.79 (0.36)	134.91 (0.35)	135.65 (0.35)
	Placebo-adjusted mean (95% CI) difference		-3.33 (-4.47, -2.18)***	-2.58 (-3.72, -1.45)***
Diastolic BP (DBP) (mmHg)	N analysed at baseline/week 164	2322/981	2322/1034	2323/1070
	Mean (SE) DBP at baseline	76.83 (0.21)	76.60 (0.20)	76.68 (0.20)
	Placebo-adjusted mean (95% CI) difference		-0.52 (-1.19, 0.15)	-0.19 (-0.86, 0.48)
Heart rate (HR) (bpm)	N analysed at baseline/week 164	2322/981	2322/1034	2323/1070
	Mean (SE) HR at baseline	70.74 (0.23)	70.96 (0.22)	70.52 (0.22)
	Placebo-adjusted mean (95% CI) difference		-0.53 (-1.28, 0.22)	-0.42 (-1.16, 0.32)
Pulse pressure (PP) (mmHg)	N analysed at baseline/week 164	2322/981	2322/1034	2323/1070
	Mean (SE) PP at baseline	58.96 (0.31)	58.30 (0.31)	58.97 (0.31)
	Placebo-adjusted mean (95% CI) difference		-2.69 (-3.63, -1.75)***	-2.33 (-3.26, -1.40)***
Mean Arterial Pressure (MAP) (mmHg)	N analysed at baseline/week 164	2322/981	2322/1034	2323/1070
	Mean (SE) MAP at baseline	96.49 (0.22)	96.04 (0.22)	96.33 (0.21)
	Placebo-adjusted mean (95% CI) difference		-1.48 (-2.22, -0.75)***	-1.01 (-1.74, -0.28)**
Double product (DP) (mmHg x bpm)	N analysed at baseline/week 164	2322/981	2322/1034	2323/1070
	Mean (SE) DP at baseline	9596.78 (39.35)	9567.95 (38.92)	9555.47 (38.34)
	Placebo-adjusted mean (95% CI) difference		-295.31 (-422.16, -168.46)***	-224.14 (-350.18, -98.10)***

Differences are analysed from baseline to week 164. P-values for adjusted means based on mixed model repeated measures analysis in patients who received ≥1 dose of study drug. *p<0.05; **p<0.01; ***p<0.001 (all vs placebo).

Conclusions: Empagliflozin had favorable effects on BP, arterial stiffness, vascular resistance and on the indirect measure of cardiac workload. Further analyses are needed to determine the potential contribution of these changes to the reduction in CV mortality.

S2069 Vitamin D and Cardiovascular Mortality: An Individual Participant Data Meta-Analysis With Standardized 25-Hydroxy-vitamin D

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Background: Vitamin-D deficiency (25(OH)D) is associated with an increased risk for cardiovascular (CV)-mortality. Nevertheless cut-off values remain debated and interventional studies reported largely negative results. We therefore performed an individual-participant meta-analysis investigating the association between standardized 25(OH)D and CV-mortality.

Methods: In a European consortium of eight prospective studies, including seven general population and one hospital based cohort, we used vitamin-D standardization program protocols to standardize 25(OH)D measurements. Meta-analyses using individual participant data (IPD) were performed to study the associations of 25(OH)D with CV-mortality implementing parametric (Weibull) survival model and restricted cubic splines

Results: We analysed 26916 study participants (median age: 61.6years, 58%females, median 25(OH)D: 53.8nmol/L). During a median follow-up of 10.5years, 1810 fatal CV event occured. Excessively increased CV-risk was seen in patients with 25(OH)D levels below 30nmol/L (HR=2.21 95%CI 1·50-3·26), representing 11.0% of the population studied.

Conclusions: In the IPD meta-analysis using standardized measurement of 25(OH)D we observed an association between 25(OH)D ≤30nmol/L and increased risk of CV-mortality. Treating individuals with 25(OH)D levels ≥50nmol/L, which are not associated with a substantially increased CV-risk, is unlikely to result in a clinically meaningful benefit.

557 Effect of Different Cut Points for Defining Success Post-Catheter Ablation for Persistent Atrial Fibrillation - A Sub-Study of the STAR AF II Trial

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Introduction: The 30-seconds definition for success post atrial fibrillation (AF) ablation has been chosen as the gold standard but little is known how choosing another cut point would affect ablation trial outcomes.

