NORSKE ABSTRAKTER PRESENTERT PÅ AHA

557 Evidence Against the J-shaped Curve in Treated Hypertensive Patients with Increased Cardiovascular Risk: The VALUE Trial

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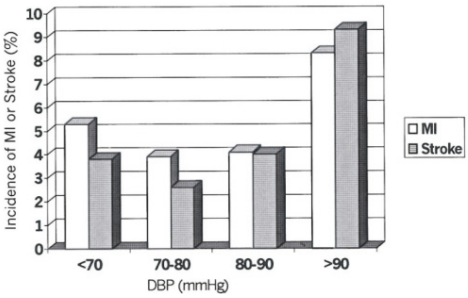
Introduction: It has been postulated that low blood pressure (BP) during treatment is associated with increased risk for cardiovascular (CV) disease.

Hypothesis: We tested whether low BP had unfavorable effect on CV outcomes in a high risk population of 15,244 hypertensive patients of whom 45% had a coronary heart disease (CHD) history.

Methods: Patients were followed for 4.2 years (mean) in the VALUE Trial with no difference of the primary endpoint between valsartan and amlodipine arms. Cox proportional hazard models were used to evaluate relationships between average on-treatment BP and clinical outcomes, unadjusted and adjusted for baseline covariates such as age, BMI, history of CHD, history of stroke, left ventricular hypertrophy, diabetes mellitus, smoking, cholesterol and proteinuria.

Results: Diastolic BP ≥90 mmHg but not diastolic BP <70 mmHg was associated with increased CV outcomes after covariate adjustment. We had similar results for death, myocardial infarction (MI), heart failure and stroke. Nadir for MI was at diastolic BP of 76 mmHg and for stroke 60 mmHg. The ratio of MI to stroke increased with lower diastolic BP (fig), but there was no significant J-curve regardless of CHD history. Also, systolic BP ≥140 but not <130 mmHg was associated with increased risk for CV outcomes, and systolic BP <130 mmHg significantly prevented stroke.

Conclusions: Patients in BP strata ≥140/90 mmHg, but not patients in BP strata <130/70 mmHg, were at increased risk for adverse outcomes in this hypertensive, high risk population. Our data provide evidence against a J-curve in the treatment of hypertensive patients with high risk and support the concept "of the lower the better" in stroke prevention. However, the increase in the ratio of MI to stroke with lower diastolic BP indicates target organ heterogeneity in that the optimal on-treatment diastolic BP for cerebroprotection is below the one for cardioprotection.



M 4007 Long-term Tolerability of Ticagrelor in the PEGASUS-TIMI 54 Trial

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Ticagrelor initiated in patients with prior MI reduced the incidence of CV death, MI, or stroke by 15-16% in PEGASUS-TIMI 54. Premature discontinuation was higher with ticagrelor than pla-

cebo. We investigated the rates and reasons for drug discontinuation and the long-term efficacy of ticagrelor in patients who stayed on therapy.

Methods: Rates and causes of treatment discontinuation were evaluated overall and by timing relative to randomization. Efficacy analyses were performed examining events occurring while pts were on study drug and up to 7 days after the last dose.

Results: Over the duration of the trial (median 33 mos), 32%, 29%, and 21% of patients stopped study drug in the ticagrelor 90 mg, 60 mg and placebo arms, respectively (P<0.001). 10-11% of patients in each arm stopped study drug because of patient decision or administrative reason. Conversely, rates of study drug discontinuation due to an adverse event (AE) were 8.9% in the placebo arm, but 19% and 16.4% in the ticagrelor 90 mg and 60 mg arms (P<0.01). The most frequent AEs leading to discontinuation were bleeding (6.5%, 5.1%, 1.2%, p<0.001) and dyspnea (6.2%, 4.3%, 0.7%, p<0.001). In the ticagrelor arms, only 14% of bleeds were major and only 12% of cases of dyspnea were severe. The rates of AEs leading to drug discontinuation and the differences between arms were greater in the first year and then greatly attenuated thereafter (Fig Left). Overall, in terms of events while on study drug, ticagrelor substantially reduced the risk of CV death, MI or stroke (HR 0.79, 95% CI 0.70-0.88, P<0.0001) as well as each of the individual components and was associated with lower all-cause mortality (Fig Right).

Conclusion: When initiated in stable patients with prior MI, discontinuation of ticagrelor was driven primarily by non-severe AEs occurring early after randomization. In patients who remained on study drug, there was a substantial benefit to ticagrelor, suggesting counseling on adherence could improve outcomes.

M 4070 Nadolol Seems to Be Superior to Selective Beta Blockers in Patients With Catecholaminergic Polymorphic Ventricular Tachycardia: Is a Smaller Arrhythmic Window Part of the Explanation?

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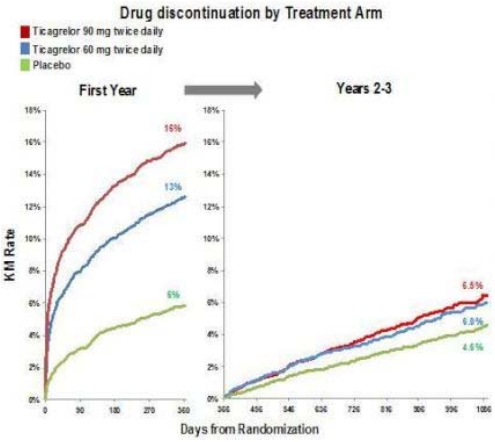
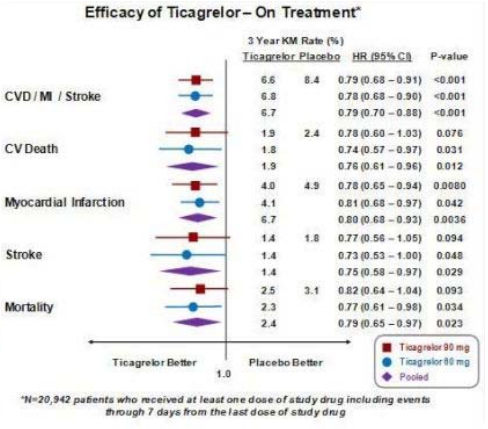
Introduction: Catecholaminergic polymorphic ventricular tachycardia (CPVT) is an inheritable arrhythmogenic disease, and typically presents as syncope or sudden cardiac death during exercise. Beta blockers are first choice therapy but little is known about antiarrhythmic effects of different beta blockers in CPVT. Nadolol has shown superior antiarrhythmic effect in other cardiomyopathies.

Hypothesis: We hypothesized that nadolol is superior to selective beta blockers in arrhythmia protection in CPVT patients.

