NORSKE ABSTRAKTER PRESENTERT PÅ AHA.

155 Duration of Pre-shock Compression Pause Does Not Affect Defibrillation Success in Out-of-Hospital Cardiac Arrest Treated With Either Manual or Load-Distributing Band Compressions

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Background: Guidelines emphasize minimizing pre-shock chest compression pauses prior to a defibrillation attempt. Study results on the influence of pre-shock pauses on first shock defibrillation failure are inconclusive. We wanted to study how preshock pauses influenced shock success for manual and load-distributing band compressions prior to shocks (M-c and LDB-c) in the Circulation Improving Resuscitation Care (CIRC) study database.

Methods: Initial rhythm, pre-shock rhythm, rhythm 5 sec after shock, M-c or LDB-c, and number of shocks were recorded based on ECG and transthoracic impedance. Shock success was defined as VF/VT termination at least 5 sec after shock. Shocks without analyzable pre-shock pause, post-shock rhythm, or compressions prior to shock, and shocks not indicated were excluded. Pre-shock pauses were measured from the last compression to shock delivered, and divided into 5 groups: Group A shock during compressions (LDB-c only), group B pre-shock time <10 sec (excluding shock during compressions), group C 10- 19 sec, group D 20-29 sec, and group E ≥30 sec. Differences between groups were calculated using chi-square test.

Results: We included 2807 of 2969 M-c and 1715 of 1791 LDB-c shocks. Median pre-shock time was 4 seconds (IQR 3-16) for M-c, and 0 seconds (IQR 0-6) for LDB-c. The table shows first shock success for M-c and LDB-c related to initial VF/VT, and all initial rhythms and all shocks for the five pre-shock pause groups.

Conclusion: Different pre-shock pauses or shock during compressions did not affect shock success for M-c or LDB-c. However, the impact on ROSC and neurologic outcome requires further investigation.

	Shock success, M-c	Shock success, LDB-c
Initial VF/VT first shock[a, b]		
Group A, Shock during compressions	-	130 (78%)
Group B, pre-shock pause <10 sec	282 (83%)	33 (85%)
Group C, pre-shock pause 10-19 sec	108 (86%)	23 (84%)
Group D, pre-shock pause 20-29 sec	84 (90%)	13 (93%)
Group E, pre-shock pause ≥ 30 sec	41 (87%)	7 (100%)
All initial rhythms, all shocks[c, d]		
Group A, Shock during compressions	-	861 (79%)
Group B, pre-shock pause <10 sec	1480 (80%)	201 (78%)
Group C, pre-shock pause 10-19 sec	367 (83%)	163 (80%)
Group D, pre-shock pause 20-29 sec	290 (87%)	90 (87%)
Group E, pre-shock pause ≥ 30 sec	147 (85%)	62 (89%)

M-c [a]p=0.33 and LDB-c [b]p=0.38. M-c [c]p=0.01 and LDB-c [d]p=0.17

162 During a Cardiopulmonary Resuscitation Cycle it is Necessary to Re-verify a Shockable Rhythm Prior to Defibrillation Attempts

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Background: AHA Guidelines recommend two minutes of CPR post-shock followed by ECG analysis and defibrillation if the patient still has shockable rhythm. This requires a pre-shock chest compression pause, which probably reduces the likelihood of return of spontaneous circulation (ROSC) post-shock. This immediate pre-shock pause could be avoided if rhythm analysis occurred earlier in the cycle. In the Circulation Improving Resuscitation Care (CIRC) study ECG was analyzed both one minute post-shock and immediately prior to defibrillation This database therefore enabled studying whether a second pre-shock ECG analysis was warranted. If not, CPR could continue uninterrupted in the pre-shock phase.

Methods: The randomized controlled CIRC trial included patients with out-of-hospital cardiac arrest (OHCA) of presumed cardiac etiology. Defibrillator data was used to categorize ECG rhythms as shockable or non-shockable one minute post-shock and immediately before next possible shock, and to record chest compressions and ventilations from transthoracic impedance (TTI) analysis. Episodes without rhythm analysiis due to compression artefacts or with lack of ECG or transthoracic impedanceTTI data were excluded from the analysis. ROSC was documented based on end-tidal CO2-measures, TTI and patient record.

Results: Of 4,231 patients with OHCA, 1657 (39%) received one shock or more and 1603 of these had analysable data. These patients received 4820 analysable shocks. Of these, 1513 (31%) had a shockable rhythm one minute post-shock, wich was also present immediately before the next possible shock in 1500 (99,1%) instances. Among the 13 shocks where the shockable rhythm one minute post-shock converted to a non-shockable rhythm prior to next possible shock, three instances were identified as ROSC.

Conclusion: This study suggests that it is necessary to reverify VF/VT prior to a defibrillation attempt if determined earlier in the same CPR cycle. Further studies are needed to document the effect of providing shocks to rhythms that are not indicated for shocks. organized rhythms.

167 EMS Provider Documentation Changes the Predictive Value of Bystander CPR

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Background: It is accepted that bystander CPR improves survival from out-of-hospital cardiac arrest (OHCA). The Utstein template advocates for collection of bystander CPR data. The Circulation Improving Resuscitation Care (CIRC) Trial failed to identify a survival benefit from bystander CPR. We hypothesis that this may be because the definition of bystander CPR is not standardized and likely varies between providers. The objective of this subgroup analysis was to determine if analysis of explicit documentation of bystander CPR components is a better predictor of patient survival.

Methods: We conducted a secondary analysis of the CIRC trial; a randomized controlled trial of Emergency Medical Services (EMS) treated OHCA comparing integrated AutoPulse-CPR to Manual-CPR. EMS data was abstracted from EMS agency medical records by trained research coordinators. There were 4 variables for bystander CPR: 1) a general bystander CPR variable, 2) bystander compressions, 3) bystander ventilations, and 4) bystander AED use. A general bystander CPR variable was present on all patient care reports. Some agencies had check boxes for the remaining variables, while the others obtained them from the medical record narrative. Logistic regression was used to determine the association of each of these variables with hospital discharge.

Results: CIRC enrolled 4,231 patients. Bystander CPR was performed for 2,059 patients (49%), but was not found to be predictive of survival (OR 0.96, 95% CI: 0.90-1.02). The bystander CPR components were all found to be associated with survival: bystander compressions (documented for 936, OR 1.410, 95% CI: 1.13-1.77), bystander ventilations (documented for 315, OR 1.58, 95% CI: 1.14-2.20), bystander AED use (documented for 215, OR 1.93, 95% CI: 1.33-2.79).

Conclusion: Each component of bystander CPR was found to be associated with survival to hospital discharge, even though general documentation of bystander CPR was not. An explicit definition of bystander CPR should be developed and EMS providers should be trained to identify and document the type of bystander CPR that is provided.

168 Integrated Autopulse CPR Improves Survival From Out-of Hospital Cardiac Arrests Compared to Manual CPR After Controlling for EMS Response Times

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Background: The randomized controlled trial, Circulation Improving Resuscitation Care (CIRC), found that Emergency Medical Services (EMS) treated Out-of-Hospital Cardiac arrest (OHCA) survival was equivalent for integrated AutoPulse CPR (iA-CPR) and high quality Manual CPR (M-CPR) after controlling for covariates (study site, patient age, witnessed arrest, and initial rhythm). Recently, early compressions have been emphasized. In CIRC we did not control for the effect of EMS response times. Consequently, we wanted to determine the influence of EMS response time on survival to hospital discharge and to reanalyze the CIRC trial data controlling for this time.

Methods: We conducted a secondary analysis of the CIRC patients with witnessed arrest and shockable initial rhythm. The EMS response time was calculated by subtracting EMS documented arrival time from 9-1-1 call received time. A dichotomous variable was collected where EMS documented if there was a delay in accessing the patient after arrival at the scene (the actual time of the delay was not available). Logistic regression analysis was conducted controlling for the study covariates (study site and patient age), as well as response time, and patient access delay.

Results: Of 4,231 patients in the CIRC trial, 659 (16%) had a witnessed cardiac arrest with an initial shockable rhythm and complete response

time and survival data. Response time and number of access delay in the M-CPR (349 patients) arm compared to iA-CPR (310 patients) were 7.25 minutes and 33 delays versus 7.35 minutes and 67 delays, respectively. Increasing EMS response time (OR 0.93; 95% CI: 0.88-0.99, p=0.026) and access delay (OR 0.59; 95% CI: 0.36-0.99, p=0.046) were found to be negatively associated with survival to hospital discharge. Controlling for the study covariates, EMS response time, and access delay, logistic regression found improved survival to hospital discharge with iA-CPR (OR 1.46; 95% CI: 1.03-2.07, p=0.036).

Conclusion: EMS response time and access delay are significant predictors of hospital survival and their effect should be controlled. Compared to high quality M-CPR, iA-CPR resulted in a statistically significant improvement in survival to hospital discharge for adult witnessed shockable OHCA patients.

286 Survival to Hospital Discharge With Fixed 360 Joules Versus 200 Escalating to 360 Joules Defibrillation Strategies in Out-of-Hospital Cardiac Arrest of Presumed Cardiac Etiology

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Background: There is lack of evidence for fixed or escalating shock energy levels impact on survival to hospital discharge during CPR. According to the 2010 CPR consensus "maintaining the same initial energy level during subsequent shocks is acceptable. It is reasonable to increase the energy level when possible." We studied shock success and survival to hospital discharge with fixed 360 Joules (J) versus escalating 200 to 360 J shocks, in patients in the Circulation Improving Resuscitation Care (CIRC) trial.

Methods: Initial rhythm, pre-shock rhythm, rhythm 5 seconds after shock, shock energy levels and number of shocks were recorded. Patients uncategorizable as fixed or escalating shock energy protocol, without any indicated shocks or without any analyzable result from the shock were excluded from analysis. Shock success was defined as VF/VT termination at least 5 seconds after shock. Shock success between groups was calculated using chi-square test. Logistic regression determined the association between defibrillation strategy and survival to hospital discharge, after adjusting for age, initial rhythm, number of shocks, and witnessed arrests.

Results: In CIRC 1657 (39%) of 4231 patients received at least one shock with analyzable defibrillator data. We included 914 fixed and 411 escalating patients. Median number of shocks per patient was 2 (IQR 1-4) in both groups. These patients received 3819 indicated shocks, 2662 in the fixed group and 1157 in the escalating group. There were 2178 (81.8%) successful shocks in the fixed group versus 963 (83.2%) in the escalating group (OR 0.91, 95% CI 0.76-1.09, p=0.29). A sub-analysis of patients whose initial rhythm was VF/VT found first shock success for 409 (83.1%) of the 492 in the fixed group versus 237 (86.5%) of the 274 in the escalating group (OR 0.77, 95% CI 0.51-1.17, p=0.22). Survival to hospital discharge for patients in the fixed group had an unadjusted OR 0.83, (95% CI 0.62-1.12, p=0.23) and adjusted OR 1.10 (95% CI 0.78-1.54, p=0.61) compared to the escalating group.

Conclusion: There was no difference in individual shock success between defibrillation strategies. Further, there was no difference in patient survival to hospital discharge between the fixed versus escalating defibrillation strategies.

287 Shock Success Rates with Sternal-apical vs. Anterior-posterior Pad Positioning During Out-of-hospital Cardiac Arrest

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Background: Shock success rates for sternal-apical (SA) and anterior-posterior (AP) defibrillator pad positions have not been compared clinically. Houston Fire EMS historically used AP, but changed to SA position, enabling shock success rate comparisons in out-of-hospital cardiac arrest (OHCA) patients.

Methods: Patients treated with manual CPR and biphasic LifePak 500/12 defibrillators (Physio-Control, Redmond, US) were included from January 2006 to April 2007 for AP and from March 2009 to January 2011 for SA, this excluded the transition period when either position may have been used. ECG files were reviewed and initial rhythm, immediate pre-shock and five seconds post-shock rhythms were recorded as shockable or non-shockable. Only indicated shocks were included in analysis of shock success defined as termination of ventricular arrhythmias for at least five seconds. Data were analyzed using SPSS, and differences between the SA and AP groups were calculated using chi-square test and odds ratios (OR).

Results: Of 989 shocked patients, 917 (93%) received 3074 indicated shocks. Of these indicated shocks 1163 of 1436 (81.0%) were successful in 476 SA patients vs. 1303 of 1638 (79.5%) in 441 AP patients (OR 1.10, 95% CI: 0.92-1.31, p=0.32). Median number of indicated shocks was 3 (IQR 1-4) in SA group and 3 (IQR 1-5) in AP group. Initial rhythm was shockable in 269 (57%) SA patients and in 277 (63%) AP patients (p=0.05) with 797 of 993 shocks (80.3%) being successful in this subgroup of SA patients vs. 859 of 1069 (80.4%) in the AP patients (OR 0.99, 95% CI: 0.80-1.24, p=0.96).

Conclusion: There was no significant difference in shock success rate between sternal-apical and anterior-posterior defibrillator pads positioning during manual CPR of OHCA patients.

303 Frequency of Newborn Resuscitation and Stabilization in Three Normal-Risk Delivery Units in Norway

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Introduction: Most newborn infants transition from intra- to extrauterine life without interventions; yet neonatal morbidity remains a significant health problem in both resource rich and resource poor health care systems. Although advanced resuscitation of newborn infants with chest compressions, intravenous drugs, and fluids is relatively rare, there are limited data on the frequency of neonatal stabilization and resuscitation measures in normal-risk delivery units.

Methods: Prospective, observational study conducted in the delivery units in three hospitals in Norway. All newborn infants assessed for stabilization and/or resuscitation during one month were included. After each incident, data on resuscitation measures and outcome were registered and reviewed by study personnel at every on-call team shift during the study period. Approval was obtained from department heads and institutional review boards.

Results: 1507 babies were live born during the study period, mean weight 3.3 kg and gestational age 39.4 weeks.: 113 (7 %) needed resuscitation interventions beyond drying and stimulation. Suctioning of oropharynx was performed in 77 babies (5 %) and tracheal suctioning in 10 (1%). Positive pressure ventilation (PPV) was provided by a T-piece resuscitator and/or by a selfinflating bag to 58 (4 %) with 39 (3 %) receiving supplementary oxygen. In addition CPAP (but no PPV) was provided to 17 (1 %). One needed chest compressions. Tracheal intubation was accomplished in 4 infants of whom 3 were prematurely born and treated with tracheal surfactant. Intravenous access was established in 8 infants, two received saline infusions and one received epinephrine. After initial resuscitation, 64 (4 %) were admitted to the neonatal intensive care unit and two died. Twenty-one events were handled exclusively by midwifes, 244 by pediatric residents and 39 by attending neonatologists.

Conclusion: Most newborns do not need advanced resuscitation procedures. However, even in low risk deliveries, more than 4 % of newborns required assisted ventilation. Correct assessment of need for ventilatory support and correct execution of positive pressure ventilation needs to be ensured.

304 Conversion of Ventricular Fibrillation to an Organized Rhythm Without a Defibrillator

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Background: Reports of pulseless ventricular tachycardia (VT) or ventricular fibrillation (VF) converting to an organized rhythm without defibrillator use are rare. We wish to report a series of such cases in the randomized Circulation Improving Resuscitation Care (CIRC) trial comparing outcome between integrated AutoPulse CPR (iA-CPR) and Manual-CPR (M-CPR) in patients with out-of-hospital cardiac arrest (OHCA) of presumed cardiac etiology.

Methods: Defibrillator ECGs were studied to determine rhythm one minute after defibrillation attempts and rhythm immediately before the next defibrillation attempt. Rhythms were categorized as VF, pulseless VT, asystole or an organized rhythm. Organized rhythms were classified as either pulseless electrical activity (PEA) or as return of spontaneous circulation (ROSC) if accompanied by a steep increase in EtCO2, trans-thoracic impedance showing typical "dips," and a detectable pulse.

Results: In 1603 patients with analyzable date and a shockable rhythm there were 13 cases of VF/VT (10/3) conversions to PEA or ROSC during periods with external chest compressions without defibrillation attempts. In eight of the 10 VF cases chest compressions converted VF to PEA (5 iA-CPR vs 3 M-CPR) and in two to ROSC (2 iA-CPR vs 0 M-CPR). With VT one case converted to PEA (M-CPR) and two to ROSC (2 iA-CPR vs 0 M-CPR). Examples will be presented.

Conclusion: This study documents that conversion of VF or VT to an organized rhythm during CPR without electrical assistance is possible but rare.