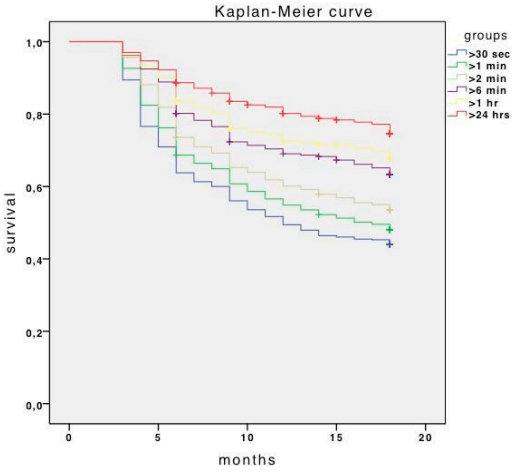
Hypothesis: This study sought to compare success rates based on different thresholds of defining success.

Methods: Data were collected from patients included in the STAR AF II Trial. Patients were followed-up for 18 months with visit, ECG, and 24 hour Holter at 3, 6, 9, 12 and 18 months. In addition, Trans-telephonic monitoring (TTM) transmission was performed weekly for 18 months

and whenever symptoms were reported. After a 3 months blanking period, recurrences were re-analyzed and defined as episodes of AF/AFL/AT >30 seconds (group A), >1 minute (group B), >2 minutes (group C), >6 minutes (group D), >1 hour (group E) and >24 hours (group F). Arrhythmia-free survival curves were generated by the Kaplan-Meier method and compared with the log-rank test.

Results: Five hundred and thirty patients were included in the analysis. Compliance with follow-ups was 85% and for weekly TTM 75%. The pooled success rate for all the three arms in the study was 44% using freedom-from-AF/AFL/AT >30 seconds, for the other cut-off points, the pooled success was 48.1% (B), 53.6% (C), 63.8% (D), 68.3% (E) and 75.1% (F). Log-rank test showed a significant difference between the six survival curves ($p < .0001$, figure). Compared to group A there was no significant difference in outcome for group B ($p = .095$). However, all the other cut-offs were significantly higher than A.

Conclusions: The success rate significantly increases as higher thresholds for defining success are used. There is little difference between 30 seconds and one minute, but all other thresholds result in significantly higher success rates.



739 Relationship of Incident Atrial Fibrillation to the Electrocardiographic Strain Pattern in Hypertensive Patients With Electrocardiographic Left Ventricular Hypertrophy

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Background: Atrial fibrillation (AF) is strongly related to hypertension and to left ventricular hypertrophy (LVH) and both regression of ECG LVH and achievement of lower systolic blood pressure (SBP) are associated with lower incidence of AF. The ECG strain pattern of lateral ST depression and T-wave inversion has been associated with more severe LVH, decreased LV systolic function and an increased risk of cardiovascular mortality and morbidity, including new heart failure (HF). However, whether ECG strain is associated with an increased risk of new AF is unclear.

Methods: Risk of new-onset AF was examined in relation to the presence of the strain pattern on baseline ECG in 7921 hypertensive patients with ECG LVH with no history of AF, who were in sinus rhythm on their baseline ECG, had baseline strain determination and were randomized to losartan- vs atenolol-based treatment.

Results: During 4.7±1.1 years follow-up, new-onset AF was diagnosed in 621 patients (7.8%). Baseline ECG strain was present in 882 patients (11.1%) and was associated with a significantly higher 5-year incidence of AF in Kaplan-Meier estimates (12.2 vs 7.4%, $p<0.001$) and with a 66% greater risk of new AF in a univariate Cox model (HR 1.66, 95% CI 1.34-2.06, $p<0.001$), compared with the absence of ECG strain. After adjusting for other univariate predictors of new AF in this population, including age, sex, race, prior anti-hypertensive treatment, randomized treatment allocation, prevalent diabetes, history of ischemic heart disease, prior myocardial infarction, stroke or HF, baseline serum cholesterol and urine albumin/creatinine ratio entered as standard covariates and incident HF and on-treatment diastolic BP, SBP, heart rate and Cornell product LVH entered as time-varying covariates, ECG strain remained associated with a 39% greater risk of new-onset AF (HR 1.39, 95% CI 1.09-1.76, $p=0.008$).