Methods: We included 34 CPVT patients (age 34±19 yrs, 44% female, 88% RYR2 mutation positive). We serially performed 2 bicycle exercise tests in each patient; 1)>6 weeks on maximum tolerated dose of selective beta blockers. 2)>6 weeks on maximum tolerated dose of nadolol. We recorded resting and maximum heart rate (HR), HR at first arrhythmia and the most severe arrhythmia occurring. Arrhythmic window was defined as the difference between maximum HR and HR at first arrhythmia. Severity of arrhythmias was scored as arrhythmic score: no arrhythmias (0point), single ventricular extra systoles (1point), bigemini (2points), couplets (3points) and nonsustained VT (4points).

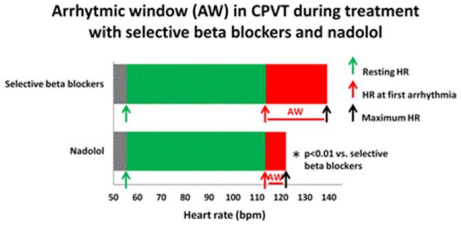
Results: Resting HR was similar on nadolol and selective beta blockers (54±10bpm vs.





56±14bpm, p=0.50), while maximum heart rate was lower on nadolol (122±21bpm vs. 139±24bpm, p<0.01). First arrhythmias occurred at similar HR at both exercise tests (113±21bpm vs. 113±19bpm, p=1.0). Consequently, arrhythmic window was smaller during nadolol treatment (17±10bpm vs. 32±26bpm, p=0.03) (Figure) and also the arrhythmic score was lower than on selective beta blockers (1.1±1.2 vs. 2.4±0.9, p<0.01).

Conclusion: Arrhythmic score was lower on nadolol compared to selective beta blockers. Also, arrhythmic window, representing the span of heart rates where arrhythmias may occur and progress in severity, was smaller. This suggests that nadolol should be the beta blocker of choice in CPVT patients.v



M 4301 Increasing Heart Rate in Left Bundle Branch Block Results in Incomplete Relaxation and Increases Left Ventricular Diastolic Stiffness

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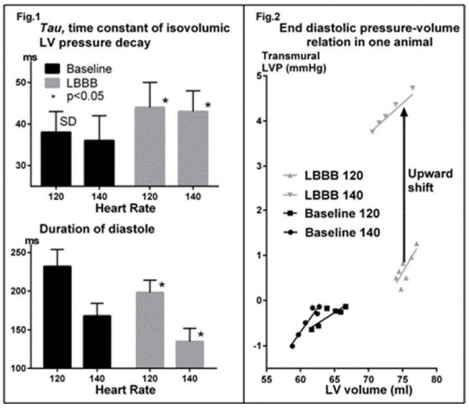
Introduction: Left bundle branch block (LBBB) slows LV pressure decay and shortens diastole. At low heart rates (HR) this may not compromise filling as diastolic duration is sufficient for complete relaxation.

Purpose: We investigated if further abbreviation of diastole at increased HR could cause incomplete relaxation, particularly in the late activated LV lateral wall; thereby increasing diastolic LV stiffness, which may cause increased filling pressure.

Methods: We analyzed data from a study of 10 canines where HR was increased from 120 to 140 by atrial pacing before and after induction of LBBB. Ventricular and pericardial pressures, LV volume and regional segment lengths (SL) were measured. Global diastolic stiffness was calculated from end diastolic (ED) transmural LV pressure-volume (PV) relations and regional stiffness from pressure-SL relations in septum and lateral wall. A mathematical model was used to estimate the increase in filling pressure due to incomplete relaxation at HR 160 and 180.

Results: In LBBB, *tau* was prolonged and diastole abbreviated at both HR 120 and 140, compared to baseline (Fig. 1). Increased HR during LBBB stiffened the ventricle, seen as an upward shift of the ED PV relation by 1.4±1.7 mmHg (±SD), (p=0.03) whereas no shift (-0.9±1.5 mmHg) (NS) was seen at baseline (Fig. 2). Regional ED P-SL relations showed a larger upward shift of the lateral wall (1.1±1.8 mmHg) and hence a more pronounced stiffening compared to the septum (0.6±1.5 mmHg) (p<0.05), indicating more delayed lateral wall relaxation. Mathematical estimation showed an increase in filling pressure of 7 and 16 mmHg due to further diastolic abbreviation at HR 160 and 180, respectively.

Conclusions: LV diastolic stiffness is increased at high heart rates in LBBB due to incomplete relaxation, particularly of the late activated LV lateral wall. Diastolic stiffening by increased HR may lead to exercise intolerance and dyspnoea in LBBB patients due to elevated filling pressure.



T 4184 Chromogranin B Levels are Increased in Myocardial Tissue in the Dyssynchronous Left Ventricle and Relate to Abnormalities in Regional Myocardial Deformation

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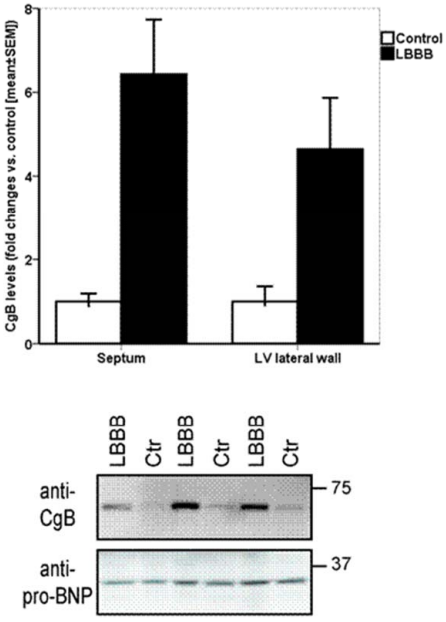
Introduction: Left bundle branch block (LBBB) induces abnormal activation and deformation of the LV wall. Chromogranin B (CgB) levels are increased in myocardium and plasma of heart

failure patients and are linked to cardiomyocyte Ca^{2+} handling.

Hypothesis: That CgB expression is increased in distinct LV regions during LBBB and may be related to regional deformation abnormalities.

Methods: CgB and pro-B-type natriuretic peptide (proBNP) protein levels were measured in biopsies from septum and LV lateral wall in 6 dogs with chronic LBBB (16 weeks), 8 control animals, and in 8 dogs with LBBB that received cardiac resynchronization therapy (CRT) between 8 and 16 weeks after creation of LBBB. Regional myocardial strain was assessed by speckle tracking echocardiography, LV volumes by MRI, and hemodynamics were assessed by invasive pressure measurements (LV dP/dt max and min, *tau*, LVP max and min, and LV end-diastolic pressure).