308 There is a Correlation Between Neurologic Score and Discharge Location for Patients With Out-of-Hospital Cardiac Arrest of Presumed Cardiac Origin

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Background: The Circulation Improving Resuscitation Care (CIRC) Trial found equivalent survival in out-of-hospital cardiac arrest (OHCA) patients who received integrated AutoPulse CPR (iA-CPR) compared to high quality Manual CPR (M-CPR), and no difference in neurologic outcome. However, neurologic outcome was not available for some patients, and discharge location may serve as a proxy for neurologic outcome. The objective of this study was to determine if there is a correlation between modified Rankin Scale (mRS) Score at discharge and discharge location, and to determine the association between discharge location and study intervention.

Methods: A subgroup-analysis of the CIRC randomized clinical trial comparing iA-CPR to M-CPR was conducted on patients who were discharged from hospital. Neurologic outcome was categorized as good (mRS ≤3), not good (mRS ≥4), or unknown, and according to discharge location of home or rehabilitation, nursing home or assisted living, and unknown or awaiting care, respectively. Spearman correlation was used to determine the relationship between mRS score and discharge location. Logistic Regression was used to compare iA-CPR to M-CPR in predicting neurologic outcome using discharge location and adjusting for the study covariates (study site, patient age, witnessed arrest, and initial rhythm).

Results: CIRC enrolled 4,231 patients and 429 (10%) survived to hospital discharge. mRS score was known for 310 of those patients and discharge location for 300 patients, both were known for 292. A Spearman correlation analysis between mRS score and discharge location was statistically significant ($r=0.622$, $p<0.001$). iA-CPR was documented to increase survival to hospital discharge with good neurologic outcome (using discharge location as a surrogate) compared to M-CPR (unadjusted OR 2.25, 95% CI 1.21-4.17, p=0.009). When adjusted for covariates there was a trend in favor of iA-CPR (OR 1.82, 95% CI 0.91- 3.63, p=0.09).

Conclusion: There was a correlation between mRS score and discharge location. More patients were discharged to a location with limited assistance and consequently potential better neurologic outcome in the iA-CPR group compared to the high quality M-CPR group.

9405 Lower Achieved Systolic Pressure (≤130 mm Hg) is Associated With a Decreased Risk of New Atrial Fibrillation in Hypertensive Patients With Electrocardiographic Left Ventricular Hypertrophy: The LIFE Study

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Background: There is a well-established association between hypertension and atrial fibrillation (AF), with recent studies demonstrating that even upper normal systolic blood pressures (SBP) are long-term predictors of incident AF. These findings suggest that more aggressive control of BP may reduce the risk of new AF. However, whether more aggressive reduction of SBP is associated with a lower incidence of AF remains unclear.

Methods: Risk of new-onset AF was examined in relation to last in-treatment SBP prior to AF diagnosis or last in-study measurement in the absence of new AF in 8831 hypertensive patients with ECG LVH with no history of AF, in sinus rhythm on their baseline ECG, randomly assigned to losartan- or atenolol-based treatment. Patients with in-treatment SBP ≤130 mm Hg (lowest quintile at last measurement) and SBP between 131 and 141, were compared with patients with in-treatment SBP ≥142 (median SBP at last measurement).

Results: During 4.6±1.1 years follow-up, new-onset AF was diagnosed in 701 patients (7.9%). In univariate analyses, compared with in-treatment SBP ≥142, in-treatment SBP ≤130 entered as a time-varying covariate was associated with a 46% lower risk (95% CI 31-58%) and in-treatment SBP between 131 and 141 with the same 46% lower risk (95% CI 35-55%) of developing AF. After adjusting for randomized treatment, age, sex, race, diabetes, history of ischemic heart disease, MI or heart failure, prior antihypertensive therapy, baseline serum glucose, creatinine,

HDL and total cholesterol entered as standard covariates, and for incident MI, heart failure and in-treatment Cornell product LVH, heart rate, diastolic BP and HDL treated as time-varying covariates, achievement of a SBP ≤130 remained associated with a 40% lower risk (95% CI 18-55%) and intreatment SBP of 131 to 141 with a 24% lower risk (95% CI 7-38%) of new AF.

Conclusions: Achieved SBP ≤130 is associated with a lower risk of developing new-onset AF in hypertensive patients with ECG LVH, independent of other known and possible risk factors for AF. Further study will be needed to determine whether targeting hypertensive patients without AF to lower SBP goals can reduce the burden of new AF in this high-risk population.

9449 Feasibility and Accuracy of High Resolution 4D Echocardiography for Evaluation of Left Ventricular Mass and Stroke Volume: An in vitro Phantom Study

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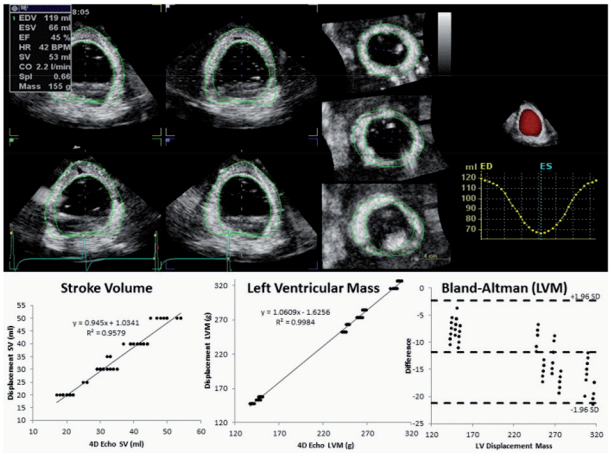
Background: This study was designed to determine the accuracy and feasibility of a new 4D echo-based semi-automated quantification of left ventricular (LV) mass (LVM) and stroke volume (SV) in an *in vitro* phantom model.

Methods: Ten freshly harvested adult pig and sheep hearts (147-326 grams) were passively driven using a pulsatile pump to simulate normal cardiac motion. Each heart was pumped at 3 stroke rates (SR) (40, 65, and 85 strokes/min) and 3 SVs (30, 50, and 70 ml at each SR).



Full-volume 4D cine loops were collected with a 3V Matrix transducer interfaced with a GE Vivid E9 ultrasound system at a maximized frame rate (≥25 FPS) using multi-beat acquisition. Images were analyzed offline using EchoPAC PC for semi-automated quantification of SV and LVM and compared to displacement values.

Results: No significant differences were detected between the values of either SV or LVM at different stroke rates (P=0.99). Data showed excellent linear correlation between 4D echo-derived SV and LVM, and displacement data (SV: R^2=0.96, p<0.001; LVM: R^2=0.99, p<0.001). Bland-Altman analyses revealed 98% and 99% of points within a 95% CI for SV and LVM respectively. Interobserver variability was shown to be excellent (SV: R^2=0.92, p<0.001; LVM: R^2=0.99, p<0.001).

Conclusions: 4D echo-based quantification may be an accurate and feasible method for determination of LV mass and stoke volume and a physiologically relevant range of stroke volumes and stroke rates.

9464 International Incidence of Complications After Catheter Ablation of Persistent Atrial Fibrillation (AF): Insights From the Multicenter, Prospective, Randomized STAR AF II Trial

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Background: Complication rates after AF ablation are mostly reported in single center experiences or surveys. Little international, multicenter, prospective data on the contemporary incidence of complications is available. We report the incidence of complications from the large STAR AF II randomized trial.

Methods: The STAR AF II trial is an international, randomized trial comparing 3 different strategies for ablation of persistent AF: pulmonary vein isolation (PVI) alone, PVI + linear ablation, and PVI + ablation of com-

plex fractionated electrograms. 48 centers were involved across Canada, Australia, Korea, China, & 8 countries in Europe. Post-ablation, patients were all followed for 18 months. All adverse events were reported by protocol and were classified as "serious" if it was fatal, life-threatening, disabling, or required/prolonged hospitalization. Adverse events were also reviewed by an independent data safety monitoring board and classified as either being related or unrelated to the ablation procedure. Adverse events related to the ablation procedure were included in this analysis.

Results: Patients (n=589) were enrolled in the STAR AF II trial (age 60±10 years, 79% male, EF 56±10%, LA diameter 44±9 mm). The most common post-procedural complications were access site hematoma (n=16, 2.7%), fluid overload/pulmonary edema (n=16, 2.7%), and transient pericarditis (n=15, 2.5%). Access site arterio-venous fistulas or pseudoaneurysms occurred in 7 patients (1.2%). Complications related to sedation occurred in 5 patients (0.8%). Cardiac tamponade (n=3, 0.5%), stroke or transient ischemic attack (n=3, 0.5%), and symptomatic PV stenosis (n=1, 0.2%) were uncommon. None of the neurological events resulted in permanent deficit. There was one atrio-esophageal fistula complicated by stroke which was successfully stented, but the patient died of aspiration pneumonia three months later.

Conclusions: The most common complications were access site hematoma, fluid overload, and transient pericarditis. The rates of serious adverse events such as tamponade, stroke and symptomatic PV stenosis were quite low. There was one atrioesophageal fistula that caused late death despite successful repair.

9878 Small Aortic Roots - Clinical Characteristics and Implications for Assessment of Aortic Stenosis in Asymptomatic Patients With Preserved Ejection Fraction

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Background: The aim was to characterize asymptomatic aortic stenosis (AS) patients with small aortic roots and the implications for assessment of AS severity. Methods: We analysed data from 1563 patients with asymptomatic AS enrolled in the Simvastatin Ezetimibe in Aortic Stenosis study. Severe AS was defined by aortic valve area (AVA) as <1.0cm², by AVA indexed for body surface area (AVAI) as <0.6cm²/m² and by energy loss index (ELI) as <0.6cm²/m². Inconsistently graded severe AS was defined as the combination of AVA or ELI <1.0 cm² and mean aortic gradient ≤40mmHg.

Results: A small aortic root (lowest tertile of aortic sinotubular junction diameter, <2.60cm) was present in 32.6% of patients. This group included more women (67.8% vs. 25.0%) and patients with hypertension and patients had smaller body surface area, height and left ventricular (LV) dimensions and higher age and pulse pressure/stroke volume index (PP/SVi) compared to the rest of the study population (all p<0.001). AS severity measured by peak jet velocity or mean gradient did not differ between groups. The prevalence of inconsistently graded severe AS was more common in patients with small aortic roots when using AVA (38.3 vs. 23.5%, p<0.001), but not when using ELI (23.8 vs. 24.0%, p=0.920). In multivariate logistic regression, having small aortic root was associated with a higher prevalence of inconsistently graded severe AS using AVA, independent of female gender, higher PP/SVi and lower height and smaller LV dimensions and wall thickness (Table). Conclusion: In asymptomatic AS the use of ELI for grading of AS rather than AVA lowered the prevalence of inconsistently graded severe AS among patients with small aortic roots. However inconsistently graded severe AS remained common using the currently recommended cut-off values for grading of AS.
Table. Covariates of small aortic root in multivariate analysis.

Variables	OR	95% CI	p-value
Inconsistently graded severe AS	1.362	1.049-1.769	<0.05
Gender (female)	3.033	2.181-4.217	<0.001
Height (cm)	0.025	0.004-0.166	<0.001
LV end-diastolic diameter (cm)	0.763	0.593-0.982	<0.05
PP/SVi (mmHg*m²/ml)	1.368	1.078-1.736	<0.05
Posterior wall thickness (mm)	0.443	0.220-0.896	<0.05
Age (years)	0.998	0.985-1.012	0.803

10213 Digoxin Use and Risk of Mortality in Hypertensive Patients With Atrial Fibrillation: The LIFE Study

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Background: Digoxin (dig) is widely used for rate control of atrial fibrillation (AF). However, recent studies have reported conflicting results on the association of dig use in AF with mortality. Moreover, the relationship of dig use to mortality in hypertensive patients with AF has not been examined.

Methods: Risk of all-cause mortality was examined in relation to in-treatment use of dig in 937 hypertensive patients in AF at baseline (n=134) or who developed AF during follow-up (n=803) with data on dig use at baseline and during treatment, randomly assigned to losartan- or atenolol-based treatment.

Results: During 4.7±1.1 years follow-up, 167 patients died (17.8%) and 372 (39.7%) were on dig at some time. In univariate Cox analyses, in-treatment dig use, entered as a time-varying covariate, was associated with a 61% higher risk of death (95% CI 18-119%). After adjusting for other univariate predictors of death in this population, including age, diabetes, history of ischemic heart disease, stroke or heart failure, baseline Cornell product, QRS duration, heart rate, serum glucose, creatinine and HDL, and a propensity score for dig use entered as standard covariates, and for in-treatment heart rate, systolic pressure and Sokolow-Lyon voltage treated as time-varying covariates, dig use was no longer a significant predictor of mortality (HR 1.06, 95% CI 0.75-1.51, p=0.745). In parallel analyses excluding the 175 patients on dig at baseline, in-treatment dig use was no longer a univariate (HR 1.10, 95% CI 0.71-1.68) or multivariate (HR 0.85, 95% CI 0.54-1.34) predictor of death. Similarly, if the 45 patients with a history of heart failure were excluded, in-treatment dig use was of borderline significance in univariate analyses (HR 1.38, 95% CI 0.99-1.93) but was not a significant predictor of death in multivariate Cox analyses (HR 0.97, 95% CI 0.67-1.41).

Conclusions: In hypertensive patients with existing or new AF, dig use is not associated with a significantly increased risk of all-cause mortality after adjusting for other independent predictors of death and for the factors associated with the propensity to use dig in this population. These findings suggest that factors other than dig use may account for the increased mortality found with dig use in some studies.

10291 Fibroblast Growth Factor (FGF)-23, Cardiovascular Prognosis, and Benefit of Angiotensin-Converting Enzyme Inhibition in Patients With Stable Coronary Artery Disease

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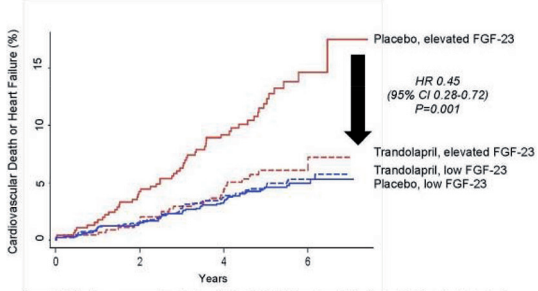
Background: Fibroblast growth factor (FGF)-23 is an endocrine regulator of mineral metabolism. Higher levels of FGF-23 are associated with adverse cardiovascular events in patients with reduced renal function. Whether FGF-23 identifies high-risk patients independent of renal function and established cardiovascular biomarkers, and whether it identifies patients that derive greater clinical benefit from ACE inhibitor therapy, is unknown.

Methods: We measured FGF-23 levels in 3,627 patients with stable ischemic heart disease (SIHD) and preserved systolic function who were randomized to trandolapril or placebo within the Prevention of Events With Angiotensin-Converting Enzyme trial and followed for a median of 5.2 years.

Results: After adjustment for clinical risk predictors, left ventricular ejection fraction, markers of renal function, and established cardiovascular biomarkers, FGF-23 levels in the top quartile were independently associated with an increased

Figure. Cumulative incidence curves for the composite of cardiovascular death or heart failure in patients categorized by FGF-23 level and treatment with trandolapril.



Legend: Blue lines represent patients with low FGF-23 levels; solid indicates 1362 patients treated with placebo; dashed, 1359 patients treated with trandolapril. Red lines represent patients with high FGF-23 levels; solid indicates 453 patients treated with placebo; dashed, 453 patients treated with trandolapril. HR indicates hazard ratio; CI, confidence interval.

risk of cardiovascular death or heart failure among patients allocated to placebo (HR, 1.72; 95% CI, 1.09-2.73; *P*=0.02) and significantly improved metrics of discrimination. Furthermore, among patients in the top quartile of FGF-23 levels, trandolapril significantly reduced the incidence of cardiovascular death or heart failure (HR, 0.45; 95% CI, 0.28-0.72), whereas there was no clinical benefit in the remaining patients (HR, 1.07; 95% CI, 0.75-1.52; *P*-interaction=0.0039). This interaction was independent of and additive to stratification based on renal function.

Conclusions: Elevated levels of FGF-23 are associated with cardiovascular death and incident heart failure in SIHD patients and identify patients who derive significant clinical benefit from ACE inhibitor therapy regardless of renal function.

