NORSKE ABTRAKTER PRESENTERT PÅ ESC

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Long-term systolic blood pressure trajectories predict risk of incident atrial fibrillation in a general population cohort study

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Background: Elevated blood pressure (BP) is an important risk factor for atrial fibrillation (AF). However, the association between long-term BP changes and the risk of AF has not been fully elucidated.

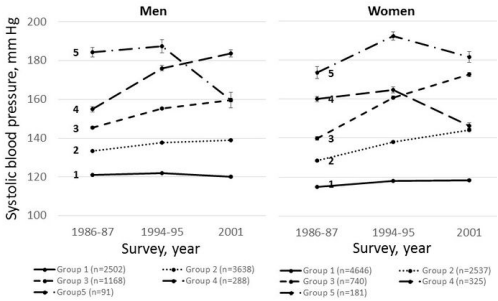
Purpose: To identify sex-specific individual long-term systolic BP patterns (trajectories), and to explore associations between the trajectories and risk of incident AF in the general population.

Methods: A total of 16,116 men and women aged 20 years or older who attended at least two of three surveys of a longitudinal population study conducted between 1986 and 2001 (the exposure period) were then followed up for incident AF through 2013. Trajectory analysis was used to identify individual systolic BP trajectories over the exposure period, and Cox regression was used to estimate associations between the trajectories and future risk of AF adjusted for potential confounders.

Results: Five systolic BP trajectory groups were identified (figure). In men, groups 1 and 2 were normotensive throughout the exposure period, group 3 had mild hypertension with a tendency to increase BP, group 4 and 5 were hypertensive throughout, but group 4 increased and group 5 decreased their systolic BP substantially. In total, 8% of men developed AF during follow-up. In men when group 1 used as the reference, groups 3 and 4 were associated with increased risk of AF: hazard ratios were 1.38 (95% CI: 1.09; 1.76) and 1.51 (1.09; 2.10), respectively. In women, systolic BP trajectory groups 1 and 2 were similar to those seen in men, groups 3 and 4 were hypertensive throughout, but systolic BP increased in group 3 and decreased in group 4, group 5 had the highest systolic BP throughout with no tendency to decrease. In total, 5% of women developed AF, and the risk of AF was increased in groups 3, 4 and 5 with hazard ratios of 1.73 (1.27; 2.36), 2.22 (1.55; 3.18) and 1.87 (1.25; 2.80), respectively when compared to group 1. Interaction between the trajectory groups and sex was significant: p<0.001.

Conclusion(s): We identified five trajectory groups that describe long-term patterns of systolic BP changes in individuals and represent cumulative exposure. Long-term systolic BP trajectories were associated with increased risk of AF in both sexes. Our results support the importance of a life course approach to BP management for the prevention of AF.

Means (95% confidence intervals) of systolic blood pressure by the trajectory group and survey in men and women



Mitral annulus disjunction is associated with severe ventricular arrhythmias independently of mitral valve prolapse

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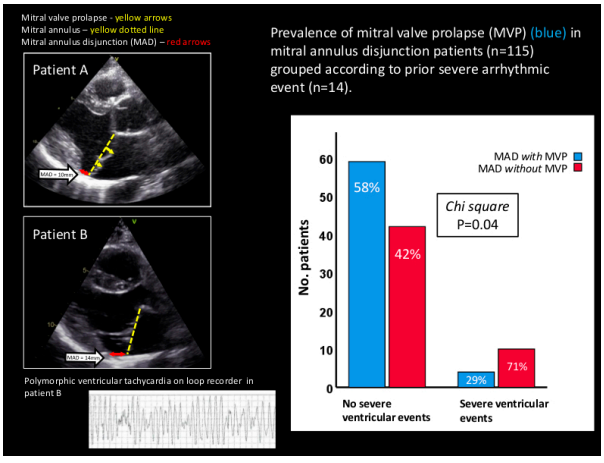
Background: Mitral valve prolapse (MVP) has been associated with sudden cardiac death. Mitral annulus disjunction (MAD) is an abnormal atrial displacement of the mitral valve leaflet hinge point, and has been proposed as a marker for sudden cardiac death in MVP patients. However, risk of ventricular arrhythmias in MAD itself, and in the absence of MVP, is poorly described.

Purpose: To describe the clinical presentation and prevalence of severe ventricular arrhythmias in patients with MAD with and without MVP.

Methods: We included consecutive patients from two hospitals with MAD defined as disjunction of >1 mm by study echocardiogram. We performed clinical examination and evaluated medical records for previous history of severe arrhythmic events, defined as aborted cardiac arrest or sustained ventricular tachycardia. Patients were excluded if they had non-mitral valvular disease, cardiomyopathies, channelopathies or obstructive coronary artery disease. We recorded the presence of MVP, measured MAD in the posterolateral wall (figure) in parasternal long-axis view, and measured left ventricular ejection fraction (EF).