Results: LBBB animals had increased end-diastolic volumes (55±1 vs.45±4 mL, p=0.038) but normal LV ejection fraction (50±3 vs. 55±4 %, p=0.42) compared to control animals. CgB levels were increased in both septum (p<0.001) and LV lateral wall (p=0.01) in LBBB compared to controls, despite no changes in LV proBNP levels, and with the most prominent increment found in the septum (Figure). In LBBB+CRT animals, CgB levels were 36±18% (septum) and 50±11% (LV later wall) lower compared to LBBB animals, but this difference was not statistically significant. Septal CgB levels correlated with septal early systolic rebound stretch (r=0.76, p=0.017) and lateral wall CgB levels with lateral wall pre-ejection stretch (r=0.76, p=0.018), while no correlations were found with LV dimensions or indices of global hemodynamic function.



Conclusion: Myocardial CgB expression was increased in the absence of elevated proBNP levels in LBBB animals with preserved systolic function. Local CgB levels appear to relate to abnormal local early-systolic mechanical loading.

T 4185 The Novel Cardiac Biomarker Secretoneurin Provides Independent Prognostic Information in Severe Sepsis and Septic Shock: Data from the ALBIOS Study

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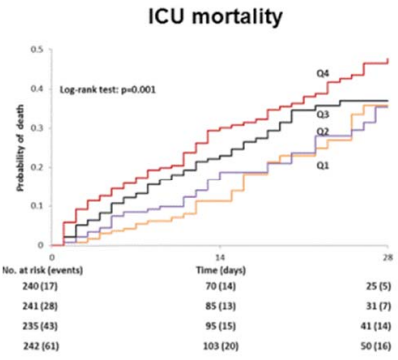
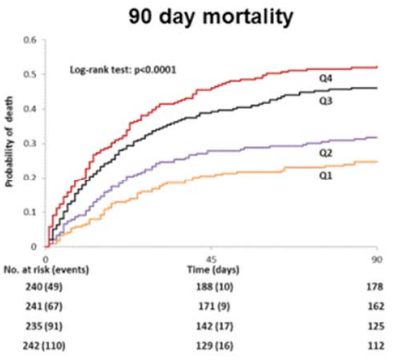
Background: Plasma secretoneurin (SN) is directly correlated to cardiomyocyte Ca^{2+} handling and provides independent prognostic information in cardiovascular disease. Whether SN may predict mortality in patients with severe sepsis or septic shock is not established.

Methods: We measured SN levels in serial plasma samples collected on days 1, 2, and 7 in 958 patients enrolled in the multicenter, open-label, randomized, controlled ALBIOS trial, that tested either 20% albumin and crystalloid solutions or crystalloid solutions alone in patients with severe sepsis or septic shock. Endpoints were ICU or 90 day mortality.

Results: SN levels on day 1 were higher in non-survivors compared to survivors, both for ICU mortality (235 [Q1-Q3 188-290] vs. 192 [155-246] pmol/L, p<0.0001) and for 90 day mortality (227 [183-283] vs. 188 [154-234] pmol/L, p<0.0001). Admission SN levels were influenced by age and lactate, creatinine and NT-proBNP levels. Stratifying patients according





to SN quartiles on day 1 separated survivors and non-survivors during follow-up (Figure). After adjusting for clinical risk factors, SAPS II and SOFA scores, and cardiac biomarkers (hs-cTnT and NT-proBNP), SN levels (logarithmical transformed) on day 1 remained significantly associated with ICU mortality (OR 1.29 [95% CI 1.07-1.55], p=0.007) and 90 day mortality (OR 1.22 [1.02-1.47], p=0.03). SN levels on day 2, but not day 7, were also independently associated with ICU and 90 day mortality. SN levels on day 1 and 2 improved prognostic accuracy for ICU and 90 day mortality as assessed by the category-free net reclassification index. We found no interactions between SN levels and randomization to albumin replacement for prediction of mortality during follow-up. Changes in SN levels over time were not predictive of subsequent mortality.

Conclusion: SN provides incremental information to established risk models and cardiovascular biomarkers in patients with severe sepsis and septic shock.

S 4237 Prediction of Clinical Outcome in Patients with Aortic Stenosis by Left Ventricular Mechanical Dispersion

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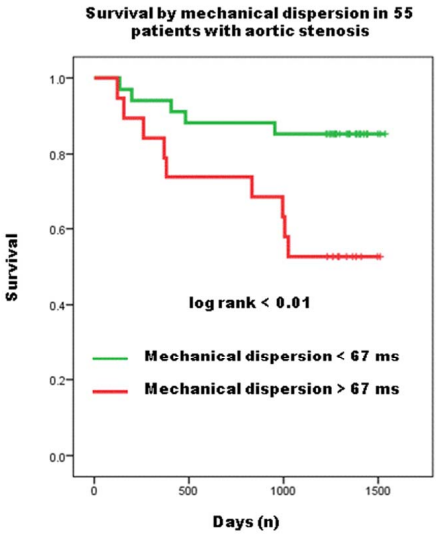
Introduction: There is a need for new parameters to improve risk stratification and assess outcome in patients with aortic stenosis (AS). Left ventricular (LV) mechanical dispersion by strain echocardiography reflects heterogeneous myocardial contraction and is a novel marker of sudden cardiac death in structural and primary electrical heart disease. We hypothesized that mechanical dispersion provides valuable prognostic information in patients with AS, and that mechanical dispersion can be used as a clinical tool for risk stratification in these patients

Methods: We included 55 patients (56% women,75±9 years) with moderate to severe AS. Global longitudinal strain (GLS) was assessed by speckle tracking echocardiography from a 16 LV segments model. Mechanical dispersion was calculated as standard deviation of time from Q/R on ECG to peak strain in 16 LV segments.

Results: Average aortic valve area was 0.7±0.2 cm2. Most patients had LV septal hypertrophy (12±2 mm) and preserved LV ejection fraction (EF) (57±10%). Aortic valve replacement (AVR) was performed in 37 (67%) patients. During 38±14 months follow-up, 15(27%) patients died (no 30-day mortality after AVR). LV ejection fraction (EF) and GLS were similar in the survival and non-survival group (58±9% vs. 54±13%, p=0.16, and -17.0±3.4% vs. -16.7±4.0%, p=0.78, respectively). Mechanical dispersion was the only echocardiographic parameter that differed between survivors and non-survivors (56±18ms vs. 69±19ms, p=0.02). C-statistics for mechanical dispersion showed an AUC of 0.70 (0.55-0.86) and a value of > 67 ms indicated worse survival (log rank < 0.01) (Fig.1)



Conclusions: LV mechanical dispersion was significantly higher in the AS non-survivors. Increased mechanical dispersion may be an additional risk marker and could give valuable prognostic information in patients with AS and preserved LVEF.