10438 Echocardiographic Mechanical Dispersion is a Marker for Ventricular Arrhythmia in Patients With Cardiac Resynchronization Therapy

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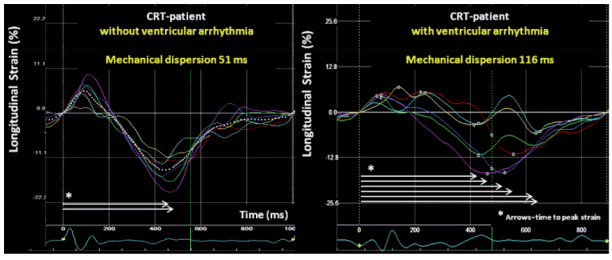
Background: Mechanisms and predictors of ventricular arrhythmia (VA) in heart failure patients eligible for cardiac resynchronization therapy (CRT) are not fully clarified. Mechanical dispersion reflects left ventricular (LV) dyssynchrony of myocardial contraction and has been shown to predict VA in different cardiomyopathies. We assessed left ventricular (LV) function and mechanical dispersion to explore mechanisms of VA in heart failure patients treated with CRT. We hypothesized that improvement of mechanical dispersion by CRT, would be associated with less VA.

Methods: We investigated candidates for CRT treatment with LV ejection fraction (EF) < 35%, QRS > 120 ms, NYHA functional class 2-4 and no VA prior to CRT implantation. Speckle tracking strain analyses from 2D echocardiographic examination were performed before and 6 months after CRT-implantation. Mechanical dispersion was calculated as standard deviation of time to peak negative longitudinal strain from 16 LV segments. VA was defined as non-sustained or sustained ventricular tachycardia/fibrillation during 2 years following CRT implantation.

Results: We included 56 patients (age 64±9 years, EF 29±10%, NYHA class 2.8±0.4,), 41% with ischemic and 59% with non-ischemic cardiomyopathy. In all patients, mechanical dispersion decreased from baseline to 6 months after CRT (122±54ms vs. 79±33ms, p<0.001). VA was documented in 11 patients (20%). Mechanical dispersion at 6 months was higher in those patients with documented VA during 2 years follow up compared to those without VA (104±47 vs. 75±28ms, p=0.02) (Figure).

Conclusions: Mechanical dispersion at 6 months after CRT implantation was higher in patients who experienced VA during 2 years follow up than those without VA. Mechanical dispersion may reflect the mechanisms for VA in CRT patients and be important in the evaluation of CRT patients.



10468 Clinical and Experimental Aortic Stenosis; Attenuation of Activated Pro-Hypertrophic NFAT Transcription Factor Isoforms During Reverse Remodeling

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Aortic stenosis (AS) is a common valvular lesion causing hypertrophy and failure. Activation of nuclear factor of activated T-cell (NFAT) transcription factors by Ca2+-calcineurin is a central pro-hypertrophic pathway, yet it is unknown if all four NFATc1-c4 isoforms are activated. Moreover, it is uncertain whether NFAT signaling is reversible such as in aortic valve replacement (AVR) for AS. We investigated NFATc1-c4 activation and reversibility in clinical and experimental AS. Using antibodies validated for NFATc1-c4 specificity, myocardial NFATc activation was studied in biopsies sampled peroperatively from AS patients (n=34), and in experimental aortic banding

(AB)/debanding (DB), in wild-type (n=105) and NFATluciferase (n=51) mice. NFATc1-c4 proteins were substantially up-regulated in AS despite minor mRNA changes. Increased NFAT activation was confirmed by 1.5-/2.6-fold increase mRNA/protein of a direct target gene of NFATc, RCAN1-4, despite considerable phosphorylation (inactive NFAT). Positive correlations to RCAN1-4 suggested all isoforms to contribute to NFAT activation. Increased protein levels of Ca2+-regulatory channels (LTCC 4.8-fold, TTCC 6.5-fold, RyR2 6.8-fold, NCX1 2.1-fold, PMCA 2.8-fold, PLN 1.4-fold and serca2 2.1-fold) indicated elevated Ca2+ to activate NFAT. In mice, AB for 24 hrs, 1-3 weeks (hypertrophy) and 16-18 weeks (end-stage failure) increased RCAN1-4 mRNA/protein 2-12-fold. 1week of DB after 1week of AB reduced hypertrophy (ventricular weight, wall thickness) and failure (lung weight, atrial diameter), normalized body weight and improved fractional shortening. Importantly, DB caused complete reversal of RCAN1-4 (8.4- to 0.9-fold) and reduced NFAT-luciferase activity (8.3- to 2.6-fold). In contrast to AS, in human end-stage failure, NFATc4 was dephosphorylated, and after left ventricular assist device (LVAD), RCAN1-4 protein was reversed in two out five patients, suggesting lower potential for reversibility.

Our data suggest that all four NFATc isoforms participate in the early human hypertrophic response. Attenuated NFAT signaling by relief of pressure overload in mice indicates reversal of NFAT activation in AS patients after AVR.

10920 Mechanical Dispersion by Strain Echocardiography is a Marker of Ventricular Arrhythmias in Lamin A/C Mutation Positive Subjects

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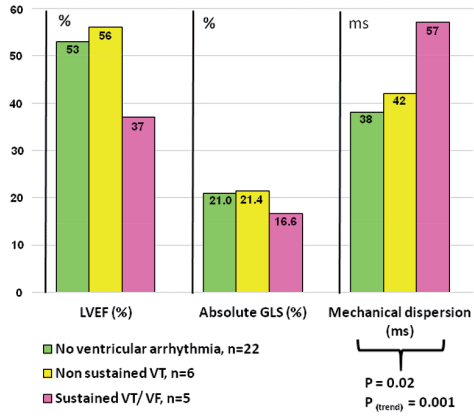
Background: Mutations in the Lamin A/C gene cause a malignant type of familial dilated cardiomyopathy (DCM) with increased risk of ventricular arrhythmia (VA) and sudden cardiac death even before development of DCM. Echocardiographic mechanical dispersion, reflecting contraction heterogeneity, has been shown to accurately predict VA in different cardiomyopathies. We explored if mechanical dispersion could predict VA in Lamin A/C mutation positive subjects.

Methods: We included 33 Lamin A/C mutation positive probands (39%) and family members (61%) (age 35±16 years, follow-up time 42 [31] months). VA was documented and defined as non-sustained ventricular tachycardia (VT), sustained VT or ventricular fibrillation (VF). By echocardiography, left ventricular (LV) function was assessed as ejection fraction (EF) and as global longitudinal strain (GLS) from 2D speckle tracking. GLS was calculated as average peak strain from 16 LV segments. Mechanical dispersion was defined as the standard deviation of time to peak strain from the 16 LV segments.

Results: Eleven (33%) subjects had documented VA (6 (18%) had non-sustained VT and 5 (15%) had sustained VT/VF). Mechanical dispersion was significantly increased in those with VA compared to those without (49±14 ms vs. 38±10 ms, p = 0.02). GLS and EF were not markers of VA (19.2±5.3% vs. 21.0±2.9%, p=0.22 and 47±15% vs 53±7%, p=0.14). There was a significant linear trend towards an increase of mechanical dispersion along with severity of VA (38ms, 42ms and 57 ms in subjects without VA, with non-sustained VT and sustained VT/VF respectively, p=0.001) (Figure).

Conclusion: Mechanical dispersion was a marker of VA in Lamin A/C mutation positive subjects. Heterogeneous contraction may reflect underlying myocardial arrhythmogenic changes. Assessment of mechanical dispersion may help prediction of VA in Lamin A/C mutation positive subjects independently of EF and GLS.

Ventricular arrhythmias´ relation to parameters of function in Lamin A/C mutation positive subjects



11032 Impact of Obesity on Grading of Aortic Stenosis (a SEAS Substudy)

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Background: We hypothesized that the disproportionate increase of body surface area (BSA) in obesity may lead to overestimation of aortic valve stenosis (AS) severity when the indexed valve area is used.

Methods: Baseline data from 1524 patients enrolled in the Simvastatin and Ezetimibe in Aortic Stenosis (SEAS) study were used to calculate aortic valve area (AVA) and pressure recovery adjusted AVA (energy loss [EL]) and their indexed values (AVAI and ELI). Obesity was defined as body mass index (BMI) ≥30 kg/m 2.

Results: Peak aortic jet velocity, mean aortic gradient, AVA and EL did not differ between obese (n=321) and non-obese (n=1203) patient groups. A total of 225 patients had non-severe AS by AVA (>1.0 cm 2), but severe AS by AVAI (<0.6 cm 2/m2) (AVAI/AVA inconsistency), and 144 patients had non-severe AS by EL (>1.0 cm 2), but severe by ELI (<0.6 cm 2/m2) (ELI/EL inconsistency). Compared to non-obese patients, more obese patients (23% vs. 13%) had AVAI/AVA inconsistency (p<0.01) (Fig.1). Adjustment for pressure recovery reduced the prevalence of inconsistency, but also ELI/EL inconsistency was more common in the obese group (13% vs. 9%, p<0.05). In univariate analyses, AVAI/AVA and ELI/EL inconsistencies were predominantly found in men and associated with larger body size, lower stroke volume, higher pressure recovery and hypertension (all p<0.05). In multivariate regression analyses, adjusting for these covariates, 1 unit higher BMI was associated with 10 % higher prevalence of AVAI/AVA inconsistency (95% CI 1.07-1.14, p<0.001) and 8 % higher prevalence of ELI/EL inconsistency (95% CI 1.04-1.12, p<0.001), respectively.

Conclusion: In obese patients with asymptomatic, mild to moderate AS, using AVA and EL indexed for BSA in grading of stenosis may lead to overestimation of AS severity.

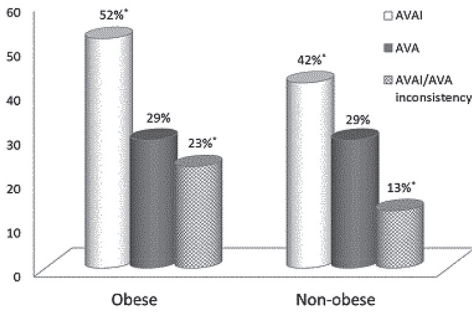

*Figure 1:Prevalence of severe AS in obese versus non-obese patients graded by AVA and AVAI (*p<0.01)*

13208 Seasonal Discrepancy in the Correlation between Vitamin D and Omega-3 Index in Patients With Acute Coronary Syndrome from Western Norway

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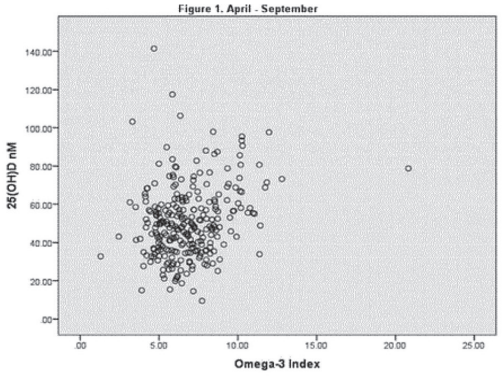
Background: Several studies have demonstrated an inverse relationship between cardiovascular risk and levels of vitamin D and omega-3 index.

Objectives: To assess the seasonal correlation between vitamin D measured as 25-hydroxyvitamin D [25(OH)D] and the omega-3 index (eicosapentaenoic acid + docosahexaenoic acid) in packed red blood cells in patients with acute coronary syndrome (ACS) recruited from western Norway.

Methods: Blood samples for 25(OH)D and omega-3 index analyses were harvested on admission in 457 patients with ACS defined by a troponin T (TnT) value ≥ 0.01 ng/ml. Seasonal (summer: April - September and winter: October - March) correlations between 25(OH)D and omega-3 index were evaluated.

Results: There were statistically significant seasonal differences between mean(SD) 25(OH)D levels: 54.7(19.3) nM from October through March (n = 190) and 50.8(18.9) nM from April through September (n = 267); p = 0.032. Corresponding levels of the omega-3 index were 6.6(2.0) % and 6.8(2.1) %, respectively; p = 0.27. There was a positive correlation between 25(OH)D and the omega-3 index during both seasons; Spearman's rank correlation coefficients were 0.244, p < 0.0001 for April - September (figure 1) and 0.366, p < 0.0001 for October - March (figure 2).

Conclusion: Significantly higher vitamin D levels and a stronger correlation between vitamin D and the omega-3 index were noted during the winter season, despite no seasonal difference in the omega-3 index. This may reflect a sea-



sonal variations in the content of vitamin D in fish products and/or more effective vitamin D absorption during the winter season

11048 Downregulation of HCN4 and the Pacemaker Current (*If*) Underlies Exercise Training-Induced Sinus Bradycardia

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Background: Sinus bradycardia, the most common arrhythmia in endurance athletes, is usually attributed to heightened vagus nerve activity. This may become maladaptive; endurance athletes have a higher incidence of sick sinus syndrome and pacemaker implantation. Here we tested an alternative hypothesis that electrophysiological remodelling of the key pacemaking ion channel, HCN4, and the corresponding pacemaker current (*If*) underlies endurance training-induced resting bradycardia.

Methods and results: Trained mice (TM; 60 min swimming twice daily for 28 days) were compared to sedentary mice (SM). TM were bradycardic (cycle length *in vivo*: SM, 81±1.3 ms; TM, 102±3 ms; n=6, $p<0.05$). The cycle length of the isolated, denervated sinus node (intrinsic heart rate) was also prolonged by exercise training (SM, 110±3 ms; TM, 150±5 ms; n=7, $p<0.05$). Block of *If* by 2 mM Cs+ increased the cycle length of the isolated sinus node (SAN) by 28±3% in SM, but only by 5±2% in TM ($p<0.05$), suggesting that *If* is downregulated by training. Patch clamp recordings showed a 47% reduction in *If* density in isolated sinus node cells from trained mice (n=17-18 cells/5 mice, $p<0.05$). qPCR showed a 60% reduction in the level of HCN4 mRNA in the SAN from TM compared to SM (n=6, $p<0.05$) and quantitative immunohistochemistry showed a 32% reduction in the protein level of HCN4 (n=4, $p<0.05$). microRNA-1 levels were increased and Tbx3 mRNA was decreased in the TM compared to SM (n=6, $p<0.05$), both of which are known transcriptional regulators of HCN4. Detraining for two weeks reversed the *in vivo* and *intrinsic* cycle length differences between groups, restored the response to block of *If* and reversed changes in HCN4, microRNA-1 and Tbx3 expression, although there was a rebound beyond the pre-training level in all cases.

Conclusions: Electrophysiological remodelling of the SAN, rather than increased vagal tone, is the primary mechanism underlying exercise training-induced bradycardia. The effects may be mediated via HCN4 transcriptional regulators, microRNA-1 and Tbx3.This is a new concept in the understanding of the heart rate adaptation to exercise and may offer insight into the early pathophysiology of sinus node disease in some athletes.

12339 Global Longitudinal Strain as a Risk Marker of Ventricular Arrthythmias in Candidates for Cardiac Resynchronization Therapy

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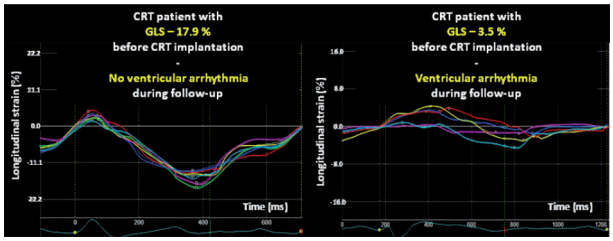

Ravinea Manotheepan, Tore Kristian Danielsen, Mani Sadredini, Oslo Univ Hosp and Univ of Oslo, Oslo, Norway; Stephen Lehnart, Heart Res Ctr Göttingen, Dept. of Cardiology & Pulmonology, Göttingen, Germany, Göttingen, Germany; Ivar Sjaastad, Mathis Korseberg Stokke, Oslo Univ Hosp and Univ of Oslo, Oslo, Norway

Background: Preimplant predictors of ventricular arrhythmia (VA) in cardiac resynchronization therapy (CRT) candidates are not fully explored. Echocardiographic strain is a sensitive method for quantification of myocardial function and has been shown to be a predictor of VA in cardiomyopathies. We aimed to explore the impact of left ventricular (LV) function, assessed by speckle tracking strain echocardiography, on VA in heart failure patients treated with CRT.

Methods: We investigated heart failure patients eligible for CRT with LV ejection fraction (EF) < 35%, QRS > 120 ms and NYHA functional class 2-4. Echocardiography was performed before and 6 months after CRT implantation. Myocardial function was assessed as EF by Simpson biplane method and global longitudinal strain (GLS) using 2D speckle tracking technique. VA was defined as non-sustained or sustained ventricular tachycardia / fibrillation during 2 years follow up from CRT implantation.