Results: We included 115 patients (49±15 years, 60% female) with confirmed MAD. Severe arrhythmic events had occurred in 14 (12%) patients (n=10 aborted cardiac arrest, n=4 sustained ventricular tachycardia). Reported symptoms were palpitations (71%), presyncope (41%), chest pain (28%) and syncope (13%), with no difference between patients with or without severe arrhythmic events. Patients with severe arrhythmic events were younger (37±13 years vs. 51±14 years, p=0.001) and had lower EF (51±5% vs. 57±7%, p=0.002) compared to patients without events. MVP was evident in 63 (54%) patients and was less frequent in patients with severe arrhythmic events (4 (29%) vs. 59 (58%), p=0.04). In a multivariable logistic regression model including EF, age and MVP, lower EF (Adjusted OR 0.86 (95% CI, 0.77–0.97, p=0.01)) and lower age (Adjusted OR 0.94 (95% CI, 0.89–0.98, p=0.006) remained independent markers for severe arrhythmic events.

Conclusions: Patients with MAD frequently presented with arrhythmic symptoms, and 12% had experienced severe arrhythmic events. MVP was found in only half of the patients with MAD and was not associated with arrhythmic events, indicating MAD itself as an arrhythmogenic entity. In patients with MAD, lower age and EF were markers of severe arrhythmic events.



MVP in MAD with severe arrhythmic events

Cardiac resynchronization therapy - Always right for the right ventricle?

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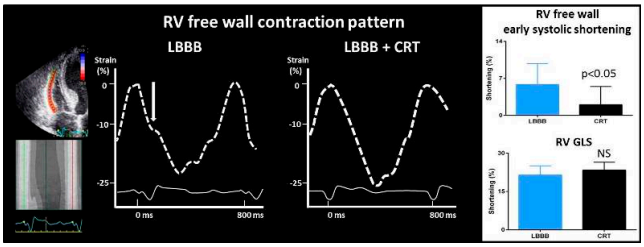
Background: Right ventricular (RV) function influences prognosis in recipients of cardiac resynchronization therapy (CRT). However, direct impact of left bundle branch block (LBBB) and CRT on RV function is not well understood.

Purpose: To study the immediate response of CRT on RV function in LBBB.

Methods: 14 patients with LBBB and non-ischaemic cardiomyopathy (QRS 169±17ms) were studied shortly before and during CRT. RV longitudinal strain was measured by speckle tracking echocardiography. Global RV free wall systolic strain (GLS) was calculated. In 10 anaesthetized dogs we measured RV dimensions by sonomicrometry and



Representative patient and mean data

pressure by micromanometer and induced LBBB by RF ablation. RV work was calculated from RV pressure-dimension loops.

Results: In patients, LBBB was associated with an abnormal and distinctive early-systolic contraction pattern in the RV free wall, with a steep initial shortening followed by a small plateau before it continued to contract (arrow in left panel of Figure). The abnormal RV free wall shortening coincided with pre-ejection shortening in the septum. This early systolic RV shortening was markedly attenuated by CRT ($p<0.05$). However, RV free wall GLS was unchanged (Figure, right panel). Similar RV free wall contraction pattern as in patients, were observed in the dog model during LBBB. However, with CRT there was a marked increase in RV free wall work from 23±14 to 36±15mm*mmHg ($p<0.01$).

Conclusions: Patients with LBBB had an abnormal RV contraction pattern occurring in early systole, which was reduced by CRT. The animal model showed that CRT increased workload on the RV free wall despite no improvement in total strain. Therefore, in hearts with intact RV function the RV free wall may compensate well during CRT, whereas hearts with a failing RV may not tolerate the increased workload and may respond poorly to CRT.

Reduced left ventricular lateral wall contractility leads to recovery of septal function in left bundle branch block

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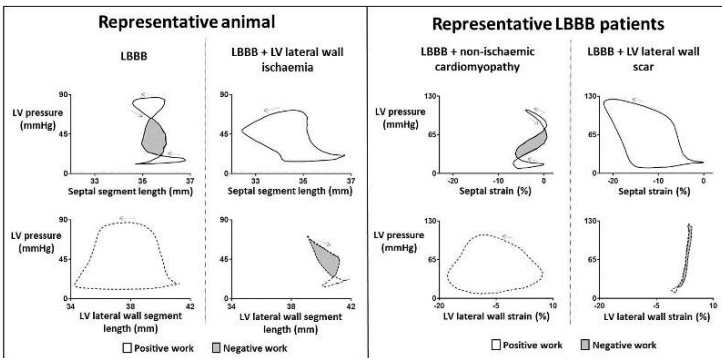
Introduction: Reduced septal work is a main feature of left bundle branch block (LBBB) and considered as a target for cardiac resynchronization therapy (CRT). We hypothesized that septal contractile function in LBBB is modified by crosstalk with the left ventricular (LV) lateral wall.