Conclusions: The presence of strain on a baseline ECG is strongly associated with an increased risk of developing new-onset AF in hypertensive patients with ECG LVH, independent of other AF risk factors and the effects of incident HF, LVH regression and SBP reduction. These findings suggest that hypertensive patients with ECG strain should be followed closely for development of new AF.

711 The Relationship of All-Cause Mortality to Average On-Treatment Systolic Blood Pressure is Significantly Related to Baseline Systolic Blood Pressure: Implications for Interpretation of the SPRINT Study

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Background: The SPRINT study demonstrated that targeting systolic blood pressure (SBP) <120 mm Hg was associated with lower cardiovascular event and mortality rates. However, in the LIFE study, a lower achieved SBP (<130 mm Hg) was associated with increased mortality. Mean baseline SBP in SPRINT was 140 and a third of the population had a baseline SBP ≤132, raising the question of whether the lower baseline SBP in SPRINT could in part account for these differences.

Methods: All-cause mortality in relation to tertiles of on-treatment average SBP achieved was examined in patients with baseline SBP ≤ or > 25th percentile value of 164 mm Hg during 4.8±0.9 years follow-up in 7998 non-diabetic hypertensive patients with ECG left ventricular hypertrophy randomly assigned to losartan- or atenolol-based treatment. Average on-treatment SBP <142 (lowest tertile) and average SBP 142 to <152 (middle tertile) were compared with average SBP ≥152 (highest tertile and reference group).

Results: In the overall population, there was a highly significant interaction between baseline SBP ≤164 and average on-treatment SBP <142 in Cox analysis (χ^2=15.48, p<0.001). Among patients with baseline SBP >164, in multivariate Cox analyses adjusting for other potential predictors of mortality and a propensity score for having baseline SBP ≤164, compared with average on-treatment SBP ≥152 an average on-treatment SBP <142 was associated with 32% increased risk of mortality (HR 1.32, 95% CI 1.01-1.65), whereas average SBP of 142 to <152 was associated with 24% lower mortality risk (HR 0.76, 95% CI 0.59-0.98). In contrast, in parallel Cox analyses among patients with baseline SBP ≤164, both an average on-treatment SBP <142 (HR 0.60, 95% CI 0.36-0.99) and average SBP of 142 to <152 (HR 0.51, 95% CI 0.30-0.89) were associated with statistically significant lower risks of mortality compared with average SBP ≥152.

Conclusions: All-cause mortality risk associated with achievement of an average SBP <142 is strongly related to baseline SBP level in LIFE. These findings suggest that the lower mortality associated with a lower targeted SBP in SPRINT may not be applicable to patients with considerably higher baseline SBP than SPRINT patients. Further study is necessary to better understand these findings.

805 Seasonal Variations in Cardiovascular-related Mortality But Not Hospitalization Are Modulated by Temperature and Not Climate Type: a Systematic Review and Meta-analysis of 4.5 Million Events in 26 Countries

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Introduction: We undertook a systematic review and meta-analysis of seasonal variations in cardiovascular-related events across a range of climatic conditions.

Methods: A systematic review of bibliographic databases (inception to December 31 2015) was performed according to PRISMA guidelines. Eligible articles (48/163 fully assessed) reported the effect of seasonality on CVD mortality or hospitalization for a full calendar year at a region/population level. Study regions were coded by Köppen-Geiger Climate Classification and by summer and winter mean temperature. Meta-analyses on counts of events occurring in the month/season of peak versus trough activity were performed on large-scale, regional studies (n=24) with ≥10,000 events. Sub-group analyses of climatic variations, CVD subtypes and participant demographics were performed.

Results: Forty-eight studies from 26 countries (17 European) comprised 2.9 and 1.6 million CVD hospitalizations and deaths, respectively. The majority emanated from Moist Mid-latitude (Mild) Climates (n=31) with a range of sub-climate categories represented. All but three studies reported seasonal patterns in CVD events with a predominant pattern of winter peaks (n=40). Meta-analysis revealed more CVD-related deaths [IRR 1.23, 95% CI 1.16-1.31; n=12] and hospitalizations [IRR 1.20, 95% CI 1.14-1.25; n=19] during peak versus trough season (p<0.0001). Seasonal variation in CVD mortality (but not morbidity), was greater [IRR 1.21, 95% CI 1.15-1.27] in studies with a mean absolute temperature difference <17°C *versus* ≥17°C (p<0.0001). Seasonal variations were also greater in women [IRR 1.07 95% CI 1·03-1·11] and in older adults [IRR 1.04 95% CI 1.00-1.08], p<0.001 for both.