S 2060 Urinary Homocysteine Thiolactone Predicts Acute Myocardial Infarction in a Randomized Controlled Homocysteine-lowering B-vitamin Trial

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Introduction-Elevated plasma total homocysteine (tHcy) is associated with increased risk of coronary artery disease (CAD) and stroke. However, tHcy-lowering by B-vitamin therapy has no effect on cardiovascular disease (CVD), suggesting that tHcy is not causally related to CVD. One Hcy metabolite, Hcy-thiolactone (HTL), not accounted for in clinical tHcy assays, has been independently implicated in CVD. HTL is generated in the human body by methionyl-tRNA synthetase during protein biosynthesis and is cleared by the kidney.

Hypothesis-Our objective was to test the predictive value of urinary HTL as risk marker of incident acute myocardial infarction (AMI) and to evaluate potential effect modification by B vitamin treatment and status.

Methods and Results-We analyzed urinary HTL in samples from 2048 patients (20.5% female, mean age 61.7 years) who underwent coronary angiography for stable angina pectoris and were recruited to the Western Norway B Vitamin Intervention Trial. Linear regression was used to study determinants of baseline urinary HTL/creatinine and no association was observed with established risk factors such as age, gender, hypertension, body mass index, diabetes, apolipoprotein B and A1. Cox regression was used to study its association with subsequent risk of AMI. During median 4.7-years follow-up, 183 patients (8.9%) suffered from AMI. After adjustment for age, gender, diabetes, smoking, extent of CAD at angiography and left ventricular ejection fraction, per tertile increment in HTL/creatinine was significantly associated with AMI (RR 1.23; 95% CI 1.025-1.474; P=0.026). No significant effect-modification by folate/B12 or B6 treatment was observed. The association was entirely confined to patients with low (below median) levels of the inactive B6 metabolite pyridoxic acid (P-interaction 0.020), and identified patients with low risk. The risk association of plasma tHcy was confined to patients with elevated pyridoxic acid (P-interaction 0.001), and identified patients with high risk.

Conclusions-Urinary HTL is a risk predictor of AMI in patients with CAD independent from established risk factors and plasma tHcy, but related to vitamin B6 metabolism. These surprising results should encourage further research into HTL and CVD.

S 2132 Gender Differences in Cardiovascular- and Cancer Mortality During Long-term Follow-up After Acute Myocardial Infarction

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Background: The existence of gender differences in cause-specific mortality after acute myocardial infarction (AMI) is unknown. Aim: To study gender differences in all-cause and cause-specific mortality in women and men with AMI. Methods: Consecutive AMI patients were enrolled in a prospective cohort study during 2005-2011. Cardiovascular (CV) risk factors, treatment and in-hospital complications were registered. Date and cause of death were obtained from the Norwegian cause of death

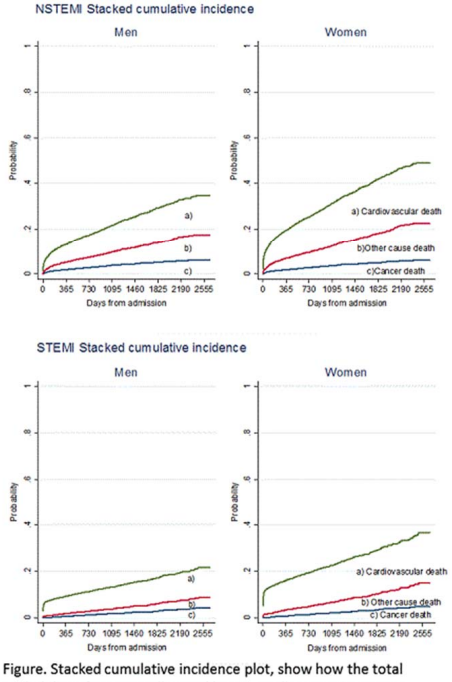

Figure. Stacked cumulative incidence plot, show how the total probability of one was allocated between all competing events, including the possibility of survival during follow-up in men and women. NSTEMI patients n=5159, STEMI patients n=4899.

registry, with censoring date set to Dec 31, 2012. Patients with ST-elevation myocardial infarction (STEMI) and non-STEMI (NSTEMI) were analysed separately. We used Kaplan Meier- and cumulative incidence function-plots to assess gender differences in CV, cancer and all-cause mortality. Cox- and Fine-Gray regression models, adjusted for age, estimated the effect of female gender. Results: We included 5159 NSTEMI (34% women) and 4899 STEMI (25% women) patients. Women were older and had more complications compared to men. After a median follow-up time of 1043 and 1262 days for NSTEMI and STEMI, respectively, 1461 NSTEMI (28%) and 886 STEMI (18%) patients had died. After adjustment for age, NSTEMI women had lower (HR 0.89 [95% CI: 0.80-0.99]) and STEMI women similar (HR 1.05 [95% CI: 0.91-1.22]) risk of all-cause mortality compared to men. There were no gender differences in CV mortality. We observed a non-significant trend toward lower cancer mortality in women than men with NSTEMI (adjusted subhazard ratio 0.76 [95% CI:0.56-1.03]). In both genders, CV death was more prevalent (Figure) and occurred earlier than cancer death.

Conclusion: After adjustment for age, there were no excess risks of all-cause or CV mortality in women versus men with AMI during long-term follow-up. Possible gender differences in risk of cancer mortality needs further investigation.

T 2138 Chronic Obstructive Pulmonary Disease and Sudden Cardiac Death in Hypertensive Patients: The LIFE Study

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Background: Chronic obstructive pulmonary disease (COPD) is associated with an increased risk of cardiovascular (CV) disease and CV mortality. A recent large, population-based study suggested that COPD is associated with an increased risk of sudden cardiac death (SCD). However, whether COPD predicts SCD in hypertensive patients during aggressive blood pressure (BP) lowering has not been examined.

Methods: Risk of SCD was examined in relation to a history of COPD in 9193 hypertensive patients with ECG left ventricular hypertrophy (LVH) who were randomly assigned to losartan- or atenolol-based treatment. A history of COPD was present in 385 patients (4.2%). SCD, a prespecified secondary endpoint in LIFE, was defined as death that was sudden and unexpected, including observed arrhythmic deaths and those not attributable to myocardial infarction (MI), intractable heart failure (HF) or other identifiable cause, occurring within 24 hours of symptom onset or when the subject was last seen alive if unwitnessed SCD.

Results: During mean follow-up of 4.8±0.9 years, 178 patients (2.4%) had SCD, with a higher incidence rate per 1000 person-years in those with COPD: 9.0; 95% CI, 6.1-11.9 vs 3.8; 95% CI, 3.4-4.2; p=0.001. In a univariate Cox model, COPD was associated with a > 2-fold increased risk of SCD (HR 2.36, 95% CI 1.42-3.95, p=0.001). In a multivariable Cox regression model that adjusted for other predictors of SCD in this population (randomized treatment, age, gender, race, history of atrial fibrillation, stroke or transient ischemic attack, baseline serum creatinine and glucose entered as standard covariates and incident MI, incident HF and in-treatment diastolic pressure, heart rate, QRS duration, HDL cholesterol, and use of hydrochlorothiazide or a statin entered as time-varying covariates), COPD remained associated with a nearly 2-fold increased risk of SCD (HR, 1.82; 95% CI, 1.04-3.18, p=0.035).