Results: We included 73 patients (age 64±10 years, NYHA class 2.8±0.4, EF 28±9%), 44% had ischemic and 56% had non-ischemic cardiomyopathy. VA occurred in 19 patients (26%) during 24 [11-24] months of follow up. LV function by GLS was lower in patients with VA compared to those without VA during follow-up, both before (-6.5±3.9% vs. -8.8±3.6%, p=0.03) (Figure) and 6 months after CRT implantation (5.9±5.8% vs. 9.7±4.7%, p=0.01). EF was not a marker of VA, neither before (26±10% vs. 29±9%, p=0.26) nor 6 months after CRT implantation (36±8 vs. 41±12%, p=0.18).

Conclusion: Myocardial function by GLS before CRT implantation was a marker of subsequent VA in CRT candidates, while EF was not. We suggest that GLS may be used in addition to EF as a tool for risk prediction of VA in CRT candidates.

12612 Exercise Training Reduces Ca2+-Calmodulin-dependent Protein Kinase Type II Dependent Phosphorylation of the Cardiac Ryanodine Receptor and Ca2+ Leak From the Sarcoplasmic Reticulum in Mice With Mutant Cardiac Ryanodine Receptor 2<

Introduction: Catecholaminergic Polymorphic Ventricular Tachycardia caused by RyR2 mutations predisposes to stress-induced arrhythmias due to disrupted Ca2+ handling in ventricular cardiomyocytes. We tested the effect of exercise training (ET) on Ca2+ handling in mice with a human RyR2 mutation (RyR-R2474S).

Methods and results: C57Bl6 mice were employed to test the efficacy of a two week ET protocol, comprising five eight-minute intervals at 80-90 % of the running speed at maximal oxygen uptake (VO2max, ml/kg/min), and two-minute active rest periods at 60 %. ET mice (C57Bl6-ET) increased VO2max by 7 % compared to baseline (152±2 vs. 142±2, P<0.05), while no change was found in sedentary mice (C57Bl6-SED) (139±1 vs. 140±1). Autophosphorylated CaMKII was reduced in C57Bl6-ET compared to C57Bl6-SED (52±9 vs. 100±8 %, P<0.05), as was CaMKII-dependent Ser2814-phosphorylated RyR2 (37±12 vs. 100±15 %, P<0.05). Thr17-phosphorylated phospholamban was unaltered (69±18 vs. 100±5). Contrary, C57Bl6-ET exhibited increased PKA-dependent Ser16-phosphorylated phospholamban (140±11 vs. 100±9 %, P<0.05) but no change in Ser2808-phosphorylated RyR2. ET RyR2-R2474S mice (RyR2-RS-ET) increased VO2max by 10±3 % compared to baseline (135±3 vs. 123±2, P<0.05), while VO2max in RyR2-RS-SED decreased by 5±2 % (124±2 vs. 131±3, P<0.05). RyR2-RS-ET compared to RyR2-RS SED showed decreased levels of Ser2814-phosphorylated RyR2 (38±3 vs. 100±13 %, P<0.05), but no alterations in Thr17-phosphorylated phospholamban. Contrary, RyR-RS-ET mice exhibited increased levels of Ser2808-phosphorylated RyR2 (150±14 vs. 100±16 %, P<0.05) and Ser16-phosphorylated phospholamban (167±25 vs. 100±14 %, P<0.05). Whole-cell Ca2+ imaging in ventricular cardiomyocytes showed decreased SR Ca2+ leak normalized to SR Ca2+ content in RyR2-RS-ET vs. SED (F/F0: 11±2 vs. 25±5, P<0.05).

Conclusion: Two weeks of high-intensity exercise training in C57Bl6-WT and RyR2-RS increased VO2max, decreased CaMKIIdependent phosphorylation of RyR2, and reduced SR Ca2+ leak. These effects of ET may decrease the propensity for arrhythmias in CPVT

12767 Syndecan-4 Regulates Myocardial Stiffness by Inducing Myofibroblast Differentiation, Extracellular Matrix Production and Collagen Cross-linking in Response to Pressure Overload

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Pressure overload of the heart leads to remodeling of the left ventricle (LV) involving excessive production of extracellular matrix (ECM) by activated cardiac fibroblasts that differentiate into contractile myofibroblasts. This compromises heart function by increasing myocardial stiffness. The molecular mechanisms underlying stress-induced myofibroblast differentiation and the role of this process in regulating cardiac stiffness are poorly defined. We recently identified the focal adhesion proteoglycan syndecan-4 as important for myofibroblast differentiation in response to mechanical stress. Here we investigate the effect of syndecan-4 deletion on the mechanical properties of the LV following pressure overload. Passive tension was reduced in muscle fiber bundles from LVs of syndecan-4-/- (syn4-/-) mice compared to wild-type (WT) mice and increased in both genotypes following aortic banding, albeit to a lower degree in syn4-/- mice. Salt extraction of myosin and actin filaments was performed to eliminate the effect of titin, a cardiac protein which is central in determining passive tension. This had no effect on passive tension following aortic banding, indicating that the reduced passive tension in syn4-/- mice was due to alterations in the extracellular matrix and not changes in titin. Consistent with this, quantification of ECM, fibroblasts and blood vessels by electron microscopy, revealed increased number of fibroblasts in LVs of WT mice and reduced amount of ECM in syn4-/- mice. Furthermore, total collagen content was only significantly increased in LVs of WT mice. Initial effects of 24 hrs aortic banding included a ~50-fold increase in mRNA levels of the collagen cross-linking enzyme lysyl oxidase (LOX) in WT LVs, whereas this response was significantly blunted (~25-fold increase) in syn4-/- mice. Supporting these findings, LOX activity was reduced in LVs of syn4-/- mice, indicating impaired cross-linking of collagen in syn4-/- mice.

In conclusion, we demonstrate reduced passive tension in LV tissue of syn4-/- mice likely due to inhibited differentiation of fibroblasts into myofibroblasts, reduced extracellular matrix production and attenuated collagen cross-linking.

12826 Geometric Factors Explain why Left Ventricular Ejection Fraction may be Preserved in Ventricles With Reduced Global Longitudinal Strain

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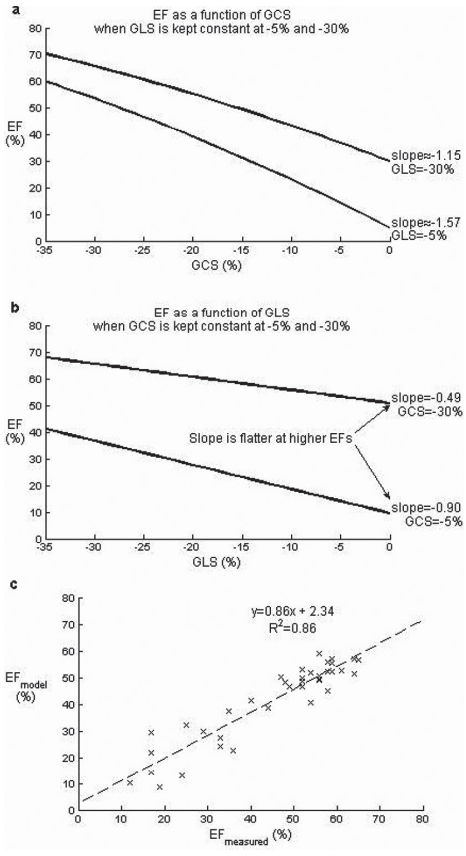
Aim: A significant reduction in left ventricular (LV) global longitudinal strain (GLS) without a significant reduction in ejection fraction (EF) is reported regularly. Our aim was to investigate if this apparent contradiction could be explained by geometric factors. We therefore derived the relation between EF and wall strains using a geometric model and compared the findings from this model with measurements from patients.

Methods: Based on an ellipsoidal LV model we derived the mathematical relation between EF, GLS, and global circumferential strain (GCS) as EF=(1-(1+GCS/100%)2*(1+GLS/100%))*100%. We measured EF, GLS, and GCS by echocardiography in 37 patients with verified or suspected cardiovascular disease. The geometric model was validated by comparing measured EF with predicted EF from the model using the measured GLS and GCS as inputs to the equation.

Results: EF was dominated by its quadratic dependency on GCS in the model: A change in GCS was amplified to a large change in EF as a result of the steep slope between them (Fig. a). In contrast a change in GLS resulted in a small change in EF due to the flat slope, particularly at high EF, of the weaker, linear relation between EF and GLS (Fig. b). In the patients mean EF was 45±16%, GLS was -14±6%, and GCS was -18±7% .The predicted EF from the model was in very good agreement with real measurements (Fig. c). Interestingly, there was a significant relation between EF and GLS in patients with EF<50% (R2=0.65, p<0.05), while this relation was not significant in patients with EF≥50% (R2=0.08, p=ns), consistent with the weaker relation between EF and GLS at higher EFs in the model.

Conclusions: EF reflects predominantly circumferential shortening, while longitudinal shortening has relatively small impact. This could explain the intuitively inconsistent finding that there may be a significant reduction of GLS with no significant change in EF and indicate that GLS may be a more sensitive marker of myocardial function than EF.



12990 Physical Activity, General and Abdominal Obesity and Mortality in European Men and Women

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Background: The higher risk of death due to excess adiposity may be attenuated by physical activity (PA). We examined the independent and combined associations between PA, body mass index (BMI), and waist circumference (WC) and all-cause mortality and estimated the population attributable fraction (PAF) and the years of life gained for these exposures.

Methods and Results: BMI and WC were measured among 334,161 European men and women. PA was assessed by a validated questionnaire and categorised into four groups. The combined associations between PA, general and abdominal obesity with mortality were examined with Cox proportional hazards models, adjusted for age, sex, education, smoking, and alcohol intake. Centre-specific PAF associated with inactivity, obesity (BMI>30) and abdominal obesity (>102 cm for men, >88cm for women) were calculated and combined in random-effects meta-analysis. Life-tables analyses were used to estimate gains in life expectancy for PA, BMI and WC. Across all centres, the mean follow-up time was 12.4 years, corresponding to 4,154,915 person-years. There were 11,086 deaths among men and 10,352 deaths among women. Compared to active and normal-weight (BMI 18,5 - 25) individuals, active and obese (BMI>30) individuals had a 48% greater hazard of mortality (HR 1.48, 95% CI,1.35-1.63), and normal-weight and inactive individuals had a 56% increased hazard (HR 1.56, 95% CI, 1.46-1.67). Abdominally obese participants, had a 75% higher hazard compared to the reference group (active, abdominally lean) following adjustment for confounders. Avoiding all inactivity would theoretically reduce mortality by 7.35% (95% CI, 5.88-8.83) and increase life expectancy by 0.70 years (95%CI, 0.56-0.84). Corresponding estimates for avoiding obesity (BMI>30) were 3.66% (95% CI, 2.30-5.01) and 0.34 years (95% CI, 0.21- 0.48).

Conclusions: The hypothetical number of premature deaths reduced by avoiding inactivity in European adults may be twice that of an approach that removed generalized obesity. These results suggest that public health programmes should prioritise reductions in inactivity and that even small shifts in activity levels could have major public health benefits.

13025 Modulation of the Sodium-calcium Exchanger 1 (NCX1) by Calpain; Molecular Interactions and Identification of a Calpain Cleavage Site

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Introduction: Chronic heart disease due to pressure overload, such as in hypertension and aortic stenosis (AS), is a major cause of morbidity and mortality. In response to pressure overload, altered Ca 2+ homeostasis is a key determinant of cardiac remodeling and contractility. Aberrant activation of calpain, a ubiquitous Ca 2+ dependent-protease can contribute to pathophysiology

associated with loss of Ca 2+ control in cardiomyocytes. Calpain cleaves NCX1 and modulates NCX1 exchange rate but underlying molecular mechanisms of NCX1 and calpain interaction remain to be determined. The effect of calpain on modulation of NCX1 was examined in this study.

Results: Investigation of NCX1 protein in left ventricular biopsies from AS patients and in the failing left ventricle of rats following aortic banding (AB) showed that both full-length NCX1 and a 75 kDa proteolytic NCX1 fragment were increased compared to control biopsies and sham-operated rats, respectively. We demonstrated that calpain-1 bound directly to two sites in cytoplasmic part of NCX1. By bioinformatics and mutation analysis we identified M369 as a putative calpain cleavage site residing within the α-catenin-like domain (CLD) in NCX1. Importantly, cleavage of NCX1 at M369 corresponded to a proteolytic fragment of 75 kDa. Competitive in vitro assay of calpain cleavage of NCX1 with a peptide containing M369 abolished the cleavage reaction. In order to investigate the functional role of calpain cleavage at M369 and the 75 kDa proteolytic NCX1 fragment, we mutated the identified site to a Tobacco Etch Virus (TEV) protease cleavage site. Co-transfection of NCX1(TEV) with the TEV protease resulted in specific cleavage of NCX1 at M369 in the membrane fraction.

Conclusion: We have identified a direct NCX1-calpain interaction, a calpain cleavage site at M369 in the α-catenin-like domain (CLD) in NCX1 and increased levels of full length NCX1 and the 75 kDa proteolytic NCX1 fragment in the pressure overloaded rat and AS biopsies. Our findings provide insight into a calpain-dependent mechanism that might be important for regulating Ca2+ homeostasis during heart failure progression.

13368 Angiotensin-Receptor Neprilysin-Inhibitor Reduces Adverse Cardiac Remodeling after Experimental Myocardial Infarction by Direct Effect on Cardiac Hypertrophy and Fibrosis

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Purpose: Dual-acting angiotensin-receptor neprilysin (NEP) inhibitors (ARNi), a novel drug class blocking both the angiotensin-II (AngII) receptor and breakdown of natriuretic peptides by NEP, may be of benefit in patients with hypertension and heart failure. Direct effects of ARNi on cardiac cells have not been previously evaluated.

Methods: Initially, to establish effects on cardiac remodeling, adult rats were subjected to myocardial infarction (MI) by surgical ligation of the left anterior descending coronary artery (LAD). MI-rats were randomized to treatment with the ARNi LCZ696 (68 mg/kg body weight administered PO; MI-ARNi, n=11) or vehicle (MI-Vhc, n=6), commencing one week post-MI, with cardiac structure and function assessed at 5 weeks post-MI. To assess direct effects of ARNi on cardiac cells, we quantified AngIIstimulated (100nM) cardiomyocyte (CM) hypertrophy and cardiac fibroblast (CF) collagen accumulation by 3[H]leucineincorporation over 60 h (CM) and 3[H]proline-incorporation over 48 h (CF), respectively. Cells were pretreated with increasing doses of valsartan (VAL) with or without NEP inhibitor LBQ657 (LBQ; 10μM).

Results: See table. MI-ARNi-treated rats had lower cardiac weights and improved cardiac structure and systolic function compared to MI-Vhc. In vitro, VAL showed robust dose-dependent inhibition on cardiac hypertrophy and fibrosis. Addition of LBQ further enhanced the inhibitory effects of VAL, and the highest combined VAL+LBQ dose completely abrogated AngIImediated effects.

Conclusions: ARNi attenuated post-MI cardiac remodeling, contributed to by direct anti-fibrotic and anti-hypertrophic actions that appear superior to VAL alone.

Cardiac effects of ARNi in vitro and in vivo

	Post-MI rats			
	Heart weight (mg)	LVEDD (mm)	LVSD (mm)	EF (%)
MI-Vhc	1319 ± 21	10.5 ± 0.3	8.4 ± 0.7	47 ± 5
MI-ARNi	1168 ± 35$^{\&}$	9.7 ± 0.2$^{\&}$	7.6 ± 0.2	60 ± 2$^{\&}$
	Cardiomyocytes			
VAL dose (μM)	0.0	0.03	0.1	1.0
VAL	128 ± 2****	116 ± 1$^{\#\#}$	111 ± 2$^{\#\#\#}$	109 ± 3$^{\#\#\#}$
VAL+ LBQ	109 ± 2$^{\#\#\#}$	107 ± 3$^{\#\#\#}$	110 ± 3$^{\#\#\#}$	98 ± 3$^{\#\#\#}$
	Cardiac fibroblasts			
VAL dose (μM)	0.0	0.03	0.1	1.0
VAL	211 ± 6****	164 ± 6$^{\#\#\#}$	144 ± 5$^{\#\#\#}$	113 ± 3$^{\#\#\#}$
VAL+ LBQ	170 ± 11$^{\#\#\#}$	123 ± 7$^{\#\#\#}$	115 ± 4$^{\#\#\#}$	101 ± 3$^{\#\#\#}$

MI-study: LVEDD and LVSD, LV enddiastolic and systolic diameter; EF, ejection fraction. $^{\&}$p<0.05 vs MI-Vhc.
In vitro data normalized to unstimulated control (=100%). ****p<0.0001 vs control, $^{\#\#\#}$p<0.001 vs stimulated control.
ARNi, angiotensin-receptor neprilysin inhibitor; VAL, Valsartan (angiotensin receptor blocker); LBQ, LBQ657 (neprilysin-inhibitor).