Conclusions: Seasonal variation, largely winter peaks, in CVD events occurs in a range of climates across the globe. Paradoxically, in milder climates seasonal mortality may be worse. This has clinical implications for public health measures in this vulnerable population, particularly elderly women.

110 Haemodynamic Outcomes During Piston-Based Mechanical CPR With or Without Active Decompression in a Porcine Model of Cardiac Arrest

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Introduction: Active compression-decompression (ACD) cardiopulmonary resuscitation (CPR) has been associated with higher cardiac output, coronary perfusion pressure, carotid and brain blood flow compared to standard mechanical chest compressions. Mechanical ACD-CPR devices previously studied are not suitable in the clinical setting of out-of-hospital cardiac arrest, creating a need for a human mechanical ACD-CPR device. We modified LUCAS® 2 (Jolife AB/Physio-Control, Lund, Sweden) to deliver ACD-CPR, hypothesizing that it would improve hemodynamic outcomes compared to standard LUCAS 2 CPR in pigs with cardiac arrest.

Materials and methods: The modified LUCAS 2 capable of delivering 5cm compressions with or without 2cm active decompression above normal anatomical chest level was studied in a randomized crossover design on nine Norwegian domestic pigs. Ventricular fibrillation was induced and left untreated for 2 min. Each pig received ACD-CPR and regular CPR in three phases of 180 sec in a balanced design, with the first technique repeated last. Aortic-, right atrial-, intracranial- and oesophageal pressures were measured and coronary perfusion pressure calculated. Cerebral and carotid blood flow were continuously measured. Cardiac output was measured once with each CPR technique. Two-sided paired samples t-test was used for continuous parametric data and Wilcoxon test for non-parametric data. $P<0.05$ was considered significant.

Results: The experimental protocol was finished in eight of the nine pigs. Cardiac output (L/min, median - 25/75 percentiles: 1.5 - 1.1, 1.7 vs. 1.1, 0.8, 1.5, $p<0.01$), cerebral blood flow (AU, 283 vs. 252, mean difference: 30.8, 95% CI; 2.9 - 58.7, $p=0.03$), and carotid blood flow (ml/min, 88 vs. 78, mean difference: 10.6, 95% CI: 5.3 - 15.9, $p<0.01$) were significantly higher during ACD-CPR compared to standard mechanical CPR. There were no significant differences in measured or calculated pressures.

Conclusion: Brain and carotid blood flow improved with ACD-CPR compared to standard CPR with the modified LUCAS 2 device in pigs with cardiac arrest. There was no difference in coronary perfusion pressure. ACD-CPR should be further studied in the clinical setting of out-of-hospital cardiac arrest.

140 Comparison of Cardiac Output Assessment With Two Different Minimally-invasive Pulse Contour Analysis-monitoring Devices and Echocardiography During Mild Therapeutic Hypothermia and Normothermia

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Background: Post-cardiac arrest myocardial dysfunction and hemodynamic instability characterize survivors of out-of-hospital cardiac arrest (OHCA). There is a need for optimal hemodynamic monitoring including cardiac output, during both mild therapeutic hypothermia (MTH) and the following normothermic period. Clinical practice using less invasive techniques based on arterial waveform analyses have gained increased interest.

Hypothesis: Minimally invasive hemodynamic monitoring devices with thermodilution calibration provide more precise cardiac output (CO) measurements during MTH than measurements without calibration.

Methods: Comatose OHCA survivors receiving MTH underwent hemodynamic monitoring with arterial pulse contour analyses with transpulmonary thermodilution calibration (PiCCO2 plus system, Pulsion Medical systems, Munich, Germany) and without calibration (FloTrac pressure sensor, Vigileo monitor, Edwards Lifescience, Irvine, USA) every eight hours during 24 hours of MTH and the following 24 hours of normothermia. CO was also measured by transthoracic echocardiography (TTE) during stable hypothermia and normothermia. Results: Twenty-six patients were included. Mean age was 64 years, 73% males, 77% had initial shockable rhythm. Median CO (l/min, 95% CI) measurements for CO-PiCCO2, CO-Vigileo, and CO-TTE were 3.7 (3.2-4.6), 4.0 (3.3-4.8), 3.6 (3.2-4.2) during hypothermia, and 6.5 (5.6-9.1), 5.6 (4.5-7.5), 5.8 (4.7-7.5)) during normothermia, respectively. Bias (1SD) between CO-PiCCO2 and CO-TTE was 0.05 (0.97) l/min during hypothermia and 1.16 (1.11) l/min during normothermia, respectively. Bias between CO-Vigileo and CO-TTE

were 0.40 (1.56) during hypothermia and 0.11 (1.51) l/min during normothermia. Bias between CO-Vigileo and CO- PiCCO2 were 0.34 (1.16) during hypothermia and 1.06 (1.75) l/min during normothermia.