Purpose: To test the hypothesis that reduced LV lateral wall contractility leads to recovery of septal work in LBBB.

Methods: In 10 anaesthetized dogs we induced LBBB by radiofrequency ablation and occluded the circumflex coronary (CX) artery to reduce LV lateral wall contractility. Septal and LV lateral wall segment lengths were measured by sonomicrometry and regional work calculated as the area of the pressure-segment length loop. Work performed during counterclockwise rotation of the loop was defined as positive, whereas work performed during clockwise rotation of the loop was defined as negative (figure).

Furthermore, we used speckle-tracking echocardiography to study 24 LBBB patients referred for CRT implantation; 8 patients with LV lateral wall scar and 16 patients with non-ischaemic cardiomyopathy. There was no difference in LV ejection fraction between the two groups. Using a previously validated method for non-invasive estimation of LV pressure, regional work was calculated by pressure-strain analysis.

Results: Induction of LBBB caused characteristic regional work distribution with high values of LV lateral wall work and low values of septal work in all animals. CX occlusion, however, resulted in a major loss of LV lateral wall work, which declined from 417±84 (mean±SD) to 74±65 mmHg·mm ($p<0.001$). This was followed by a marked increase in septal work from 5±62 to 108±47 mmHg·mm ($p<0.001$) (figure).



Results from the clinical study resembled findings from the experimental study. In patients with non-ischaemic cardiomyopathy LV lateral wall work was 3144±1425 as compared to 1146±836 mmHg·% in patients with LV lateral wall scar (p<0.01). On the other hand, septal work was only 272±922 in non-ischaemic cardiomyopathy patients as compared to 1722±851 mmHg·% in LV lateral wall scar patients (p<0.01) (figure).

Conclusions: In LBBB, septal function is markedly improved or normalized in hearts with LV lateral wall dysfunction. Since recovery of septal function is one of the main mechanisms of improved LV function with CRT, hearts with lateral wall infarcts may have limited potential for response.

Cyclic variations of C-reactive protein levels

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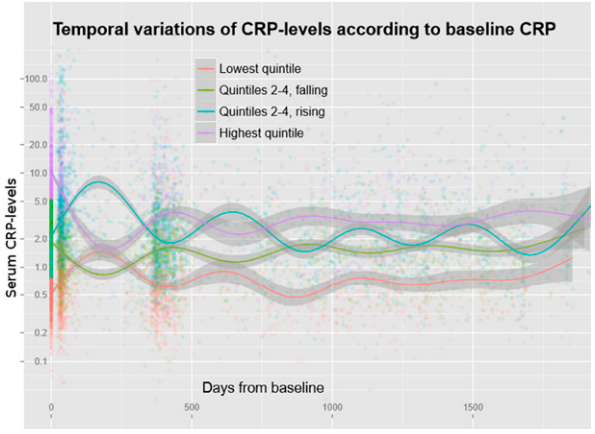
Background: Inflammation is a major risk factor of disease, including cardiovascular disease. C-reactive protein (CRP) is a measure of inflammation. Following an index event (i.e. myocardial infarction), the risk of a new event is initially high, but gradually declining over time. We hypothesize that both the index event and the residual risk is partly caused by the underlying inflammation, rather than the residual risk being caused by the index event. Further, we hypothesize that the inflammatory process is non-constant, showing non-linear, cyclical variation. Assuming an index event is most likely to occur at the peak of the inflammation cycle, this may explain the gradually declining risk thereafter.

Purpose: To study temporal patterns in CRP levels and whether CRP is associated with non-linear time-dependent risk of all-cause death.

Methods: We studied 3088 patients undergoing coronary angiography because of stable angina pectoris or acute myocardial infarction, who where originally included in the Western Norway B-Vitamin Intervention Trial. Blood was sampled at baseline, after one month, one year and at the end of the study (median 38 months). CRP was measured using an ultrasensitive immunoassay. The patients where categorized according to baseline CRP levels. The upper and lower quintiles were analyzed as such. Those in the 20–80 percentile brackets were divided into two groups, according to whether CRP levels were rising or falling between baseline and the first control. General additive models were used to graphically display the temporal variation. Each group was modeled separately and the model was set to automatically choose the optimal degrees of freedom. The two extreme CRP quintiles were further explored as determinants of cumulative mortality incidence during extended follow-up of about ten years.