13397 The Impact of Sample Volume Placement on E/e' Measurements: Different Reference Thresholds

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Pulsed wave tissue Doppler imaging (TDI) has become an integral part of the echocardiographic assessment of diastolic left ventricular (LV) function. Used in combination with mitral inflow velocity (E) the ratio of E to annular velocity (e'), E/e', is a surrogate for LV filling pressure. We sought to define the difference between E/e' assessed at the septal or lateral mitral annulus and developed reference ranges for each.

Methods: We used the EchoNoRMAL database, which is an individual-person meta-analysis that includes population-based echocardiographic data from adults aged 18-80 free of cardiovascular disease and/or risk factors. This analysis is restricted to 2924 adults with both septal and lateral pulsed wave TDI. We compared the mean (standard deviation) E/e' for each location and determined predictors of E/e' using linear regression. Using a centile regression approach, we determined age appropriate upper reference values for each site (95th centile).

Results: Mean pulsed wave TDI-derived septal E/e' was higher than lateral E/e' in men: 7.7(2.1) vs 5.9(1.8)($p<0.001$); and women: 7.8(2.3) vs 6.1(1.9)($p<0.001$). E/e' septal was not significantly different between genders ($p=0.10$) however E/e' lateral was ($p=0.0003$). E/e' increased with age, and in gender-specific multivariable analyses, E/e' septal was associated with age but not heart rate or systolic blood pressure (SBP). E/e' lateral was associated with age and SBP. The 95th centile of E/e' in men at age 50 was 11.0 (septal) and 8.6 (lateral), and in women 11.4 (septal) and 9.2 (lateral).

Conclusion: This study has documented the significant difference in E/e' derived from the septum and lateral walls, and small but significant differences were observed between genders at both sites. The upper reference value varied by gender and sample volume location. These differences have implications for the clinical utility of E/e' measurements.

13592 M-Mode versus 2D Echocardiography-based Measurements of LV Dimensions: Different Reference Thresholds

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LV dimensions and wall thickness by M-Mode echocardiography (echo) appear to be larger than 2D based measurements. This has implications for determining upper limits of normal for measurements acquired by each technique.

Methods: The EchoNoRMAL database is an individual-person meta-analysis of population-based echo data from adults aged 18-80 years free of cardiovascular disease and/or risk factors. M-mode dimensions were available in 9805 individuals (23 studies), and 2D dimensions in 3582 individuals (7 studies). M-mode and 2D measurements were performed by leading-edge to leading-edge method from parasternal long (PSLAX) and short axis (PSSAX) views. Using a centile regression approach, we determined age-appropriate upper reference values for each method (95th centile).

Results: LV end-diastolic dimension (LVEDD, cm) was significantly larger by M-mode than 2D in European men (M-mode 5.2; 2D 5.0) and women (M-mode 4.7; 2D 4.5) in the PSLAX view ($p<0.0001$). LVEDD by M-mode was smaller than 2D measurement in the PSSAX view in women (M-mode 4.7, 2D 4.8, $p=0.014$). For both genders, LVEDD by 2D was significantly smaller in the PSLAX than in the PSSAX view (men: PSLAX 5.0, PSSAX 5.2; women: PSLAX 4.5, PSSAX 4.8, $p<0.0001$). Men had significantly larger LVEDD than women irrespective of the method and the view used ($p<0.0001$). In linear regression, age, heart rate, systolic blood pressure, gender and year of echo all had a significant association with LVEDD by either method. The 95th centile of LVEDD in men at age 50 was 6.0cm (M-mode) and 5.8cm (2D). For women at age 50, it was 5.5cm (M-mode) and 5.3cm(2D).

Conclusion: There are significant differences in age-adjusted LVEDD values based on gender, echo method (2D vs M-mode) and the view used for image acquisition. LVEDD by M-mode is larger than by 2D, and 2D measurement from the PSSAX (vs PSLAX) view results in larger LVEDD. These important differences have implications

for defining the upper limits of normal values for LV dimensions.

13787 Increased or Stable Chronotropic Index over 7 years Predict Reduced Risks of Allcause and Cardiovascular Mortality among Healthy Middle-aged Men

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Background The chronotropic index (CI), a measure of the ability to increase heart rate (HR) during exercise, is previously reported to predict morbidity and mortality. CI reflects the combined effects of age, resting HR and physical fitness. The predictive value of changes in CI over time has not been studied before, and we tested if change in CI over seven years influences risks of all-cause and cardiovascular (CV) mortality through 28 years.

Methods CI was calculated after symptom-limited ECG tests among 1420 healthy men at two separate examinations, in 1972- 75 and in 1979-82. All-cause and CV mortality were registered in a nationwide survey of all participants' hospital charts through 2008. CI was defined as measured heart rate reserve (the difference between maximal and resting HR) divided by agepredicted heart rate reserve. Changes in CI between baseline and follow-up were divided into quartiles. Relative risks of allcause and CV mortality were calculated by Cox proportional hazard regression adjusting for baseline values of physical fitness, age, systolic blood pressure, smoking status, total serum cholesterol and CI.

Results A total of 740 events of all-cause mortality and 310 events of CV mortality were registered. Incidence of all-cause mortality was lowest in the quartiles with stable or increased CRI (Q3 and Q4). Q3 had a 34% and 31% reduced risk of allcause and CV mortality respectively, compared to the group with greatest reduction in CI (Q1). The quartile with the greatest increase in CI (Q4) had a 32% and 36% reduced risk of all-cause and CV mortality respectively, compared with Q1 (See table).

Table: Relative risks of all-cause and cardiovascular mortality.

	Q1	Q2	Q3	Q4
N	355	355	355	355
ΔCRI (mean)	–0.16	–0.04	0.02	0.11
ΔCRI (range)	–0.60 to –0.08	–0.08 to –0.01	–0.01 to 0.05	0.05 to 0.44
Crude all-cause mortality	236 (66%)	177 (50%)	149 (42%)	178 (50%)
Age-adjusted				
All-cause mortality	1.00	0.74 (0.61 – 0.90)	0.62 (0.50 – 0.76)	0.67 (0.55 – 0.81)
CV mortality	1.00	0.72 (0.53 – 0.98)	0.64 (0.46 – 0.87)	0.62 (0.45 – 0.84)
Multiple-adjusted*				
All-cause mortality	1.00	0.78 (0.64 – 0.95)	0.66 (0.53 – 0.81)	0.68 (0.56 – 0.83)
CV mortality	1.00	0.73 (0.54 – 0.99)	0.69 (0.50 – 0.94)	0.64 (0.47 – 0.87)

*Adjusted for baseline values of physical fitness, age, systolic blood pressure, smoking status, total serum cholesterol and chronotropic index

Conclusion Our results indicate that a stable or increased CI reduces the long-term risks of all-cause and CV death. Given the ease with which the chronotropic index can be assessed during a clinical examination, its high predictive value-and since simple measures like physical training can modify this parameter-it should perhaps be more applied in preventive medicine.

14309 Left Atrial Volume and Function Indices: Trends With Age and Gender

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Left atrial (LA) volume is an established biomarker for underlying cardiovascular pathology and for adverse clinical outcomes. Combining LA functional parameters with LA volume has been shown to be a more powerful prognostic marker. However, there are conflicting data on the relationship with age and gender.

Methods: We used the EchoNoRMAL database, which is an individual-person meta-analysis that includes population-based echocardiographic data from 23301 adults aged 18-80 free of cardiovascular disease and/or risk factors. The effects of age and gender on LA volumes and functional parameters (LA ejection fraction (LAEF) and LA expansion index (LAEI)) was assessed using linear regression in the subset of 1089 subjects (49% women) with both minimum (LAVmin) and maximum (LAVmax) LA volumes.

Results: Mean age was 44 yrs (range 18-80yrs), mean (SD) LAVmax 42 ml (14) and LAVmin 18 ml (8). Both volumes were significantly larger in males (LAVmax: males 44 ml, females 40 ml; LAVmin: males 20 ml, females

17 ml, both p<0.0001) however LAVmax indexed to BSA was larger in females (25.3 v 23.9 ml/m2, p=0.01). There was no age associated difference in LAVmax, though LAVmin was larger with increased age (0.5 ml per 10 years). In the whole group, mean LAEF was 56% (12) and LAEI was 1.5 (0.7). There was a small yet significant decrease in LAEF with increased age (0.9% per 10 years), and in LAEI (0.06 per 10 years).

Conclusion: This study demonstrates the lack of any age related change in LAVmax in a large group of normal subjects; therefore changes in LA volume, when observed, should be regarded as consequent to underlying cardiovascular pathology. A gender-based difference in indexed and non-indexed LAVmax was observed. LA functional parameters decreased with age and may be more sensitive markers of age related changes in LV diastolic function than LA volume.

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14360 Ratiometric and Allometric Relations Between Left Atrial Dimension and Measures of Body Size: the EchoNoRMAL Collaboration

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Normalization for body size is an accepted method to compare cardiovascular parameters among subjects with differing body shape. As largely demonstrated for LV mass, normalization should take into account the geometric relations between measures of body size and the parameter to normalize, avoiding a ratiometric approach for measures that cannot be linearly related. Taking advantage of the EchoNoRMAL collaboration, we analysed the relations between maximal left atrial (LA) dimension (LAD) and measures of body size to generate gender-specific normal reference values.

Methods: The EchoNoRMAL database is an individual-person meta-analysis including population-based echocardiographic data from

18 to 80 yr olds (n=23301, 46±16 yrs) free of CV disease. This analysis is restricted to 6869 non-obese European subjects (3310 women) with m-mode LAD and anthropometric measures. We determined sex-specific limits for normalized LAD (LADi) using ratiometric or allometric approaches depending on geometric relationships with height, weight and body surface area (BSA).

Results: Men had slightly greater body mass index, height, and weight than women (all p<0.001). Thus LAD was greater in men (3.6±0.5 cm) than women (3.3±0.5 cm, p<0.001). For normalization, LAD was ratiometrically divided by height (being both linear measures), whereas sex-specific allometric signals (b) were generated for body weight and BSA based on the best-fitting power regression y=axb. As geometrically expected, the b for weight (a 3-dimensional variable) was close to the 0.33 (0.36 in women, 0.41 in men), and the b for BSA (a 2-dimensional variable) was approaching 0.5 (0.55 in women, 0.60 in men for BSA).

Conclusion: Sex-specific reference values of the three measures of LADi were derived (Table).

	Women		Men	
LAD/height	cm/m	2.5	cm/m	2.6
LAD/weight	$cm/kg^{0.36}$	0.9	$cm/kg^{0.41}$	0.8
LAD/BSA	$cm/m^{2\times0.55}$	3.1	$cm/m^{2\times0.60}$	3.0

Table: sex-specific 95th centile of the three measures of LAD index.

14408 Lack of Collagen Type 8 in Pressure Overload Causes Left Ventricular Dilatation and Overt Heart Failure in Mice, Suggesting a Role in Transition to Heart Failure in Patients With Aortic Stenosis

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Background. Aortic stenosis causes left ventricular (LV) pressure overload resulting in LV remodeling. A key step in the transition from compensated hypertrophy to overt heart failure (HF) is LV dilatation. Collagen type 8 (col8) is a non-fibrillar collagen bridging extracellular matrix molecules and lack of col8 might therefore result in LV dilatation. Importantly, we have previously reported that pressure overload reduces col8, correlating to LV dilatation. Here we examined the role of col8 in LV dilatation and failure progression using col8 knock-out (KO) mice and aortic banding (AB) to induce pressure overload.

Methods. We induced pressure overload in wild type (WT) and KO mice. Echocardiography and lung weights were used to evaluate LV geometry and degree of HF. Collagen composition was analyzed by real-time PCR and hydroxyproline HPLC. The study was performed in a blinded manner. The gradient across AB was comparable in both groups of mice.

Results. In contrast to WT mice developing concentric hypertrophy, already 24h after AB there was a LV dilatation in KO mice (LVIDd=4.90±0.06mm) compared to WT (LVIDd=4.58±0.06mm, p<0.05) which was also present 16 weeks after AB (LVIDd=6.34±0.17mm in KO mice vs. LVIDd=5.80±0.09mm in WT mice, p<0.05). Furthermore, early mortality due to signs of pulmonary congestion was higher in KO mice (39.4%) than in WT (25.0%, p<0.05), where lung weight was 26.0% higher in KO mice compared to WT. At 48h, AB KO mice did not show any increase in mRNA expression of fibrillar collagens type 1 and 3 (col1/3) in contrast to an 193% increase of col1 and 168% increase of col3 mRNA in WT mice. After six weeks of AB, increases in col1 and col3 mRNA were significantly less pronounced in KO mice compared to WT (163% and 279%, 160% and 223%, for col1/3 respectively). In accordance with attenuated col1/3 mRNA expression 48h after AB, after six weeks of AB, total collagen was increased by only 84% in KO compared to 164% in WT mice.

Conclusion. Since lack of col8 caused reduced production of the main structural collagens 1 and 3, we suggest an important role for the non-fibrillar col8 in synthesis and regulation of fibrillar collagens and proper structure of the extracellular matrix in the heart, preventing LV dilatation and transition to HF in pressure overload.

14566 Combining High Sensitivity Troponin I and T Measurements Improves Prediction of Long-Term Clinical Outcomes in Patients With Atrial Fibrillation - An Aristotle Substudy

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Background Cardiac troponin levels predict clinical outcomes in patients with atrial fibrillation (AF). However, it is not known whether cardiac troponin I (cTnI) and cardiac troponin T (cTnT) provide complementary prognostic information. In this study we investigated if the combined use of cTnI and cTnT improves the prognostication in AF patients.

Methods: At randomization plasma cTnI and cTnT were analyzed in 14,806 AF patients in the ARISTOTLE trial using high sensitivity assays. Patients were grouped according to median levels of troponin: group 1 with both troponins lower than median, group 2 with low cTnI and high cTnT, group 3 high cTnI and low cTnT, and group 4 with both troponins above median. The associations between troponin concentrations and stroke or systemic embolism, cardiac death, and myocardial infarction were evaluated using Cox models.

Results: Both troponins were measurable in almost all subjects, 98.5% with cTnI (median 5.4 ng/L) and 99.4% with cTnT (median 10.9 ng/L). The correlation between the cTnI and cTnT was, however, moderate (Spearman 0.70). During median 1.9 years follow-up, patients with high values of both troponins had a significantly higher risk for all outcomes as compared to those with low levels of both cTnI and cTnT (Table). Importantly, patients having low levels according to only one troponin subtype but not the other presented a significantly higher risk with a hazard ratio (95% confidence intervals) up to 1.49 (1.04-2.12) for stroke/systemic embolism, HR 2.82 (1.97-4.05) for cardiac death, and HR 3.04 (1.65-5.62) for myocardial infarction.

Conclusions: Cardiac troponin I and T are detectable in almost all AF patients, although their correlation is moderate. The risk of stroke, cardiac death, and myocardial infarction is highest in patients with elevated levels of both troponins. Our findings show that different cardiac troponins provide complementary and additive information and may lead to improved risk stratification in AF.