Conclusion: Our results revealed low bias and reasonable precision between CO measurements with PiCCO2, Vigileo and TEE during hypothermia. Arterial pulse contour analyses may be used to monitor cardiac output during MTH. Precision was not improved by transpulmonary thermodilution calibration.

161 Simulation Study of Effect of a Novel Ventilation Feedback Device Combined With Just-in-time, Just-in-place Ventilation Training

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Introduction: Directive feedback devices improve chest compression quality and may improve skill acquisition and retention during training, and are therefore recommended in current resuscitation guidelines. Current feedback devices guide chest compressions, but ventilation quality is largely ignored. The objective of this study was to evaluate whether professional in-hospital advanced life support providers who receive ventilation training with continuous ventilation feedback, compared to no ventilation training and feedback, had improved CPR performance during a simulated CPR and post-ROSC scenario.

Methods: Twenty in-hospital advanced life support teams were randomized to either ventilation feedback augmented training or control, and tested in a simulated cardiac arrest and post-ROSC scenario. Scenarios were performed on adapted SimMan 3G manikins and data was collected using LLEAP software (both: Laerdal Medical, Stavanger, Norway). Primary outcome was ventilation quality during CPR and immediately post-ROSC (percentage of 30-second- segments with respiratory rate within guideline recommended range 4-10 ventilations/minute during CPR and 6-15 ventilations/minute post-ROSC).

Results: Two of the teams with ventilation feedback had to be excluded due to technical issues with the feedback device leaving 8 teams with feedback and 10 teams without feedback. After intubation the teams with feedback had median (IQR) 80 % (58-94) of 30-second-segments with 4-10 ventilations/minute compared to 42 % (11-85) for the group without feedback (p=0.068). The group with feedback was significantly more compliant with current guidelines with none 30-seconds-segments with hyperventilation (> 20 ventilations/minute) compared to the group without feedback where 5 of the teams had segments with hyperventilation (p=0.036). The median (IQR) ventilation rates during CPR were 12 /minute (10-15) in the groups with feedback and 18 /minute (12-24) in the groups without feedback (p=0.12). There were no significant differences in any ventilation parameters between the two groups before intubation and post-ROSC.

Conclusions: Training with the use of a continuous ventilation feedback device improved ventilation performance during simulated CPR.

245 Current Population Incidence and Survival From Out-of-Hospital Cardiac Arrest in a Norwegian Region With Complete Follow-Up

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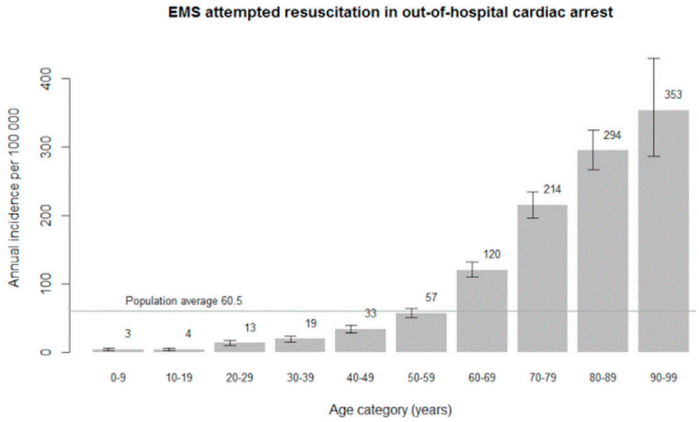
Introduction: Population measures of cardiac arrest incidence and survival are important components of the chain of survival, and thus useful for community emergency medical service (EMS) planning and benchmarking. The Norwegian unique person identification number allows for complete case tracking and follow-up. Aims of this study were to report relevant population statistics, including trends over the last 9 years, for out-of-hospital cardiac arrest in a modern EMS with a well-established cardiac arrest registry.