Results: Levels of CRP showed distinct periodically variations with a cyclic pattern, with peak and trough (cycle phase) determined by baseline levels and directional change during the first month (figure). The wave lengths were similar in all subgroups, at approximately 460 days. The incidence of mortality was higher in the upper CRP quintile, compared to the lowest. However, both quintiles also displayed modest time-dependent variation, with a cyclical pattern in opposite phases.

Conclusions: Serum CRP levels appear to vary temporally with a cyclical pattern, with a wave length of approximately 460 days. Incidence of mortality also seem to vary cyclically, determined



by baseline CRP. Cyclical variation of CRP, as a proxy for inflammation, may partly explain the non-linear temporal risk of fatal disease.

Detection of mechanical activation of the left ventricle using high frame rate ultrasound imaging

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Introduction: A non-invasive method for regional mapping of mechanical activation could be useful in the diagnosis of pathologies affecting cardiac contraction patterns. With the advent of high frame rate echocardiography, there is potential to uncover rapid events not seen by conventional imaging. Novel echo acquisition and signal processing methods were tested for the assessment of mechanical activation.

Purpose: To assess the feasibility of using high frame rate ultrasound imaging to determine spatio-temporal information about onset of mechanical activation in the left ventricle.

Methods: High frame rate ultrasound imaging (1000 to 1200 fps) was performed on 3 anesthetized open chest dogs during epicardial right ventricle (RV) and left ventricle (LV) free wall pacing. Combined sonomicrometry and electromyography (EMG) was recorded simultaneously.

The activation of the LV was mapped by tracking the propagation of the mechanical wave that occurred in the tissue after pacing. The wave propagation was estimated using Clutter Filter Wave Imaging (CFWI). CFWI was configured to highlight tissue moving at a velocity above 2.5 cm/s. An activation map showing the arrival times of the propagating activation wave, as estimated by CFWI, was computed for each pacing experiment.

The timing of mechanical activation from CFWI was compared to electrical activation and to mechanical activation in terms of strain rate measured by sonomicrometry.

Results: Figure 1a shows the mechanical activation map from pacing of the RV free wall. Early activation can be seen in the mid to apical septum, then spreading bilaterally with the latest activation in the basal lateral wall. The delays between activation of the basal septum and the lateral wall, measured using EMG and CFWI were 24.3±4.3 and 23.6±1 ms, respectively, with a difference of 0.7±4.4 ms. The difference between mechanical activation measured by sonomicrometry and CFWI was 1.7±6.7 ms.

Figure 1b shows the mechanical activation map from pacing of the LV lateral wall. Mechanical activation started in the mid lateral wall, then spreading bilaterally with the latest activation in the basal septum. The delays between activation of the basal septum and the lateral wall, measured using EMG and CFWI were 35.4±10.01 and 33.5±8.04 ms, respectively, with a difference of 1.9±12.8 ms. The difference between mechanical activation measured by sonomicrometry and CFWI was 3.4±4.1 ms.

Conclusion: This pilot study showed that mechanical activation measured by CFWI had good agreement with invasive measurements. Thus, this novel CFWI method shows potential as a non-invasive tool for LV mechanical activation mapping.

Left ventricular free wall pacing causes excessive work load in septum and right ventricular free wall-a mirror image of left bundle branch block

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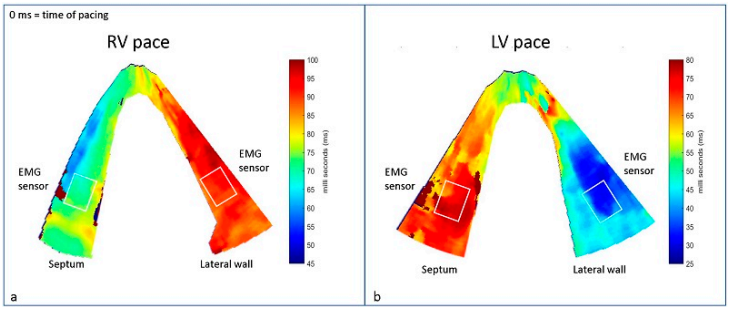