Table. Clinical outcomes according to different levels of cardiac troponin I and T

Clinical Outcome	Combination of cTnI and cTnT level	n	Events (%/yr)	Hazard ratio* (95% CI)	p-value**
Stroke or systemic embolism	Both low	5819	102 (0.89)		<0.0001
	cTnI low, cTnT high	1651	41 (1.30)	1.44 (1.01-2.08)	
	cTnI high, cTnT low	1660	43 (1.32)	1.49 (1.04-2.12)	
	Both high	5676	209 (2.04)	2.26 (1.79-2.87)	
Cardiac death	Both low	5819	66 (0.56)		<0.0001
	cTnI low, cTnT high	1651	31 (0.96)	1.71 (1.11-2.61)	
	cTnI high, cTnT low	1660	53 (1.59)	2.82 (1.97-4.05)	
	Both high	5676	387 (3.67)	6.50 (5.01-8.44)	
Myocardial infarction	Both low	5819	22 (0.19)		<0.0001
	cTnI low, cTnT high	1651	14 (0.44)	2.32 (1.19-4.54)	
	cTnI high, cTnT low	1660	19 (0.58)	3.04 (1.65-5.62)	
	Both high	5676	94 (0.91)	4.77 (3.00-7.59)	

*'Both low' as reference **Effect of combination of cTnI and cTnT level

15183 Circulating MicroRNA-210 Levels Are Increased in Patients With Moderate to Severe Aortic Stenosis and Provide Independent Prognostic Information Regarding Mortality

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Background: Micro-RNA(miR)-210 production is increased by cellular hypoxia, and circulating miR-210 levels have been found inversely correlated to maximal oxygen uptake. As poor physical capacity is an established risk factor in patients with aortic stenosis (AS), we hypothesized that circulating miR-210 levels are increased in patients with AS and associated with a poor prognosis.

Methods: Circulating miR-210 levels were measured by RT-qPCR in 57 patients with moderate to severe AS and in 10 age and gender-matched healthy controls. MiR-210 levels were normalized to miR-425 levels, and RNA extraction was controlled by measuring the spike-in control cel-miR-39. Myocardial structure and function were characterized by echocardiography and the prognostic utility of miR-210 was compared to established risk indices.

Results: All patients and control subjects had miR-210 levels within the range of detection (Cp<35). The coefficient of variation (CV) for the samples run in triplet was 0.6% for both AS patients and the control subjects. CV for the spike-in control cel-miR-39 was 2.4% for AS patients and 2.2% for the control subjects. Circulating miR-210 levels were 2.0±0.2 [mean±SEM] fold increased in AS patients compared to controls

(p=0.002). The increase in circulating miR-210 levels in patients with AS was comparable to the increment in NT-proBNP levels: [AUC] 0.82 (95% CI 0.70-0.90) vs. 0.85 (0.75-0.93), respectively, p=0.71. Elevated circulating miR-210 levels were not significantly associated with clinical variables, echocardiographic indices, creatinine clearance, or NT-proBNP levels in regression analyses. During a median follow-up of 1287 days, 15 patients (26%) died. There was a significant association between higher circulating levels of miR-210 and increased mortality during follow-up: hazard ratio [supra- vs. inframedian levels] 3.3 (95% CI 1.1-10.5), p=0.039. Adjusting for other risk indices in multivariate analysis did not attenuate the prognostic merit of circulating miR-210 levels.

Conclusion: Circulating miR-210 levels are increased in patients with AS and higher levels are associated with poor prognosis. Our data suggest that miR-210 levels reflect additional pathology in AS than measured by conventional risk indices.

15376 Serum Neutrophil Gelatinase-Associated Lipocalcin is Independently Associated With Mortality in Acute Coronary Syndromes

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Aim: Neutrophil Gelatinase-Associated Lipocalcin (NGAL) is increased in the circulation of patients with cardiovascular (CV) disease, and has been linked to kidney function as well as matrix degradation and inflammation. We hypothesized that circulating NGAL could give prognostic information for patients with acute coronary syndrome (ACS) in addition to Global Registry of Acute Coronary Events (GRACE) score and other established markers. Methode: We assessed the associations between circulating NGAL, obtained within 24 hours of admission, and mortality, CV mortality, heart failure (HF), reinfarction, stroke and the combined endpoint CV mortality, HF or reinfarction in 1121 patients admitted with ACS.

Results: After adjustment for GRACE score, left ventricular ejection fraction (LVEF), Pro brain natriuretic peptide (BNP), and C-reactive protein (CRP), NGAL was associated with mortality (hazard ratio [HR] 1.41, p=0.02) and the combined endpoint (HR 1.45, p=0.006) during long-term follow-up (median 91 months). NGAL was also significantly associated with the short-term (3 months) and late long term (median 129 months) mortality after adjustment (short term HR 2.76, p=0.005, late long term HR 1.51, p<0.001).

Conclusion: NGAL is associated with both short and long term prognosis of patients with ACS independently of GRACE score, BNP, CRP and LVEF. NGAL could therefore potentially improve selection of patients needing closer follow up after admission to hospital for ACS.

15393 High Quality CPR With Optimized Rescuer-Dispatcher Teamwork

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Background: Calling the emergency phone number and starting CPR initiates the chain of survival for sudden cardiac arrest outside hospital. Traditional CPR courses teach to call for help and to perform CPR without dispatcher assistance. Traditional telephone-CPR (TCPR) is just-in-time training for rescuers with little or no CPR knowledge, but trained rescuers also perform better with T-CPR. Mobile phone speaker allows dispatcher to continuously coach the rescuer and guide CPR performance until the ambulance arrives. We hypothesized that optimizing rescuer-dispatcher teamwork by (A) implementing T-CPR in training and (B) using continuous dispatcher instructions during CPR would improve bystander CPR quality in a simulated scenario.

Method: Participants aged 22-69 were randomized to two different CPR courses and two different dispatcher instruction sets. The standard training (CPR anytime, Laerdal Medical) and the optimized training (Rescuer School, Laerdal Medical) were without and with T-CPR practice, respectively. The purpose of the standard instructions is to initiate compression-only while the optimized continuous instructions comprise more instructions, questions and encouragement to guide CPR performance. Participants performed 10 minutes of chest compressions-only on a CPR recording manikin, in a small confined kitchen. We compared the following groups:

(1) Standard training + standard dispatcher instructions (n=19)

(2) Optimized training + optimized continuous dispatcher instructions (n=24)

Results: Participants from group 2 delivered significantly more chest compressions (median 1043 vs. 859 compressions, p=0.001) and compressed more frequently to a compression rate between 90-120 min-1 (median 88% vs.

71% of compressions, p<0.014), compared to group 1. This also resulted in less time without compressions after CPR had started (median 6 s vs. 99 s, p<0.001). There was no difference in chest compression depth (mean 47 mm vs. 47 mm, p=0.90) or in demography, education and previous CPR training between the groups.

Conclusion: In our simulated scenario rescuers trained in T-CPR demonstrated better quality CPR with continuous dispatcher instructions compared to those with standard training and standard instructions.

15398 Myocardial Function is Reduced in Patients With Long QT Syndrome Type 2 Compared to Type 1

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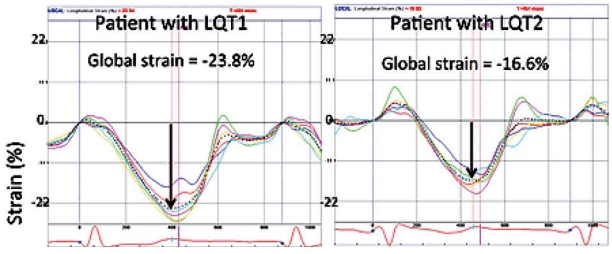
Introduction: Long QT syndrome (LQTS) is an inherited cardiac ion channelopathy predisposing to ventricular arrhythmias. The most commonly affected ion channels are IKs (KCNQ1-gene/LQT1) and IKr (KCNH2-gene/LQT2). Recent reports have indicated presence of subtle myocardial contraction abnormalities in LQTS patients by myocardial strain. We wanted to explore if myocardial function assessed by strain echocardiography shows genotype specific differences in LQT1 and LQT2 patients.

Methods: We included 153 mutation positive LQT1 and LQT2 subjects in addition to 26 age and sex matched healthy individuals. Exclusion criterion was cardiac disease of other origin. We performed echocardiography, including left ventricular (LV) ejection fraction (EF) and LV speckle tracking strain. LV global longitudinal strain was calculated as the average of maximal longitudinal shortening from 16 LV segments. QTc was measured from 12 lead ECG. LQTS symptoms were defined as cardiac syncope, documented ventricular arrhythmia or aborted cardiac arrest.

Results: Of the 153 LQTS subjects, 107 had LQT1 (mean age 37±15 yrs, 64% female, QTc 461±31 ms) and 46 had LQT2 (mean age 36±19 yrs, 54% female, QTc 463±30 ms). LQT2 subjects were more frequently symptomatic (21/46 (46%) vs. 30/107 (28%) p=0.03). Myocardial function by global strain was lower in individuals with LQT2 compared to LQT1 (-20.8±1.9%, vs. - 21.7±2.1%, p=0,02) and lower compared to healthy individuals (-22.6±2.0%, p<0.01), while EF did not differ between LQT2, LQT1 and healthy (61±7% vs. 61±5% vs. 63±6%, p=0.08).

Conclusions: Myocardial function by LV global strain was subclinically lower in LQT2 subjects compared to both LQT1 mutation positive and healthy individuals. This result supports that mechanical alterations are present in LQTS, and are most pronounced in LQT2. Moreover, genotype specific differences may indicate that there is a link between specific ion channel dysfunction and mechanical alterations.



15516 Secretoneurin is a Novel Endogenous CaMKIId Inhibitor That Regulates Cardiomyocyte Calcium Handling and is Closely Associated With Mortality in Patients With Acute Heart Failure

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Aims: To explore secretoneurin (SN), a functional fragment of secretogranin II that is increased in heart failure (HF), as a HF biomarker and possible regulator of cardiomyocyte Ca 2+ homeostasis.

Methods and Results: SN was identified in the circulation of HF patients by liquid chromatography-mass spectrometry. Measuring SN levels on admission for acute HF in 143 patients, SN provided strong and independent information regarding mortality (n=66) during follow-up (median 776 days): hazard ratio [logSN] 4.27 (95% CI 1.83-9.94), p=0.001 in multivariate analysis. SN also reclassified patients to their correct risk strata on top of other

predictors of mortality as assessed by the net reclassification index. We explored a role for SN in cardiomyocyte Ca 2+ handling in experimental models. First, we found SN to be internalized into cardiomyocytes by endocytosis and to reduce Ca 2+/calmodulin (CaM)-dependent protein kinase II δ (CaMKIIδ) activity via direct SN-CaM and SN-CaMKIIδ binding. SN also reduced CaMKIIδ-dependent phosphorylation of the ryanodine receptor, attenuated sarcoplasmic reticulum (SR) Ca 2+ leak, and increased the magnitude and kinetics of cardiomyocyte Ca2+ transients and contractions via augmented SR Ca 2+ content. Furthermore, SN reduced L-type Ca 2+ current (ICaL), and the occurrence of arrhytmogenic Ca 2+ waves.

Conclusions: We have identified SN as a novel, endogenous CaMKIIδ inhibitor that improves Ca 2+ handling in cardiomyocyte. Since circulating SN levels are closely associated with mortality in HF patients, we believe SN production may be a compensatory mechanism that counteracts HF-induced alterations in cardiomyocyte Ca 2+ handling in the most severely ill HF patients.

15613 Re-Analysis of Landmark Statin Trials in Heart Failure Patients Using Competing Risks Methods

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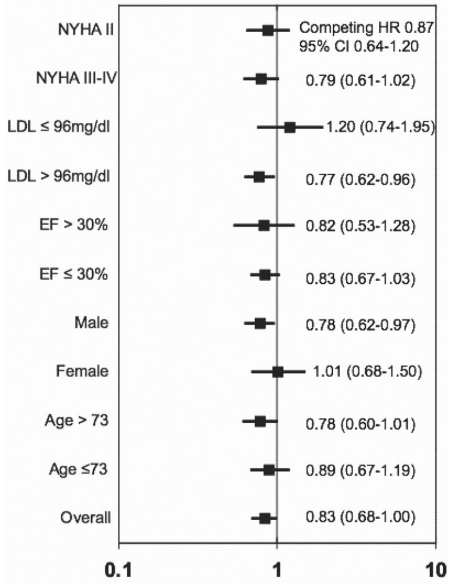
Introduction: To date, no large randomized trials of heart failure (HF) patients have demonstrated significant reductions in atherothrombotic cardiovascular (CV) events with statin use. Substantial competing risks from other causes of death among HF patients may prevent traditional survival analyses from detecting a benefit for statins.

Methods: We used the competing risks approach of Fine and Gray - which examines joint and simultaneous risks for diverse first events - to determine competing risks for fatal/non-fatal myocardial infarction (MI), fatal/non-fatal stroke, other CV death, and non-CV death. We pooled data for an individual-level meta-analysis of CORONA and GISSI-HF, two trials of HF patients randomized to rosuvastatin 10 mg daily vs placebo.

Results: CORONA (5011 patients, median follow-up 32.8 months) included patients age 60 or older with ischemic systolic HF whereas GISSI-HF (4574 patients, median follow-up 46.9 months) included patients over age 18 with HF of any etiology. CORONA participants were older than GISSI-HF participants and more likely to have advanced HF (NYHA class III or IV), prior MI and prior stroke. After accounting for competing risks, rosuvastatin decreased risk of MI among CORONA and GISSI-HF participants with ischemic HF (HR 0.81, 95% CI 0.66-0.99); this was borderline significant when GISSI-HF participants with non-ischemic etiologies of HF were included (HR 0.83, 95% CI 0.68-1.00). Among risk subgroups from CORONA and GISSIHF, rosuvastatin reduced risk for MI particularly for men and participants with elevated LDL cholesterol (Figure). There were no significant differences between rosuvastatin and placebo in risks for stroke or death from other causes.

Conclusions: Rosuvastatin appears to decrease MI risk among patients with ischemic causes of heart failure, particularly men and those with elevated LDL cholesterol. Competing risks analyses may be useful in examining cohorts with substantial comorbidities.

Figure. Hazard Ratios of Competing Risks for MI for Rosuvastatin Compared with Placebo among Risk Subgroups of Pooled CORONA and GISSI-HF Participants



15734 Coronary Artery Occlusion in N-STEMI Patients Can Be Identified by Assessing Segmental Work Which Incorporates the Effects of Afterload on Strain Measurements

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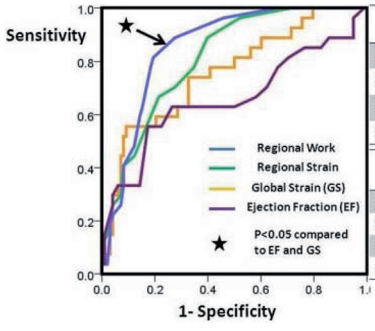
Introduction: Acute coronary artery occlusion (CAO) occurs in ≈ 30% of patients with N-STEMI. It has been shown that reduced regional segmental peak systolic strain (SPSS), measured by speckle tracking echocardiography (STE), identifies patients in need of immediate coronary intervention. The specificity was however low. We investigated if non-invasive segmental myocardial work (SeW) analysis, which adjusts strain for variations in afterload, could detect CAO.

Methods: STE was performed before coronary angiography in 126 patients with N-STEMI. Longitudinal strain was measured for each of the 18 LV-segments. LV pressure (LVP) was estimated non-invasively using a standard waveform fitted to valvular events and scaled to systolic pressure. SeW was calculated as the area of the LVP-strain loop. Empirical cut-off values were set to identify systolic dysfunction for SeW (<1700%▪mmHg) and SPSS (>-14%), and the number of segments were used in ROC analysis (Figure, left).

Results: 27 patients suffered an acute CAO. 4 or more adjacent segments with reduced SeW was significantly better than both global strain and ejection fraction at detecting the occurrence of CAO (Figure). SeW had a higher sensitivity and especially specificity compared to the equivalent region of impaired regional strain (Figure, lower right). Logistic regression analyses demonstrated that systolic blood pressure and SPSS were both independent significant covariates in estimating the occurrence of CAO. This was not true when SeW was substituted for SPSS.



	Area Under the Curve	CI (95%)
Regional Work	0.86	(0.79-0.93)
Regional Strain	0.81	(0.79-0.93)
Global Strain	0.76	(0.65-0.86)
Ejection Fraction	0.66	(0.52-0.80)

	Regional Work	Regional Strain
Sensitivity	81 %	78 %
Specificity	81 %	65 %
PPV	54 %	38 %
NPV	94 %	91 %

Conclusion: The presence of reduced regional work in patients with N-STEMI identified patients with coronary artery occlusion. This method was superior to regional and global strain parameters. Non-invasive regional work adjusted for the influence of blood pressure and is feasible as a bedside method. It has the potential of becoming an important clinical tool for selecting NSTEMI patients in need of immediate invasive treatment.