Methods: All resuscitation attempts by the EMS in Vestfold and Telemark (mixed urban/rural area 5 830.9 mi^2 [15 102 km^2] with average population 369 000; 3 325 202 person-years) from 2007 to 2015 were included. The Norwegian bureau of statistics supplied age-specific population data. Confidence intervals were calculated and trends were investigated using Poisson regression.

Results: Over 9 years, the EMS attempted resuscitation in a total of 2013 patients with cardiac arrest outside hospital. Among these, 558 (28 %) achieved stable return of spontaneous circulation (ROSC) resulting in hospital admission; 271 (13 %) were ultimately discharged. The overall population incidence was 60.5 per 100 000 person-years (95% CI: 57.9 to 63.2) and the incidence of survival to discharge 8.1 per 100 000 person-years (95 % CI: 7.2 to 9.2). The incidence rose markedly with age (figure, with 95 % CI). No time trends were observed with respect to neither incidence nor survival (p =0.9 and p= 0.2, respectively). The prevalence of initial shockable rhythms (VF or VT) was 24 %



on average and decreased slightly by 1.4 % per year (p = 0.04).

Conclusions: The observed population incidence of out-of-hospital cardiac arrest in our region suggests an annual burden of more than 3000 victims in Norway. While shockable rhythms may be declining, other trends were not observed over the last 9 years. Thirteen percent overall survival is relatively high by international standards.

324 Changes in ECG Characteristics are Related to Prognosis and Etiology in Pulseless Electrical Activity

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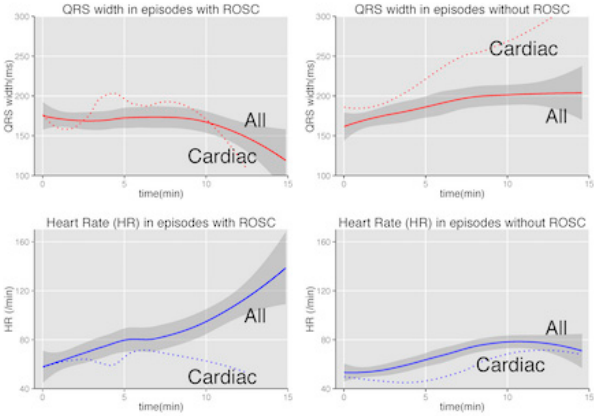
Introduction: Pulseless electrical activity (PEA) is a frequent initial rhythm in cardiac arrest. ECG characteristics have been linked to prognosis, and recognition of the cause of arrest may improve survival. The aim of this study was to examine to what extent changes in ECG characteristics observed during cardiopulmonary resuscitation (CPR) may be predictive of both the probable cause of arrest, and survival.

Methods: We analyzed QRS-complex width and heart rate in defibrillator recordings obtained during CPR efforts in 74 episodes of in-hospital cardiac arrest with initial PEA at St. Olav Hospital (Trondheim, Norway) between January 2009 and January 2012. A cardiac or non-cardiac etiology of arrest was determined in 63 of the 74 episodes included. We analyzed the resulting data using locally weighted regression scatterplot smoothing for the first 15 minutes of CPR. The primary outcome was return of spontaneous circulation (ROSC).

Results: Patients obtaining ROSC exhibited a steady increase in heart rate (approximately 5 beats/min. per min.) over the first 15 minutes (Figure). Development of QRS complex width was less clear, but an early QRS complex widening was observed among patients who did not obtain ROSC. Patients with a cardiac etiology differed from patients with a non-cardiac etiology; most notably by lacking an increase in heart rate in the patients obtaining ROSC.

Conclusion: A steady increase in heart rate during CPR is a positive prognostic sign in patients with cardiac arrest and initial PEA. Absence of such a response may prompt the rescuer to consider a cardiac etiology.



354 Urinary Biomarkers at Admission in Out-of-hospital Cardiac Arrest Patients May Predict Acute Kidney Injury and Patient Outcome

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Introduction: Urine biomarkers may be used to diagnose acute kidney injury (AKI) and predict patient outcome.

Hypothesis: Urinary AKI biomarkers sampled at admission after out-of-hospital cardiac arrest (OHCA) may predict AKI, mortality and unfavourable neurological outcome (UNO).