Figure 1. Activation map of RV and LV pace

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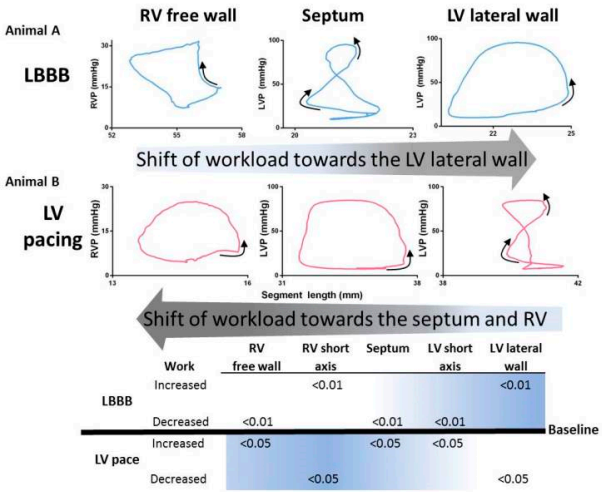
Background: Previous studies have shown that ventricular pacing causes non-uniform distribution of work in the left ventricle (LV). This is a potentially deleterious effect since excessive segmental load may be a stimulus to remodelling and may contribute to progression of heart failure.

Purpose: To determine effect of LV free wall pacing on distribution of work within the LV and between the LV and right ventricular (RV) free wall.

Methods: In 16 anaesthetized dogs, LV and RV pressures and dimensions by sonomicrometry were used to assess work as area of ventricular pressure-dimension loops. Longitudinal segment lengths were used for regional work and diameters for LV and RV short axis work. Two different activation patterns were studied, induction of LBBB by RF ablation (n=10) and pacing of the LV lateral wall (n=6) to study early activation from the septum and the LV lateral wall, respectively.

Results: Induction of LBBB caused reduction of RV free wall work from 36±15 to 23±14mm*mmHg (p<0.01) and reduction in septal work from 96±52 to 16±61mm*mmHg (p<0.01.) There was a simultaneous increase in work in the LV lateral wall from 118±89 to 194±111mm*mmHg (p<0.01). Therefore, LBBB caused a shift in workload from the early activated septum and RV free wall to the late activated LV lateral wall (Figure 1). During LV lateral wall pacing there was an opposite shift, with reduction of work in the early activated LV lateral wall from 47±39 to -6±22mm*mmHg (p<0.05), and increase of work in the late activated RV free wall from 27±18 to 36±18mm*mmHg (p<0.05) and in septum from 72±32 to 141±41mm*mmHg (p<0.05).

Conclusion: Single lead LV lateral wall pacing shifted ventricular work from the LV lateral wall to septum and RV free wall. This was opposite to effect of inducing LBBB. These results suggest that care should be exerted when placing pacing leads in the left ventricle since work load can become excessive in late activated myocardium in both ventricles. These principles should be explored in clinical studies in patients who receive LV pacing during cardiac resynchronization therapy.



Mechanical dispersion as marker of left ventricular dysfunction and prognosis in stable coronary artery disease

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Background: Assessment of global longitudinal strain (GLS) is superior to ejection fraction (EF) in evaluation of left ventricular (LV) dysfunction in patients with stabile coronary artery disease (CAD). However, the role of mechanical dispersion (MD) in this context is unresolved.

Objectives: We aimed to evaluate the potential role of MD as marker of subtle LV dysfunction and long-term prognosis in patients with stable CAD.

Methods: EF, GLS and MD were assessed in 160 patients with stable CAD, one year after successful coronary revascularization. Serum levels of high-sensitivity cardiac troponin I and amino-terminal pro B-type natriuretic peptide were quantified as markers of LV dysfunction. The primary end point was defined as all-cause mortality, whereas the secondary end point was defined as the composite of all-cause mortality and hospitalization for acute myocardial infarction or heart failure during follow-up.

Results: MD was successfully quantified in 98% of the patients (46±14 ms, [mean±SD]). There were no significant

associations between EF and the biochemical markers of LV dysfunction, while both MD and GLS correlated with hs-cTnI (R=0.450 and R=0.307, p<0.01) and NT-proBNP (R=0.379 and R=0.202, p<0.05). During a mean (±SD) follow-up of 8.5±0.4 years, 14 deaths and 29 secondary events occurred. Only MD was significantly increased in nonsurvivors, and also associated with both the primary and secondary end point in a Cox regression model, after adjustment for EF and GLS.

Conclusions: In patients with stable CAD, MD may be a promising marker of subtle LV dysfunction and adverse prognosis.

Plasma metabolites of the transsulfuration pathway and risk of new-onset atrial fibrillation among patients with stable angina pectoris

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Background/Aim: Plasma total homocysteine (tHcy) is elevated in patients with persistent vs. paroxysmal atrial fibrillation (AF), and has been related to increased risk of AF recurrence after cardioversion. Homocysteine is degraded via the transsulfuration pathway to cystathionine (Cysta) and cysteine (tCys). These homocysteine metabolites have been linked to potential pro-arrhythmic traits such as inflammation and atrial fibrosis. We evaluated the prospective association between transsulfuration pathway metabolites and new-onset atrial fibrillation among patients with suspected stable angina pectoris.