Conclusions: COPD is associated with an increased risk of SCD in hypertensive patients. The higher SCD risk in COPD patients persists after adjusting for the higher prevalence of risk factors in COPD patients, in-treatment blood pressure, incident MI and HF, and the established predictive value of in-treatment ECG LVH and heart rate for SCD in this population.

658 A 15-year Analysis and Descriptive Study of the Incidence, Clinical Characteristics, Management, and Outcomes of Lower Limb Ischemia in Type A and Type B Aortic Dissection Patients: Insights From the International Registry of Acute Aortic Dissection

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Background - This study assessed the incidence of lower limb ischemia as well as trends in management and outcomes while examining acute aortic dissection patients over a period of 15 years. Additionally, differences in clinical presentation, interventions performed, and mortality between patients with and without lower limb ischemia were investigated.

Methods - Lower limb ischemia (LLI) was evaluated among 3812 patients enrolled in the International Registry of Acute Aortic Dissection over a 15-year period that was separated into three 5-year intervals: 1996-2001, 2002-2007, and 2008-2012. The cohort was then divided by dissection type and presence or absence of LLI.

Results - Type A patients presenting with limb ischemia (N=280, 11.4%) were much more likely to have atherosclerosis (p=0.021) and to present with back, abdominal and leg pain versus chest pain (p<0.001 unless noted). Other symptoms of malperfusion, including ischemic spinal cord damage (p<0.001) and coma/altered consciousness (p=0.006) were more common in patients presenting with LLI. Surgery was less commonly performed in Type A LLI patients (79.3% vs 86.1%, p=0.002), a difference that did not change over time (p=0.453, trend p=0.479). Additionally, overall mortality was higher in LLI patients (37.5% vs 22.9%, p<0.001) and did not show improvement among the LLI cohort over time.

Type B patients with LLI (N=102, 7.5%) were more likely to be current smokers (p=0.028), to present febrile (p=0.022), and to have leg pain (p<0.001). As with Type A, ischemic spinal cord damage was more common in the LLI cohort (p<0.001). Patients with LLI were much more likely to be managed with endovascular therapy (19.6% vs 50.0%, p<0.001) than with medication alone (66.5% vs 29.4%, p<0.001), with endovascular repair increasing in LLI patients over time (p=0.008, trend p=0.002). Again, overall mortality was higher in the LLI cohort (24.5% vs 9.7%, p<0.001) and did not change over time.

Conclusions - Although Type B patients with LLI received more endovascular procedures in later years, overall mortality did not improve. Increased complications and higher mortality in the LLI cohort suggests a need for better monitoring and increased implementation of interventions in this population.

749 Active Rheumatoid Arthritis is Associated with Subclinical Left Ventricular Systolic Myocardial Dysfunction

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Introduction: Patients with rheumatoid arthritis (RA) have comparable cardiovascular risk to patients with diabetes mellitus. Lately, disease activity has emerged as a new, independent risk factor for cardiovascular disease in RA patients.

Hypothesis: We tested if RA disease activity was associated with subclinical systolic left ventricular (LV) dysfunction independent of traditional cardiovascular risk factors.

Methods: Echocardiography was performed in 78 patients with active RA (Simplified Disease Activity Index [SDAI] >3.3), 41 patients in remission (SDAI ≤3.3), and 46 controls, all without known cardiac disease. LV endocardial systolic function was determined by biplane Simpson ejection fraction and LV myocardial function by stress-corrected midwall shortening (scMWS) and global longitudinal strain (GLS).

Results: Patients with active RA had higher frequencies of hypertension, diabetes and use of disease modifying antirheumatic drugs (all p<0.05) compared to patients in remission, while age and sex did not differ from RA patients in remission (Table). LV ejection fraction was normal in all groups, while mean GLS and scMWS were reduced in RA patients with active disease compared to RA in remission (p<0.05) (Table). In multivariate analyses, having active RA was associated with lower GLS (β=0.21) and scMWS (β=-0.22, both p<0.05) independent of cardiovascular risk factors and LV ejection fraction. Assessment of RA disease activity by other composite scores yielded similar results.

Conclusions: Active RA is associated with subclinical reduced LV systolic myocardial function despite normal ejection fraction, and independent of presence of hypertension and diabetes.

Table. Clinical and echocardiographic characteristics

	Active RA (n=78)	RA in remission (n=41)	Controls (n=46)
Age (years)	61±12†	62±11†	53±9
Women	77%	76%	59%
Systolic blood pressure (mmHg)	136±22†	131±20†	117±13
Hypertension (%)	60%*†	34%†	0%
Diabetes (%)	14%*†	3%	0%
DMARD use (%)	71%*	46%	na
Ejection fraction (%)	66±6	68±5	67±5
GLS (%)	-18.9±3.1*	-20.6±3.5	-19.7±3.3
scMWS (%)	95±18*†	105±17	103±16

*p<0.05 compared to RA in remission, †p<0.05 compared to controls. na, not applicable; DMARD, disease-modifying antirheumatic drug

901 Small Aortic Root Size Has Prognostic Implications Both for Women and Men with Asymptomatic Aortic Stenosis

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Background: Sex-specific analysis of small aortic root has not been reported in asymptomatic aortic stenosis (AS) patients.

Methods: We used echocardiographic and outcome data from 1560 patients with asymptomatic initially mild-moderate AS enrolled in the Simvastatin and Ezetimibe in Aortic Stenosis study. A small aortic root was defined as an inner diameter at the aortic sinotubular junction < 1.5cm/m in women and < 1.6cm/m in men.

Results: A small aortic root was found in 17.4% patients at baseline and independently associated with higher pulse pressure/stroke volume index and aortic root wall thickness, higher pressure recovery, lower LV mass index and female sex in multivariate logistic regression analysis (all p<0.05). In sex-specific multivariate Cox regression analysis, adjusting for the known prognosticators age, hypertension and AS severity and for randomized study treatment, having a small aortic root predicted a 66% higher rate of ischemic cardiovascular events and a 2-fold higher rate of non-haemorrhagic stroke and cardiovascular death (all p<0.05) in men and a 2-fold higher rate of CABG in women (Table). Presence of small aortic root did not influence total mortality or aortic valve replacement in either gender.

Conclusion: In asymptomatic AS patients without known cardiovascular disease or diabetes, having a small aortic root was associated with increased rate of cardiovascular events in both women and men.