Methods: Prospective observational study of resuscitated, comatose OHCA patients treated with targeted temperature management to 33°C for 24 hours at Oslo University Hospital Ullevål, Oslo, Norway. AKI was diagnosed during the first three days based on the Kidney Disease Improving Global Outcomes (KDIGO) guidelines. UNO defined as cerebral performance category 3-5 and mortality were assessed after six months. Urine samples were collected at hospital admission and analyzed for cystatin C, neutrophil gelatinase-associated lipocalin (NGAL) and the NephroCheck™ test calculating the product of tissue inhibitor of metalloproteinase 2 (TIMP-2) and insulin-like growth factor-binding protein 7 (IGFBP-7). Data are compared using the Mann-Whitney U test and presented as median (interquartile range) unless otherwise noted.

Results: Among 195 included patients mean age was 60 (± 14 standard deviation) years and 165 (85 %) were males. OHCA was witnessed in 169 (87 %), 128 (66 %) had initial shockable rhythm, and time to ROSC was 25 (16-33) minutes. AKI occurred in 88 (45 %) patients, mortality was 88 (45 %) and 96 (49 %) had UNO. Patients with and without AKI had different levels of cystatin C (639 versus (vs.) 160 ng/mL, p<0.01), NGAL (439 vs.106 ng/mL, p<0.01) and NephroCheck™ (0.65 vs. 0.25, p<0.01), respectively. Non-survivors compared to survivors had higher levels of cystatin C (639 vs. 160 ng/mL, p<0.01), NGAL (506 vs. 91 ng/mL, p<0.01) and NephroCheck™ (0.45 vs. 0.28, p=0.02), respectively. Patients with and without UNO had different levels of cystatin C (612 vs. 166 ng/mL, p<0.01), NGAL (497 vs. 91 ng/mL, p<0.01) and NephroCheck™ (0.43 vs. 0.25, p=0.02), respectively.

Conclusions: In resuscitated, comatose OHCA patients urinary cystatin C, NGAL and NephroCheck™ at admission were significantly different in patients with and without AKI, and also in survivors compared to non-survivors.

355 Initial Phase NT-proBNP, but not Copeptin and High-Sensitivity Cardiac Troponin-T Yielded Valuable Information in Addition to Clinical Assessment of Out-of-Hospital Cardiac Arrest Patients

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Introduction: Sudden cardiac arrest (SCA) secondary to ventricular fibrillation may be due to different underlying heart diseases. Hs-cTnT is a commonly used marker of myocardial necrosis, but there remains a troponin-blind period shortly after symptom onset. Circulating copeptin levels have been found to be significantly elevated during the initial ischemic phase of an AMI, providing early diagnostic information. Whether this may help to differentiate the underlying cause of SCA, is not known.

Hypothesis: We analyzed copeptin, hs-cTnT and NT-proBNP to investigate whether these biomarkers could provide information to categorize out-of-hospital cardiac arrest (OHCA) patients in addition to clinical evaluation.

Methods: From February 2007 until December 2010 prehospital EDTA-blood was collected from patients aged > 18 years with OHCA of assumed cardiac origin in collaboration with EMS paramedics. For patients with return of spontaneous circulation who did not have a prehospital blood sample, EDTA-blood was taken at hospital admission. Clinical data for classification was obtained from hospital records.

Results: 77 patients with OHCA had documented VF as primary heart rhythm. They were divided into 4 groups according to the most likely cause of SCA, applying previous and current clinical information, supported by ECG, echocardiography and coronary angiography; Group 1 (n=43): SCA with first MI, Group 2 (n=10): SCA with AMI and previous MI, Group 3 (n=3): SCA without AMI and without former heart disease, Group 4 (n=18): SCA without AMI and with known heart disease.

There was no statistically significant difference between the four groups, comparing conventional copeptin, ultrasensitive copeptin and hs-cTNT. Group 4 had a significantly higher mean value for NT-proBNP of 405,1 pmol/L (SD 569,9) as compared to the other 3 groups (Group 1: NT-proBNP 68,23 pmol/L (SD 123,6), Group 2: NT-proBNP 61,99 pmol/L (SD 66,07) and Group 3: NT-proBNP 24,67 pmol/L (SD 35,18), p-value 0,001).

Conclusions: Hs-cTnT and copeptin collected during or immediately after resuscitation was not found to be useful for the diagnosis of AMI as the cause of SCA, whereas NT-proBNP was found to be significantly elevated in SCA patients with established heart disease and no AMI (Group 4).