15755 Effects of Epinephrine on Rhythm Transitions in Out-of-Hospital Cardiac Arrest

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Objectives: To study effects of intravenous epinephrine on rhythm transitions during cardiac arrest with initial or secondary ventricular fibrillation/tachycardia (VF/VT).

Methods: Post hoc analysis of patients included in a randomized controlled trial of intravenous drugs in adult, non-traumatic out-of-hospital cardiac arrest patients who were defibrillated and had a readable ECG recording. Patients who received epinephrine were compared to patients who did not. Cardiac rhythms were annotated manually using the defibrillator data. Continuous data are reported as median (interquartile range) and compared with Mann-Whitney U tests. Proportions are compared with Chisquare tests.

Results: Out of 849 patients included in the randomized trial 223 were included in this analysis; 119 in the epinephrine group and 104 in the no-epinephrine group. CPR quality was similar in the two groups. The proportion of patients with one or more VF/VT episodes after ROSC was significantly (p=0.03) higher in the epinephrine (24%) group compared to the no-epinephrine (12%) group. Most relapses from ROSC to VF/VT in the no-epinephrine group occurred during the first 20 minutes of resuscitation, whereas patients in the epinephrine group continued to experience such relapses even after 20 minutes. Fibrillations from asystole or PEA was also more common in the epinephrine group, 90% versus 69%, p<0.001. Shock resistant VF occurred in 46% of patients who received epinephrine vs. 33% in those who did not, p=0.06. The number of rhythm transitions per

patient was higher in the epinephrine compared to the no-epinephrine group, median 8 (5,13) and 2 (1,5) respectively, p<0.001.

Conclusion: Patients who received epinephrine had more rhythm transitions from ROSC and non-shockable rhythms to VF.

15913 Characteristics of Acute Aortic Dissection in Patients With Bicuspid Aortic Valve: Insights From the IRAD Registry

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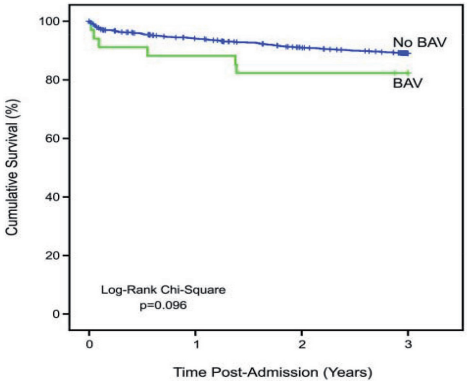
Background: Bicuspid aortic valve (BAV) is a congenital condition that predisposes patients to ascending aortic aneurysm and dissection. This study aims to characterize patients with acute aortic dissection (AAD) and BAV to improve our understanding of this aortic malformation.

Methods: We examined 3393 AAD patients enrolled in the International Registry of Acute Aortic Dissection. Demographic, morphological, and clinical characteristics as well as management type and outcomes were stratified by the presence or absence of BAV.



Results: Among 113 patients with BAV (3.3%), 93 (82.3%) presented with type A AAD while 20 (17.7%) had type B AAD. Compared to the non-BAV population, patients with BAV were younger (mean age: 53.6 ± 16.3 v. 63.5 ± 13.5 years; p<0.001), and more frequently presented at age<40 years (22.1% v. 4.9%;p<0.001). BAV patient histories revealed more known aortic aneurysms (25.5% v. 13.1%;p<.0001) and prior aortic valve replacement (14.7% v. 3.1%; p<0.001). Compared to the non-BAV population, AAD in BAV patients more frequently involved the aortic root (46.2% v. 34.7%; p=0.016) and/or arch vessels (41.6% v. 28.6%; p=0.014). Furthermore, these patients demonstrated less extension to the abdominal aorta (28.6% v. 44.6%, p=0.002). In addition, BAV subjects were more likely to present with larger a aortic dimension (Sinuses of Valsalva: 5.0 v.3.9 cm, p<0.001; ascending:5.3 v. 4.5 cm, p<0.001), and aortic valve insufficiency (52.1% v. 39.3%; p=0.013). Consequently, BAV patients more frequently underwent aortic valve (56.8% v. 21.7%; p<0.001) and/or root (66.7% v. 28.4%; p<0.001) replacement. Despite their younger age, BAV patients did not show superior 3-year post-admission survival rates (82.4% v. 89.1%; p=0.096)

Conclusions: AAD in patients with BAV presents with distinct morphological and clinical characteristics. These findings may expand our understanding of this congenital aortic malformation and improve therapeutic management.

16639 Sex Differences in Progression of Aortic Stenosis and Cardiovascular Outcome. A SEAS Substudy

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Background: Women with aortic stenosis (AS) have better left ventricular (LV) systolic function than men, as well as more concentric LV geometry in advanced disease stages. Sex differences in LV adaptation and prognosis during progression of AS have been less explored.

Methods: Doppler echocardiography and cardiovascular events were recorded during a median follow-up of 4.3 years in 979 men and 632 women aged 28-86 (mean 67±10) years

participating in the Simvastatin Ezetimibe in Aortic Stenosis (SEAS) study. LV geometry was assessed by LV mass/height2.7 and relative wall thickness, thus categorizing patients with normal LV mass/height2.7 as having normal geometry or concentric remodeling, and patients with LV hypertrophy as having eccentric or concentric hypertrophy. Study outcomes were AS-related events and ischemic cardiovascular events, as well as total mortality.

Results: Women and men had similar progression of AS (annual reduction in aortic valve area index of 0.02cm^2/m^2) during follow-up. Prevalence of LV hypertrophy increased comparably in women and men, remaining considerably higher in men throughout the study, while prevalence of concentric remodeling increased more in women: 11% at baseline vs. 29% at the last visit (both p <0.001). Compared to women, more men developed low LV ejection fraction (<50%) and low midwall shortening (<14.2%) during follow-up (both p <0.05). In multivariate Cox analyses, male gender predicted 46% higher risk of ischemic cardiovascular events, in particular more stroke and coronary artery bypass grafting, as well as 43% higher risk of death, independent of AS severity, low LV function and LV geometry (Table). AS-related events did not differ between genders.

Conclusions: Men and women have a similar rate of AS progression. Men have higher prevalence of LV hypertrophy and systolic dysfunction at all stages of AS and experience more often ischemic cardiovascular events and death.

Table. Prediction of ischemic cardiovascular events or death by male gender in multivariate Cox analyses including active study treatment, age, hypertension, moderate/severe aortic valve calcification, aortic valve area index, low ejection fraction and midwall shortening, and presence of a baseline abnormal LV geometric pattern among covariates.

Outcome	Male gender, HR [95% CI]	p
Ischemic events	1.46 [1.12-1.91]	0.006
-stroke	1.87 [1.03-3.39]	0.04
-coronary artery bypass grafting	1.77 [1.22-2.58]	0.003
Death	1.43 [1.00-2.06]	0.05

16715 Symptoms as Predictors of Outcome in Patients With Heart Failure in the Controlled Rosuvastatin Multinational Trial in Heart Failure (CORONA)

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Introduction Although fatigue and dyspnea are common in patients with heart failure (HF), few studies have looked at their relationship with prognosis. We examined the association between fatigue and dyspnea and outcomes CORONA.

Methods 5011 patients ≥60 years with symptomatic ischemic HF and LVEF ≤40% (≤35% in NYHA class II) were enrolled in CORONA. Fatigue and dyspnea "during the past few days" were measured at baseline using a five point scale for fatigue and a four point scale for dyspnea - all patients were required to have dyspnea at entry. Patients were grouped into 3 categories: fatigue score 0-1 (n=535), 2 (n=1,632) and 3-4 (n=1663); dyspnea score 1 (n=292), 2 (n=1695), and 3-4 (n=1843). We examined the association between fatigue and dyspnea and the composite outcome of cardiovascular (CV) death or HF hospitalization using Kaplan-Meier analysis and Cox proportional-hazard models in patients with a LVEF ≤35% (n=3830). Other outcomes examined included CV death, HF hospitalization and all-cause mortality. Median follow-up was 32.8 months

Results Higher fatigue and dyspnea were associated with higher rates of CV death or HF hospitalization (fatigue score 3-4 49% vs. 0-1 30%; dyspnea score 3-4 50% vs. 1 28%), and all cause mortality (fatigue score 3-4 37% vs. 0-1 24%; dyspnea score 3-4 37% vs.1 23%) (log rank p<0.0001 for all). After adjustment, higher dyspnea score was independently associated with a higher risk of the composite of CV death or HF hospitalization, its components and all-cause mortality (Table). Higher fatigue scores were associated with higher rates of HF hospitalization. (Table). These associations persisted despite adjustment for variables known to be associated with prognosis (see Table footnote), including NT-proBNP.

Table 1Multivariate analysis on symptoms

	Fatigue Adjusted*				Dyspnea Adjusted*			
	2 vs. 1		3 vs. 1		2 vs. 1		3 vs. 1	
	HR (95% CI**)	P value	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
CV death or HF hospitalization	1.13 (0.90, 1.42)	0.30	1.27 (1.00, 1.63)	0.05	1.12 (0.82, 1.52)	0.48	1.45 (1.04, 2.03)	0.03
CV death	1.05 (0.78, 1.40)	0.76	1.13 (0.83, 1.54)	0.45	1.30 (0.86, 1.97)	0.21	1.76 (1.13, 2.74)	0.01
HF hospitalization	1.29 (0.96, 1.73)	0.10	1.55 (1.13, 2.11)	0.01	1.20 (0.81, 1.79)	0.37	1.68 (1.10, 2.58)	0.02
All-cause death	1.10 (0.85, 1.43)	0.47	1.18 (0.90, 1.56)	0.23	1.37 (0.95, 1.96)	0.09	1.58 (1.07, 2.33)	0.02

*Adjusted for: Age, sex, New York Heart Association, left ventricular ejection fraction, body mass index kg/m^2, systolic blood pressure, heart rate, smoking, myocardial infarction, angina pectoris, coronary artery bypass graft, percutaneous coronary intervention, aortic aneurysm, hypertension, diabetes, baseline atrial fibrillation/flutter, stroke, intermittent claudication, pacemaker, imp. cardioverter defib, ApoA-1, ApoB, creatinine, alanine aminotransferase, creatinine kinase, triglycerides, C reactive protein, NT-proBNP.
** confidence interval

Discussion Higher dyspnea and fatigue scores are independent predictors of worse outcomes in HFrEF. Symptoms are not only a key treatment target in HF but also an important prognostic indicator.

16803 Gender Differences in the Impact of Arterial Stiffness on Outcome in Hypertensive Patient With Left Ventricular Hypertrophy (The Life Study)

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Background: Increased arterial stiffness is associated with abnormal left ventricular (LV) structure and diastolic function in hypertension, particularly in women. Increased arterial stiffness is also related to adverse outcome, but whether this prognostic impact differs between genders is unknown.

Methods: We used clinic, echocardiographic and outcome data from 360 women and 506 men with hypertension and electrocardiographic (ECG) signs of LV hypertrophy randomized to losartan or atenolol based antihypertensive treatment in the Losartan Intervention For Endpoint reduction in hypertension (LIFE) study. Arterial stiffness was estimated from the ratio of pulse pressure/Doppler stroke volume indexed for height to the power of 2.04 (PP/SVi). The association of in-treatment PP/SVi with outcome during 4.8 years follow-up was tested in time varying Cox regression models, adjusting for time-varying LV mass, and reported as hazard ratio (HR) and 95% confidence intervals (CI).

Results: At baseline, higher PP/SVi was associated with higher age, relative wall thickness and serum creatinine, having isolated systolic hypertension or diabetes, and with lower body weight, LV ejection fraction and cardiac output in both genders (all $p<0.05$). In men, higher PP/SVi was also associated with lower LV mass, and in women with previous myocardial infarction (both $p<0.05$). In time-varying Cox regression, higher in-treatment PP/SVi predicted a 29% higher rate of combined cardiovascular death, nonfatal stroke and myocardial infarction, the primary study endpoint (95% CI 1.02-1.63, p=0.035). In sexspecific models, higher in-treatment PP/SVi was associated with increased rates of stroke (HR 1.76 [95% CI 1.18-2.63]), hospitalization for heart failure (HR 1.87 [95% CI 1.28-2.73]), cardiovascular mortality (HR 2.15 [95% CI 1.11-4.17]) and total mortality (HR 1.72 [95% CI 1.14-2.59], all $p<0.05$) in women, and with increased rate of myocardial infarction (HR 1.68 [95% CI 1.14-2.48], $p<0.01$) in men.

Conclusion: In hypertensive patients with ECG LV hypertrophy, higher in-treatment PP/SVi was associated with increased cardiovascular morbidity and mortality, particularly in women. This relation was independent of LV mass.

17219 Vitamin D Supplementation Improves Endothelial Function In Type 2 Diabetes - A Randomized Controlled Trial

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Background: Cardiovascular disease is prevalent in type 2 diabetes, and both endothelial dysfunction and arterial stiffness may contribute in the pathogenesis. Studies indicate that low levels of vitamin D are associated with both type 2 diabetes and cardiovascular disease.

Aim: To evaluate the effect of vitamin D supplementation on endothelial function and arterial stiffness in subjects with type 2 diabetes in the DIVINE study. Methods: Sixty-two subjects with type 2 diabetes and hypovitaminosis D (serum 25-hydroxy-vitamin D [25(OH)D] <50 nmol/L) were included in this randomized controlled trial (NCT 00992797). Thirty-three patients were randomized to treatment and received vitamin D (400 000 IU cholecalciferol) at baseline with dose escalation to elevate serum levels to more than 100 nmol/L after 4 weeks, whereas 29 patients received placebo. Endothelial function and arterial stiffness were measured at baseline and after six months. Endothelial function was assessed as the reactive hyperaemia index (RHI) using endothelial pulse amplitude testing (Endo-PAT). Arterial stiffness was estimated as carotid-femoral pulse wave velocity (cfPWV) and augmentation index (AIx) with applanation tonometry (SphygmoCor). Serum 25(OH)D was measured using the DiaSorin-RIA.

Results: Mean (SD) age in the treatment and placebo group were 57.5 (9.4) and 57.8 (10.0) years, 51.5 % (n=17) and 44.8 % (n=13) were females, diabetes duration was 11.4 (6.5) and 7.5 (5.7) years. Treatment with vitamin D significantly improved RHI and increased the serum 25(OH)D levels, but did not change cfPWV and AIx (Table 1). In multivariable linear regression analysis, the change in RHI was significantly associated with change in serum 25(OH)D (β [CI] = 0.009 [0.001-0.017], P=0.03).

Table 1. Baseline values and change in endothelial function, arterial stiffness and vitamin D from baseline to 6 months.

	Baseline			Change		
	Treatment (*n=33*)	Control (*n=29*)	*P*	Treatment (*n=33*)	Control (*n=29*)	*P*
RHI	1.7 (0.4)	1.7 (0.5)	0.74	0.21 (0.49)	-0.03 (0.37)	0.04
cfPWV, m/s	10.18 (1.85)	9.84 (2.33)	0.54	-0.21 (0.92)	-0.10 (0.64)	0.56
AIx, %	20.0 (8.7)	20.0 (10.1)	0.98	0.8 (5.0)	3.5 (8.4)	0.54
25(OH)D, nmol/L	38.5 (9.1)	38.1 (8.5)	0.74	15.0 (11.0)	0.7 (16.0)	<0.001

Values are given as mean (SD). *P* represents the significance of between-group-comparisons for baseline values and changes after 6 months respectively.

Conclusion: Vitamin D supplementation improved endothelial function but not arterial stiffness in type 2 diabetes. Vitamin D might be a modifier of endothelial function in subjects with type 2 diabetes.