Methods: Information on new-onset atrial fibrillation was obtained by linking patient data to a national cardiovascular disease hospitalization database (CVDNOR) and the Norwegian Cause of Death Registry. Risk associations were explored by Cox regression.

Results: At baseline, 3535 patients without any prior history of atrial fibrillation were included. During median (25–75 percentile) follow-up of 7.4 (6.2–8.6) years, 392 patients (10.2%) were registered with incident atrial fibrillation. Median (25–75 percentile) baseline plasma levels of all three parameters were higher among participants who developed incident atrial fibrillation as compared to those who did not; tHcy 11.4 (9.4–14.2) vs. 10.2 (8.6–12.4) µmol/L; P<0.0001, Cysta 0.28 (0.21–0.42) vs. 0.26 (0.19–0.37) µmol/L; P=0.001, and tCys 302 (278–327) vs. 288 (265–311) µmol/L; P<0.0001, respectively.

Higher plasma tHcy and tCys were associated with increased risk of incident atrial fibrillation [age and gender adjusted HRs (95% CI) per 1 SD 1.23 (1.12–1.35) and 1.23 (1.11–1.38)]; however no prospective association was seen for plasma Cysta.

Multivariate adjustment, including BMI, smoking, diabetes, hypertension and eGFR yielded similar results.

Conclusion: Plasma tHcy and tCys were associated with new-onset atrial fibrillation among patients with stable angina pectoris. Our results motivate further studies to explore potential pathophysiological relationships between homocysteine metabolism and cardiac arrhythmias.

Septal flash and rebound stretch are different entities

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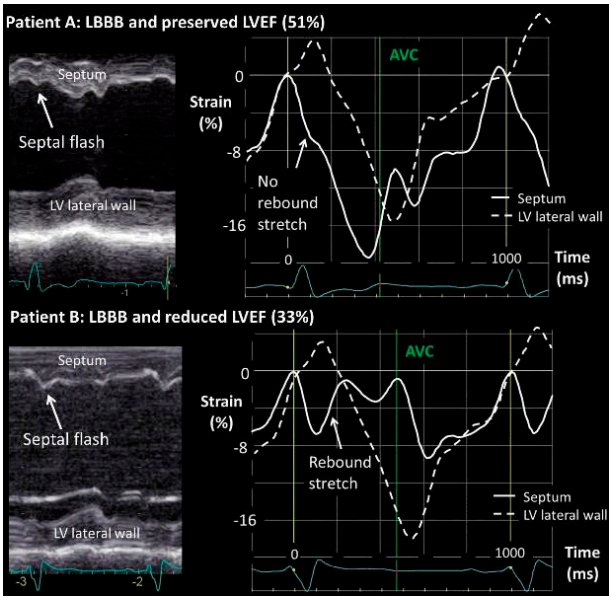
Background: Septal flash and rebound stretch are two commonly observed echocardiographic features of left bundle branch block (LBBB). Both predict response to cardiac resynchronization therapy (CRT), and have been thought to reflect the same phenomenon. Recent mathematical simulation studies, however, have indicated that they may have different underlying mechanisms.

Purpose: We aimed to investigate if septal flash and rebound stretch would appear to be different in LBBB-patients with normal and reduced ejection fraction (EF), respectively.

Methods: LBBB-patients with preserved EF (n=11) and reduced EF (n=16) underwent full echocardiographic examination. All were non-ischemic. EF was calculated by the biplane Simpson's method. Septal flash was determined visually by M-mode in the parasternal short axis view as an abnormal early systolic left-right motion of the interventricular septum. Rebound stretch was defined as a stretch during early systole following pre-ejection shortening in the septum, and was measured by strain from speckle-tracking echocardiography.

Results: EF was 56±6 and 31±5% (p<0.001) in the two groups, respectively. Septal flash was



Two representative patients

present in all patients. However, only 4 of the 11 patients with preserved EF showed rebound stretch, while 12 of the 16 patients with reduced EF did (figure). The amplitude of the stretch was also significantly lower in the group with preserved EF compared to the group with reduced EF (0.2±0.2% and 2.9±3.2%, p=0.009).

Conclusions: Septal flash was evident in all LBBB-patients, independent of LV function. Rebound stretch, however, was associated with reduced LVEF. These findings support previous findings from a mathematical simulation model that septal flash and rebound stretch are different entities, although they are both features of LBBB. Future studies should investigate if rebound stretch could improve current CRT-selection criteria.