	Ischemic cardiovascular events	Coronary artery bypass grafting	Non-haemorrhagic stroke	Cardiovascular death
Women	1.47 (0.88-2.44)	2.05 (1.03-4.08) *	1.53 (0.49-4.77)	1.82 (0.81-4.09)
Men	1.66 (1.17-2.35) *	1.31 (0.79-2.18)	2.04 (1.01-4.11) *	2.15 (1.17-3.96) *

*p<0.05

Table. Small aortic root as predictor of different cardiovascular events in multivariate analyses in women and men [HR (95%CI)].

948 Baseline Left Atrial Abnormality by Electrocardiogram Predicts Incident Stroke in Hypertensive Patients with Electrocardiographic Left Ventricular Hypertrophy

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Background: Recent findings in population-based studies suggest that abnormal P-wave terminal force in lead V_1 ($PTFV_1$), a marker of left atrial (LA) abnormalities such as fibrosis, dilatation and elevated filling pressures, is associated with incident ischemic stroke, even in the absence of atrial fibrillation (AF). However, whether $PTFV_1$ predicts incident stroke in hypertensive patients during aggressive blood pressure (BP) lowering has not been examined.

Methods: Risk of incident stroke was examined in relation to abnormal $PTFV_1$ on a baseline ECG in 1879 hypertensive patients aged 60 or younger with ECG left ventricular hypertrophy (LVH), no history of AF, in sinus rhythm on their baseline ECG with no incident AF during follow-up, who were randomly assigned to losartan- or atenolol-based treatment. Patients >60 years old were not included because of a highly significant interaction between $PTFV_1$ and age in Cox analyses. Abnormal $PTFV_1$ was defined by the presence of a negative terminal P wave in lead V_1 with amplitude x duration ≥4000 V*ms.

Results: During mean follow-up of 4.8±0.9 years, 45 patients (2.4%) experienced a definite stroke. A higher incidence of stroke occurred in those with abnormal than normal baseline $PTFV_1$: incidence rate per 1000 person-years, 7.8, 95% CI, 5.2-11.4 vs 3.4; 95% CI, 2.2-5.2; p=0.004. In univariate Cox models, abnormal $PTFV_1$ was associated with a > 2-fold increased risk of incident stroke (HR 2.31, 95% CI 1.28-4.16, p=0.005). In multivariable Cox regression models that adjusted for other significant predictors of incident stroke in this population (gender, history of stroke or transient ischemic attack, ischemic heart disease or diabetes, baseline creatinine and in-treatment systolic BP), abnormal $PTFV_1$ remained associated with a > 2-fold increased risk of incident stroke (HR, 2.06; 95% CI, 1.14-3.74, p=0.017).

Conclusions: Abnormal $PTFV_1$, a marker of LA abnormality, was strongly associated with incident stroke in hypertensive patients, independent of in-treatment systolic BP and other predictors of incident stroke. This association, in the absence of detectable AF, suggests that an underlying atrial cardiopathy may cause LA thromboembolism and a subsequent stroke without necessarily manifesting with AF.

668 What is the Optimal Blood Pressure in Patients With Asymptomatic Aortic Valve Stenosis: The SEAS Study

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Introduction: Very limited data regarding blood pressure and antihypertensive treatment in asymptomatic aortic valve stenosis (AS) have been published, and no announced consensus statement has provided recommendations for optimal blood pressure targets in this patient population.

Hypothesis: Our research question was to use the best available observational data from the Simvastatin Ezetimibe in Aortic Stenosis (SEAS) trial to identify what blood pressure (BP) would be optimal in terms of mortality in asymptomatic AS.

Methods: We evaluated 1798 patients with asymptomatic AS enrolled in the SEAS trial. Average follow-up BP was examined. Primary outcome was all-cause mortality, and secondary outcomes were cardiovascular death, heart failure, stroke and aortic valve replacement (AVR).

Results: Average blood pressure was 144/82 mmHg and half the patients had a history of hypertension. In multivariate analysis, all-cause mortality was increased for systolic BP < 120 (HR=5, p<0.001), systolic 120-139 (HR=1.5, p=0.031) and diastolic BP >= 90 mmHg (HR=1.9, p=0.015). Adjusting for time dependent in-between events such as aortic valve replacement, heart failure and non-fatal myocardial infarction did not significantly modify the risk. Patients at 75 years of age or more with history of hypertension had increased mortality risk with diastolic BP >= 90 mmHg (HR= 3.3, p=0.004). Patients below 75 years of age with a history of hypertension had an increased risk with systolic BP >= 160 mmHg (HR=2.1, p=0.049).

Conclusions: In asymptomatic aortic valve stenosis all-cause mortality is lowest at a systolic BP between 140 to 159 mmHg and at a diastolic between 70 to 89 mmHg. Patients with low systolic blood pressure, in general, had increased mortality risk, and should undertake individual clinical assessment.

673 Fibrinogen and Neopterin Predict Future Myocardial Infarction Events in Patients with Stable Coronary Heart Disease

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Background: Fibrinogen is synthesized by hepatocytes. It is a precursor of fibrin and forms bridges between platelets during thrombus formation, but it is also a marker of ongoing inflammation. Neopterin is released by monocyte/macrophage activation associated with atherosclerosis. Whether these markers interact or act independently among patients with suspected stable coronary heart disease has previously not been given much attention.

Methods: We included 3526 patients undergoing elective coronary angiography at two university hospitals in Norway during 2000-2004, with a median follow-up of 7.3 years. Cox regression analysis was used to obtain hazard ratios (HR) and 95% confidence intervals (CI) for incident AMI of fibrinogen and neopterin levels in a crude model and a model adjusted for age, gender, diabetes, current smoking, hypertension and serum apoA1 and apoB. Potential effect modifications were investigated according to strata of fibrinogen or neopterin below or above the median, as well as across subgroups of age, gender, smoking status, diabetes, serum apoA1 and apoB. A p-value <0.05 was considered significant.

Results: During follow-up, 580 patients experienced an AMI. In the unadjusted model, both fibrinogen and neopterin predicted future AMI [HR = 1.32; 95% CI 1.22-1.43; p<0.001 and HR = 1.31; 95% CI 1.23-1.40; p<0.001, respectively]. The estimates were only slightly attenuated in the multivariate model, and still associated with incident AMI when both biomarkers were added simultaneously [HR = 1.15; 95% CI 1.05-1.25; p<0.001 and HR = 1.20; 95% CI 1.12-1.28; p<0.001, respectively]. Baseline fibrinogen and neopterin levels were modestly correlated (Spearman's rho = 0.18, p-value <0.001). There were no statistically significant interaction across

subgroups (p for interaction fibrinogen and high/low neopterin = 0.26, neopterin and high/low fibrinogen = 0.46, respectively).