17341 The Matricellular Protein CCN2/CTGF Enhances Scar Healing After Myocardial Infarction and Inhibits TGFβ-Induced Myofibroblast Differentiation Limiting Myocardial Fibrosis

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Adequate scar healing is critical after myocardial infarction (MI). However, prolonged activity of myofibroblasts may cause excessive myocardial fibrosis leading to impaired cardiac function. We have previously shown that myocardial expression of CCN2 is substantially increased in ischemic heart failure. Yet, the role of CCN2 in healing of MI and in regulation of myocardial fibrosis is still poorly understood. Thus, the objective of this study is to investigate the role of CCN2 in infarct healing and myocardial fibrosis following MI. MI was induced by ligation of the left coronary artery in transgenic mice with cardiac-restricted overexpression of CCN2 (Tg-CCN2) and in non-transgenic control (NTC) mice. Fibroblasts were isolated from NTC mice and stimulated with or without recombinant (r) CCN2 (250 nmol/L) and/or TGFβ-1 (2.5 µg/ml) after first passage. Area of necrosis 24 hours after induction of MI was similar in Tg-CCN2 and NTC mice. Deposition of collagen in the infarct region was higher and increased more rapidly in Tg-CCN2 mice than in NTC mice (day 5 post-MI collagen content NTC 16.6 ± 0.8 vs Tg-CCN2 21.3 ± 0.4 µg/mg dry weight, p<0.01). Interestingly, this difference was reversed at 42 days post-MI, where infarct region collagen contents were lower in Tg-CCN2 mice versus NTC mice (114.3 ± 6.1 vs 88.9 ± 8.6 µg/mg dry weight, p < 0.05). The enhanced deposition in Tg-CCN2 mice reflected in a lower incidence of myocardial rupture in Tg-CCN2 vs NTC mice (2/41 vs 10/39, p = 0.01). Interestingly, rCCN2 reduced TGFβ-induced differentiation of fibroblasts reflected by reduced upregulation of α-smooth muscle actin. Impaired myofibroblast phenotype following exposure to rCCN2 also manifested in both reduced myofibroblast migration by 27±4% (p<0.05, n=4) and proliferation by 70±5% (p< 0.05, n=6). The mechanism of the reduced sensitivity of cardiac fibroblasts to TGFβ-induced myofibroblast transformation after prolonged exposure to rCCN2 (48h) was reduced TGFβ-stimulated phosphorylation of Smad2[Ser465/467] (59±2% reduction, p<0.001, n=3). In conclusion, we show that infarct healing is enhanced in Tg-CCN2 mice. Yet, CCN2 limits collagen deposition and myocardial fibrosis in ischemic heart failure by reducing the sensitivity of cardiac fibroblasts to TGFβ.

17353 Comparison of Medical Priority Dispatch (MPD) and Criteria Based Dispatch (CBD) when Processing Cardiac Arrest Calls

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Background: Prompt emergency medical service (EMS) system activation with rapid delivery of pre-hospital treatment is essential for patients suffering out-of-hospital cardiac arrest (OHCA). The two most commonly used dispatch tools are medical priority dispatch (MPD) and criteria based dispatch (CBD). We compared cardiac arrest call processing using these two dispatch tools in two different dispatch centres.

Methods: Observational study of adult EMS confirmed (non-EMS witnessed) OHCA calls during one year in Richmond US (MPD) and Oslo (CBD). Patients receiving CPR prior to call, interrupted calls or calls where the caller did not have access to the patients were excluded from analysis. Dispatch logs, ambulance records and digitalized dispatcher and caller voice recordings were analyzed and compared using a non-parametric Mann-Whitney U-test for continuous data and Fisher's Exact test for categorical data.

Results: The MPD-site processed 182 cardiac arrest calls and the CBD-site 232, of which 100

and 140 calls met the inclusion criteria, respectively. The recognition of cardiac arrest was not different in the MPD and CBD systems; 82% vs. 77% (p=0.42), and pre-EMS arrival CPR instructions were offered to 81% vs. 74% (p=0.22) of callers, respectively. Time to ambulance dispatch was median (95% confidence interval) 15 (13, 17) vs. 33 (29, 36) seconds (p<0.001) and time to chest compression delivery; 4.3 (3.7, 4.9) vs. 3.7 (3.0, 4.1) minutes for the MPDS and CBD systems, respectively (p=0.05).

Conclusion: Ambulance dispatch was swift in both systems but significantly faster in MPD. Although pre-arrival CPR instructions were frequently offered, chest compressions were delayed in both systems. Rapid recognition of cardiac arrest and improved instructions is needed to facilitate earlier lay rescuer CPR.

17504 Compensatory Alterations in Cardiomyocyte Ca2+ Homeostasis During Aortic Stenosis

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Concentric left ventricular hypertrophy is commonly associated with impaired myocardial relaxation, leading to reduced end diastolic volume and lower cardiac output. Indeed, diastolic dysfunction underlies approximately 50% of heart failure cases. Stiffening of the myocardium may be caused by active and/or passive mechanisms, which are respectively determined by Ca2+ homeostasis or properties of the cytoskeleton/extracellular matrix. In aortic stenosis patients with diastolic dysfunction we observed marked SERCA and NCX upregulation in ventricular biopsies, suggesting that cardiomyocyte Ca2+ homeostasis may be enhanced. To investigate this hypothesis, we examined the contribution of active and passive mechanisms to myocardial stiffness in a rat model of hypertrophy following aortic banding (AB). Experiments were performed six weeks after AB, and sham-operated animals served as controls. AB rats with detectable systolic heart failure were excluded. Hypertrophy and diastolic dysfunction in AB were confirmed in vivo by echocardiography, indicated by thickening of the posterior wall and reduced peak early diastolic tissue velocities. When stimulated to develop isometric force across a range of pacing frequencies (0.5 - 6 Hz), excised left ventricular muscle strips also exhibited slower relaxation kinetics in AB. Interestingly, isolated cardiomyocytes stimulated at the same frequencies exhibited opposite characteristics, as time to 50% relaxation was faster in AB (78±4% of SHAM at 1 Hz, P<0.05). Similarly, Ca2+ transients in single cardiomyocytes (whole-cell fluo-4 AM fluorescence) were faster to 50% decay in AB (63±2% of SHAM at 1 Hz, P<0.05). Consistent with enhanced Ca2+ removal, we measured significantly increased rates of both sarcoplasmic reticulum Ca2+ reuptake and sarcolemmal Ca2+ extrusion in AB, suggesting increased SERCA and NCX activity. In conclusion, there is a discrepancy between the phenotype of single cardiomyocytes and intact myocardial tissue in AB. We propose that enhanced Ca2+ homeostasis in aortic banding / aortic stenosis compensates for increased passive stiffness and that the primary determinants of diastolic dysfunction in this condition are alterations in the extracellular matrix or ventricular geometry.

17552 Variable T-Tubule Density and Calcium Homeostasis Across the Atria

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Although t-tubules have traditionally been thought to be absent in atrial cardiomyocytes, recent studies suggest that t-tubules exist in the atria of large mammals, albeit at lower density than in the ventricles. We postulated that cardiomyocyte function is regionally defined by variations in t-tubule density across the atria. This hypothesis was investigated by examining isolated cardiomyocytes and intact atrial tissue from rat and pig. In contrast to previous reports that t-tubules are absent in rat atria, we observed t-tubules in approximately one third of isolated rat atrial cardiomyocytes (di-8-ANEPPS staining). In a minority (≈10%) of atrial cardiomyocytes the t-tubular network was well organized, with a transverse structure resembling that of ventricular cardiomyocytes. Immunostaining showed the presence of L-type Ca 2+ channels in these t-tubules, and fast Fourier transforms revealed clear peaks indicative of transverse organization. Consistent with high between-cell variability in the distribution of ttubules and Ca2+ channels, L-type Ca 2+ current amplitude were also highly variable (SD = 1.33 in atrial vs. 0.84 in ventricular cells, P<0.05), and steeply dependent on capacitance and t-tubule density. Accordingly, confocal linescan images of Ca 2+ transients (field stimulation, Fluo-4AM) showed that Ca 2+ release synchrony varied greatly between atrial cells (SD of dyssynchrony index measurements = 3.48 in atrial vs. 1.36 in ventricular cells, P<0.05). Simultaneous imaging of the cell membrane and Ca2+ transients confirmed t-tubule functionality. In rat and pig atrial tissue cryosectioned and stained with dystrophin or wheat germ agglutinin, we observed higher t-tubule density in the epicardium than endo-

cardium (% cellular area occupied=1.51±0.06% vs. 1.08±0.06% for rat and 1.72±0.06% vs. 1.18±0.05% for pig, P<0.05). We propose that resulting transmural differences in Ca 2+ release kinetics may support synchronization of contraction across the atrial wall. We additionally observed regional differences in t-tubule density between right and left atria, and between main chamber and appendage, which may have consequences for arrhythmogenesis.

17606 Root Replacement versus More Conservative Management During Type A Acute Aortic Dissection Repair: Insights From the International Registry of Acute Aortic Dissection

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Background. How to surgically manage the aortic root in type A acute aortic dissection (TAAAD) is controversial. The aim of this study was to compare short- and mid-term outcomes of root replacement (RR) interventions vs. more conservative root management (CRM).

Methods. Out of the 1995 TAAAD enrolled in the International Registry of Acute Dissection (IRAD), 699 (35%) underwent RR management and 1296 (65%) underwent CRM. Primary endpoints for comparison were hospital mortality, 3-year survival and 3-year freedom from open aortic re-intervention. Independent predictors of hospital and 3-year survival were identified using multivariate logistic and Cox regression models. Statistical methods were used to control for treatment selection bias.

Results. As compared to CRM, RR patients were younger (56.9 vs. 62.3 years, p=0.023) and more likely to present with larger root diameter (4.7cm vs. 4.0cm, p<0.001), Marfan syndrome (8.7% vs. 2.5%, p<0.001), aortic insufficiency (64.0% vs. 50.3%, p<0.001) and hypotension/shock/tamponade (33.0%vs.26.5%; p=0.003). RR management did not increase hospital mortality (propensity-adjusted (PS) odds ratio:0.6, p=0.674). On Kaplan-Meier analysis, 3-years survival (RR: 92.5±1.7% vs. CRM: 91.6±1.3%, log-rank p=0.623) and freedom from re-intervention (RR: 93.1±2.7% vs. CRM: 92.5±2.1%, log-rank p=0.489) were similar for the two groups. PS adjusted Cox regression excluded any relationship existing between type of treatment and follow up survival (HR: 1.5; 95%CI: 0.502-5.010, p=0.432). Instead, Bblocker prescription at discharge was protective against 3-year mortality (HR: 0.4; 95%CI: 0.245-0.881; p=0.019).

Conclusions. Our observational data show that in TAAAD patients more extensive RR interventions are not associated with an increased risk of hospital mortality. Similarly favorable mid-term survival and freedom from re-intervention (>90%) of CRM and RR patients suggest a stable behavior of the non replaced aortic sinuses at 3 years. The use of aggressive RR techniques remain determined by specific dissection and non-dissection (young age, connective disease) related factors.

17817 Does a Repaired Type A Dissection Turn into a Medical Type B Dissection? Lessons From IRAD

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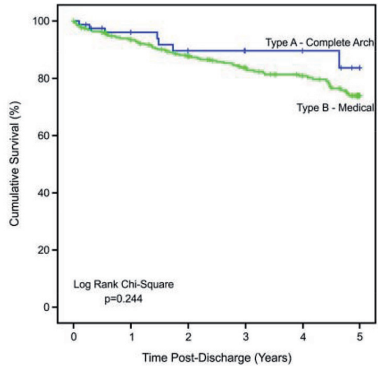
Background: Following complete arch replacement, many Type A acute aortic dissection (TAAAD) patients exhibit a residual false lumen in their descending and/or abdominal aorta. Medically-managed Type B (TBAAD) patients with descending thoracic involvement resemble these post-operative TAAAD cases. We sought to examine whether outcomes differed between

these two groups with anatomically-similar remaining dissection flaps.

Methods: We analyzed 1017 patients enrolled in the International Registry of Acute Aortic Dissection. Of these, 241 (23.7%) had TAAAD with complete arch replacement; 776 (76.3%) were medically-managed TBAAD patients with most proximal extension in the descending aorta.

Results: TAAAD patients were younger (58.0 ± 13.2 v. 64.9 ± 13.7 years, p<0.001) and more often male (80.1% v. 60.3%, p<0.001). Of the 418 (45.4%) with intimal tear identified, the tear was located in the descending aorta and therefore not resected in 4.1% of TAAAD patients, versus 39.9% of their TBAAD counterparts. Additionally, Type A patients had larger descending aortic diameters on presentation (5.0 ± 6.4 v. 4.8 ± 5.3 cm, p<0.001) but smaller abdominal aortic dimensions (2.4 ± 0.6 v. 3.0 ± 1.0 cm, p<0.001). In-hospital mortality was higher in the TAAAD cohort (24.9% v. 8.9%, p<0.001). However, a Kaplan-Meier analysis of five-year mortality showed no significant difference between groups.

Conclusions: The increased in-hospital mortality of Type A patients likely reflects the higher risks and more complicated clinical course associated with surgical repair. No long-term differences in mortality were seen between groups, despite the younger age of Type A patients and lower prevalence of a prevailing intimal tear. Further studies are warranted to determine whether aortic growth or other post-discharge outcomes differ between cohorts.



Number at Risk:

Type A - Complete Arch	79	68	41	26	19	11
Type B - Medical Management	391	344	258	206	163	83

18013 Which Measure of Renal Function is the Best Predictor of Outcome in Heart Failure? A Comparison of Cockcroft Gault, Modification of Diet in Renal Disease Study Group and Chronic Kidney Disease Epidemiology Collaboration Formulae

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Introduction: Renal function is an important predictor of prognosis in heart failure (HF). Several formulae can be used to estimate glomerular filtration (eGFR) but which of these is best at predicting outcome in HF is uncertain. We compared the performance of the Cockcroft-Gault (CG), Modification of Diet in Renal Disease Study Group (MDRD) and Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equations in predicting all-cause mortality in patients with heart failure with reduced ejection fraction (HFrEF).

Methods: We studied the 5011 patients aged ≥60 years with symptomatic (NYHA class II-IV) HF of ischemic etiology and a LVEF ≤40% (≤35% in NYHA class II) enrolled in the Controlled Rosuvastatin Multinational Trial in Heart Failure trial (CORONA). Mortality rates were calculated for patients in the eGFR categories <45, 45-59 and ≥60 ml/min/1.73m 2 (reference). The performance of the equations was compared using receiver operating characteristic curve (ROC) analysis.

Results:The rate and risk of death was highest in those with the lowest eGFR for each formula (Table). The area under the ROC for CG was 0.64, MDRD 0.59 (P<0.001 versus CG) and CKD-EPI 0.61 (P<0.0001 versus CG).

Conclusion: Risk prediction with CG was better than with MDRD or CKD-EPI in patients with HfrEF in CORONA. †Rate per 100 patient years *Reference group

18269 Prognostic Value of Insulin-Like Growth Factor Binding Protein 7 (IGFBP7) in Patients With Heart Failure: Data From CORONA

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Background: A recent proteomic analyses of cardiac tissue from a transgenic murine model of heart failure (HF) and clinical myocardial samples identified IGFBP7 as a candidate marker of HF. We investigated if serum levels of IGFBP7 were upregulated in human HF, if IGFBP7 provided independent prognostic information in these patients, and potential interactions with statin therapy.

Materials and methods: Serum IGFBP7 was measured in 187 HF patients and 57 matched healthy controls. The associations of serum IGFBP7 with adverse outcome were assessed in a subset of 1428 patients enrolled in the in the Controlled Rosuvastatin Multinational Trial in HF (CORONA) population, randomly assigned to 10 mg rosuvastatin or placebo, which included patients with HF, aged ≥60 years, in New York Heart Association classes II to IV, who had ischemic heart disease and a reduced left ventricular ejection fraction. Outcome included the primary endpoint (cardiovascular death, nonfatal myocardial infarction, nonfatal stroke; n=408), all-cause mortality (n=422), CV mortality (n=344), coronary endpoint (n=330) and CV mortality/hospitalization for worsening of heart failure (n=535).

Results: Serum IGFBP-7 levels were markedly elevated ($p<0.001$) in HF patients compared to controls (median [25th, 75th percentile]: 694 [586,874] ng/mL vs. 458 [425,499] ng/mL, $p<0.001$) and correlated with clinical severity (i.e. NYHA, $p=0.002$). In univariate analyses, IGFBP7 (continuous variable) was associated with all outcomes [HR ranging from 1.76 (coronary endpoint, $p=0.003$) to 3.08 (CV death, $p<0.001$)]. In multi-variable analyses, IGFBP7 remained significant for most endpoints after step 1 adjustment (adjusting for left ventricular ejection fraction, NYHA class, age, body mass index, diabetes, sex, intermittent claudication, heart rate, serum creatinine and apoA1) but the predictive value was markedly attenuated and not significant for any outcome after the addition of CRP and NT-proBNP. No interaction by treatment effects were observed for any outcome.

Conclusions: Serum IGFBP7 levels are elevated in patients with HF but add no predictive information beyond NT-proBNP for adverse outcome in older patients with advanced chronic systolic HF of ischemic aetiology.