Body mass index and cardiorespiratory fitness improve stroke prediction beyond classical cardiovascular risk factors

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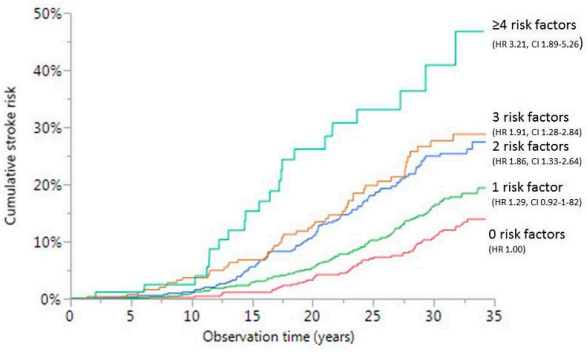
Background: The classical risk factors in the Framingham and European cardiovascular disease risk assessment models are age, gender, systolic blood pressure, total serum cholesterol and cigarette smoking.

Purpose: We aimed to investigate whether the addition of body mass index and cardiorespiratory fitness improved the prediction of stroke in a cohort of healthy middle-aged men followed for 35 years.

Methods: The study enrolled 2014 healthy men, aged 40–59 years, between 1972 and 1975. The baseline examination included fitness level measured with a maximal ergometer exercise test. Participants were followed over 35 years and stroke end-points were collected from follow-up visits, the National Cause of Death Registry and from medical records in all of the nation's hospitals. Participants in the highest quartile of baseline systolic blood pressure, total cholesterol and body mass index were grouped with those in the lowest quartile of fitness and with active smokers. We compared those having ≥1 risk factor with those having none, applying regression analyses and adjusting for age (Model 1). Finally we compared this model with a model that included body mass index and cardiorespiratory fitness (Model 2).

Results: During a median follow-up time of 31.9 years 316 first-time strokes occurred. No participants were lost to follow-up. Those who had 2 or more risk factors at baseline in Model 1 had a significantly higher stroke risk (HR 2.08, CI 1.07–3.70) than those with no risk factors. When including BMI and fitness in the model (Model 2), the participants with 4 or more risk factors had very high risk of stroke (HR 3.21, CI 1.89–5.26) compared to men with no risk factors at baseline (Fig. 1).

Model 2: Systolic blood pressure (Q4), Total cholesterol (Q4), Smoking (Yes) + Body mass index (Q4) and Cardiorespiratory fitness (Q1).



Conclusions: Our data suggest that the addition of body mass index and cardiorespiratory fitness improve a conventional stroke prediction model in healthy middle-aged men.

Hypothermia-induced diastolic dysfunction in ventricular trabeculae from human failing explanted hearts is caused by elongated contraction-relaxation cycle time and is worsened by increased heart rate

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Background: Acute myocardial infarction and ventricular arrhythmias are the most common causes of cardiac arrest. Targeted temperature management (TTM) is part of the standardized treatment for cardiac arrest patients that remain unconscious after admission. Hypothermia decreases cerebral oxygen consumption and induces physiological bradycardia reducing cardiac output; however, the effects of hypothermia on myocardial contractile function are not fully elucidated.

Purpose: Determine the effects of hypothermia on heart contractile function during different stimulation frequencies. It was hypothesized that cooling heart tissue to temperatures obtained during TTH will lead to impaired relaxation and increased diastolic tension and that increased heart rate will potentiate these effects. Second, beta-adrenergic receptor (βAR) stimulation could ameliorate the diastolic dysfunction during hypothermia.

Methods: Human left ventricular trabeculae obtained from explanted hearts from patients with terminal heart failure were stimulated at a frequency of 0.5 Hz and contraction-relaxation cycles (CRC) were recorded. Maximal developed force (Fmax), maximal rate of development of force ((dF/dt)max), time to peak force (TPF), time to 80% relaxation (TR80) and relaxation time (RT=TR80-TPF) were measured at 37–33–31–29°C. At these temperatures, stimulation frequency was increased from 0.5 to 1.0 to 1.5 Hz. At 1.5 Hz, concentration-response curves for βAR agonist isoproterenol were performed.

Results: Fmax, TPF and RT increased when temperature was lowered, whereas the (dF/dt) max decreased. At all temperatures, frequency to 1.0 and 1.5 Hz increased Fmax and (dF/dt)max, whereas TPF and RT decreased. At 31 and 29°C, diastolic tension increased at 1.5 Hz, which was ameliorated by βAR stimulation. The sensitivity to the βAR agonist isoproterenol increased by ~one log unit at 33°C and lower. At all temperatures, maximal βAR stimulation increased Fmax, (dF/dt)max and systolic tension, whereas diastolic tension was decreased progressively with lowering temperature. βAR stimulation reduced TPF and RT to the same extent at all temperatures, despite the elongated CRC.