Conclusion: Patients with increased levels of fibrinogen or neopterin are at increased risk of future AMI. Neopterin levels did not significantly interact with the prognostic utility of fibrinogen. This suggests that circulating fibrinogen and neopterin may reflect different pathophysiological mechanisms.

257 Pedicled Vein Grafts in Coronary Surgery Exhibit Reduced Intimal Hyperplasia at 6 Months

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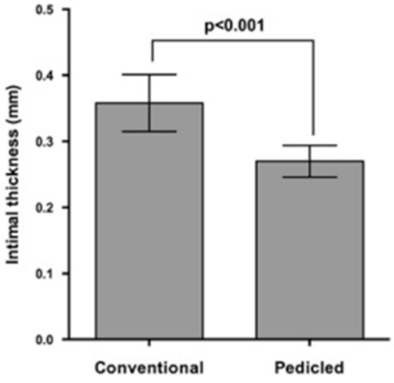
Introduction: Less-than-optimal long-term patency of the saphenous vein is one of the main obstacles for the success of CABG. Harvesting saphenous veins including a pedicle of perivascular tissue has been proposed to improve graft patency rates and endothelial function.

Hypothesis: We hypothesized that pedicled vein grafts would show less intimal hyperplasia at 6-month angiographic follow-up.

Method: Sixty patients scheduled for first time elective on-pump CABG were randomized to conventional or pedicled vein harvesting. Exclusion criteria were insulin dependent diabetes mellitus, recent smoking or renal failure. Pedicled veins were harvested with perivascular tissue and conventional veins were skeletonized. All veins were distended manually to check for leakage and stored in heparinized blood and saline. At 6 months vein grafts were examined with Intravascular Ultrasound (IVUS) and Optical Coherence Tomography (OCT). Imaging analysis was performed by an external blinded Core-lab.

Results: Fifty-four patients were available for follow-up. There were no significant differences in occlusion rates between the two groups. IVUS showed no significant difference in intima-media complex thickness (pedicled: n=28, mean 0.229 mm, SEM 0.011; conventional: n = 26, mean 0.235 mm, SEM 0.017). However, using OCT pedicled veins showed significantly less intimal thickness than conventional veins (pedicled: mean 0.270 mm, SEM 0.012; conventional: mean 0.358 mm, SEM 0.021; p<0.001). In conventional veins higher perioperative flow was positively correlated to increased intimal thickness. Such a correlation was not found in pedicled grafts. The difference in response to flow was significant using a general linear model including an interaction term (adjusted R squared = 0.254, p<0.018).

Conclusion: Performing CABG using saphenous vein grafts harvested with a pedicle of perivascular tissue provides significantly less vein graft intimal hyperplasia at 6 months.



Mean intimal thickness in conventional and pedicled veins. Error bars represent 95% CI.

124 The European Registry of Cardiac Arrest - Study One (EuReCa ONE) - Relationship Between Rates of CPR and Rates of Death in European Countries

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Background and Objectives: EuReCa collects data on out-of-hospital cardiac arrest (OHCA) in Europe. In this study (EuReCa ONE) we hypothesised that a higher rate of death is associated with a higher rate of CPR started. We investigated the relationship between the rate of CPR started and total death rates, and also between the rate of CPR started and death rates from ischaemic heart disease (IHD).

Methods: We conducted a prospective observational study of EMS attended OHCA from 1st - 31st October 2014, covering 201 million inhabitants from 27 European countries. The incidence of cases where CPR was started was calculated per 100,000/year for each country. Data on deaths from IHD and all deaths was obtained

from health statistics of the European Commission (Eurostat). Correlations between both these death rates and CPR started rates were calculated.

Results: We found a wide range of rates of CPR started (19 - 104/100,000/year) and differences in all death rates (623 - 1417/100,000/year) and IHD death rates (202 - 766/100,000/year). The figures show the relationships for each country. Correlations between the rates of CPR started and rates of death from IHD and total deaths were Pearson R^2 =0.06 (p=0.25); Pearson R^2 = 0.10 (p=0.12) respectively.

Conclusion: Correlation is low between the rate of CPR and both the rate of death from all causes and IHD. Differences in mortality rates do not explain the observed variability in the rates of CPR started.

Figure 1

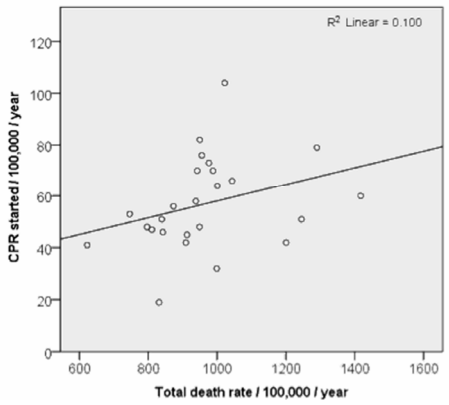
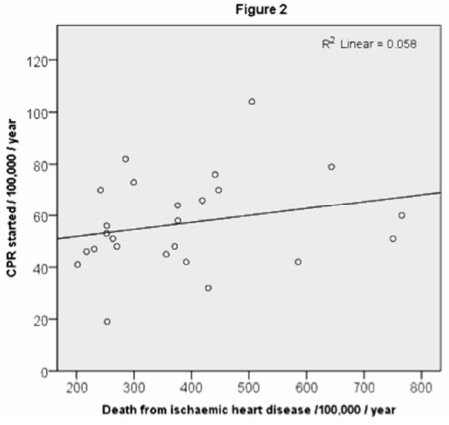


Figure 2



131 Hemodynamic Effects of Guideline-compliant Asynchronous vs. Synchronous Ventilations During Cardiopulmonary Resuscitation in a Porcine Model

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Background: Current guidelines for cardiopulmonary resuscitation (CPR) emphasize reducing pauses in chest compressions, and suggest ventilating with 1 second inspiration time and with enough volume to produce normal chest rise 10 times per minute. No specific advice is provided on how ventilations should be timed with ongoing chest compressions. We have compared hemodynamic effects of ventilating synchronously vs. asynchronously during chest compressions in a porcine model.

Methods: Twenty anaesthetized domestic pigs (approx. 30 kg) were randomized into two groups; synchronous vs. asynchronous ventilation. Ventricular fibrillation is induced electrically and left for 2 minutes before initiation of basic 30:2 CPR for 4 minutes. CPR with continuous mechanical chest compressions was continued for another 8 minutes with either synchronous or asynchronous ventilation before defibrillation was attempted. Aortic, right atrial and intracerebral pressures, carotid and cerebral blood flow and cardiac output (thermodilution) were measured. Airway monitoring included capnography and spirometry.

Results: Hemodynamics, blood gas analysis and airway pressures were similar for both groups during baseline and 30:2 CPR periods. The asynchronous group had higher median peak inspiratory airway pressure (94 vs. 57 cm H_2O, p<0.001) and lower $EtCO_2$ (1.8 vs. 3.5 kPa, p=0.023) compared to synchronous group during the last 30 seconds of CPR (after 12 minutes). Asynchronous group also had higher pH (7.55 vs. 7.35, p<0.001), lower pCO_2 (2.4 vs. 4.7, p<0.001) and higher pO_2 (62.1 vs. 29.4, p<0.001) compared to synchronous group. There were no significant differences in any of the measured hemodynamic variables between the two groups with similar coronary and cerebral perfusion pressures. ROSC was achieved in 5/10 vs. 3/10

animals in the synchronous and asynchronous groups, respectively.

Conclusion: Synchronous and asynchronous ventilation during mechanical chest compressions provide similar hemodynamics, but guideline-compliant asynchronous ventilation yields significantly higher airway pressures and hyperventilation. Implications for lung injury need to be assessed.

13 Variation in Achievable Chest Compression Depth Assessed by Cardiac MRI

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Introduction: Recommended chest compression depth during cardiopulmonary resuscitation (CPR) for adults was increased to 5-6 cm in 2010. According to the cardiac pump theory each compression squeezes blood from the heart and the amount of blood per compression would be expected to be limited by the blood filled structures directly underneath the compression point.

Methods: Cardiovascular MR (CMR) survey axial scans acquired from consenting patients referred for CMR were analyzed. We measured the external anterior-posterior (AP) diameter (AP) and the cumulative height of blood-filled structures in the perpendicular line in an axial plane from the compression point in the center of the internipple line (INL) (Compression line). Results are means with standard deviation (SD) and mean differences with 95 % confidence intervals (CI), P-values from unpaired, two-sided t-test.

Results: We included 144 patients, age 52 (17), 110 (76 %) males, 74 (60 %) having one or more pathological finding from the exam. The most prominent structure identified in the studied midline was (decreasing order): Left Atrium (41 %), Right Ventricle (31 %), Right Atrium (12 %), Left Ventricular Outflow Tract (LVOT)/Root of Aorta (8 %), Pulmonary Outflow Tract (2 %), other (6 %). Altogether, LVOT was present in 35 % and Left Ventricle in only 2 % of compression lines. Mean (SD) AP diameter for males and females was 25 (2) cm and 22 (2) cm (mean difference 2 cm (95 % CI 1, 3; P<0.001)), and the blood filled length of the compression line (APblood) were 6.5 cm (2) and 4.7 cm (2) (mean difference 1.8 cm (95 % CI 1.1, 2.5, P<0.001)), respectively. This comprised 22 % (10) and 26 % (7) of the AP diameter, for men and women, respectively. In a linear regression gender, body mass index (BMI), but not pathological findings were significant predictors of external AP diameter. Only gender was found to predict APblood.

Conclusions: In the average male 5-6 cm chest compression depth at the level of the INL seems feasible, but for over half of the women compressions deeper than 5 cm would probably compress connective and muscle tissue rather than just squeeze blood from the heart, even though the blood-filled proportion of the AP diameter was larger in women than in men.

205 Targeted Simulation and Education to Improve Cardiac Arrest Recognition and Telephone Cpr in an Emergency Medical Dispatch Centre

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Introduction: Patient outcome after out of hospital cardiac arrest (OHCA) is dependent on emergency medical dispatchers ability to recognize OHCA and provide effective telephone-assisted CPR instructions to bystanders. The American Heart Association recommends continuous quality monitoring to ensure implementation of educational interventions in emergency medical dispatch centres.

Objective: Improve dispatcher recognition of OHCA and time to first telephone assisted chest compression.

Method: Weak aspects of cardiac arrest calls in our dispatch centre were identified, and targeted interventions to improve recognition of agonal respiration and cardiac arrest and to shorten time to first chest compression were implemented. Specifically; 1) Video-based lectures focusing on agonal respiration and continuous coaching 2) Simulation training 3) Structured dispatcher feedback 4) Electronic telephone-assisted CPR training program. Dispatch logs, ambulance records and audio files of confirmed OHCA's were analyzed before and after the intervention. Recognition of cardiac arrest was reported as (1) recognized, (2) not recognized and (3) delayed recognition (defined as failure to initially clarify consciousness or abnormal breathing before moving on to further questioning).

Results: 289 and 221calls were included before and after intervention, respectively. Recognition of cardiac arrest improved from 74% to 89% (p<0.001), and delayed recognition was reduced from 14% to 5% (p=0.001). Agonal respiration continues to challenge dispatchers, but misin-

terpretation of abnormal breathing decreased from 25% to 8% (p<0.001) of calls. Median time to first chest compression was reduced by 30 seconds (204 vs. 174 seconds, respectively, p=0,039)

Conclusion: Targeted simulation and education significantly increased recognition of OHCA and reduced time to first chest compression. Continuous focus and targeted dispatcher training are important to ensure quality of care for OHCA patients.

360 ECG Patterns in Early Pulseless Electrical Activity and the Etiologies of In-Hospital Cardiac Arrest

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Introduction: The defibrillator is a mandatory diagnostic and therapeutic tool for the treatment of cardiac arrest (CA). The diagnostic potential of the defibrillator may not be fully utilized. Pulseless electrical activity (PEA) is increasingly common as the first presenting rhythm for a range of etiologies, in particular the 'reversible causes 4H4T' (figure). We investigated the etiology and its relation to the QRS duration and heart rate during PEA.

Method: We conducted a prospective observational study of all CA episodes treated by an in-hospital emergency team (ET) at St.Olav University Hospital in Trondheim/Norway during 4.5 years. Two cardiologists independently examined the ECG recorded during the first compression pause after attachment of the defibrillator, and measured the duration of three consecutive QRS complexes. The averaged QRS duration was defined as normal if shorter than 120ms and the heart rate (HR) was defined as normal if between 59 and 100/minute, leading to six simple 'patterns' of PEA: normal, wide, narrow-slow, wide-slow, narrow-fast and wide-fast. PEA episodes with reliable causes of arrest confirmed by objective diagnostic criteria were included.

Results: We identified 69 triggering causes in 51 PEA episodes. The figure shows the bivariate distribution of QRS/HR according to etiology, showing no obvious relationship. In 48 episodes (83%) the initial ECGs were outside the 'normal' range regarding QRS duration, HR, or both. Six patients survived to hospital discharge, none of their presenting ECGs were 'normal'

Conclusion: Four fifths of all presenting PEA patterns were found to be abnormal with respect to HR and QRS duration. An abnormal initial ECG did not point towards etiology nore precluded survival in this modest study sample.