Conclusion: Diastolic tension increased at higher stimulation frequency during hypothermia, indicating incomplete relaxation which may limit the volume of blood filling the ventricle. We suggest that diastolic dysfunction often reported during hypothermia results from an elongated CRC decreasing the time for ventricular filling during diastole. During hypothermia, physiological bradycardia protects the heart from diastolic dysfunction and increasing the heart rate should be avoided. In the event of insufficient cardiac output leading to organ hypoxia during hypothermia, low dose stimulation with a βAR agonist might be therapeutically beneficial, since it would increase stroke volume by enhancing contractile force generation while increasing the rate of relaxation, increasing the time in diastole.

Incidence, prevalence and survival in heart failure: a nationwide registry study from 2011-2016

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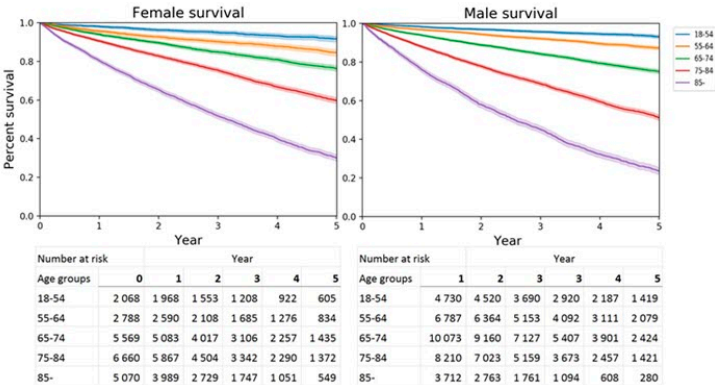
Background and purpose: The aim of this study was to calculate the incidence, prevalence and survival of heart failure (HF) in Norway in 2011–2016.

Methods: Using the nationwide Norwegian Prescription Database (NorPD) which includes all prescription drugs dispensed by pharmacies in Norway, we identified all patients ≥18 years of age with at least two dispensations associated with HF (defined by ICD-10 codes I50, I11, I13 or I42) during 2011–2016. The individual index date was set to the date of the first HF dispensation in the study period. Patients were followed until death, 5 years or end of follow-up 31.10.2017. Annual incidence and prevalence were estimated using a look-back period to March 1, 2008. However, ICD-10 codes were not fully implemented until March 2009. Comorbidities were identified as ICD-10 codes. Survival was calculated using Kaplan-Meier survival curves.

Results: A total of 84 268 unique patients with an ICD-10 code of HF for the first time were iden-

Incidence and prevalence 2011–2016

	2011	2012	2013	2014	2015	2016
Prevalence	1,20%	1,35%	1,45%	1,53%	1,62%	1,71%
Incidence	0,280%	0,258%	0,229%	0,207%	0,216%	0,221%



Number at risk	Year					
Age groups	0	1	2	3	4	5
18-54	2 068	1 968	1 553	1 208	922	605
55-64	2 788	2 590	2 108	1 685	1 276	834
65-74	5 569	5 083	4 017	3 106	2 257	1 435
75-84	6 660	5 867	4 504	3 342	2 290	1 372
85-	5 070	3 989	2 729	1 747	1 051	549

Number at risk	Year					
Age groups	1	2	3	3	4	5
18-54	4 730	4 520	3 690	2 920	2 187	1 419
55-64	6 787	6 364	5 153	4 092	3 111	2 079
65-74	10 073	9 160	7 127	5 407	3 901	2 424
75-84	8 210	7 023	5 159	3 673	2 457	1 421
85-	3 712	2 763	1 761	1 094	608	280

Kaplan Meyer survival curves

tified between 2011 and 2016. Of these, 55 669 fulfilled the inclusion criteria of ≥2 HF prescriptions. The median age was 72 years and 60% were men. Women were older than men when first diagnosed with HF (median age 76 yrs vs 70 yrs). The most common comorbidities were hypertension (74%), coronary artery disease (49%) and atrial fibrillation (32%). The overall annual incidence of HF decreased over the 6-year period from 2.80 to 2.21 per 1000, and the prevalence increased from 1.20% to 1.71% (table). Both incidence and prevalence rates were higher in men than in women. All-cause mortality after 1, 3 and 5 years was 8.8%, 22.1% and 33.8%, respectively. Survival decreased with increasing age (figure) and were lower in men than in women. In patients 75–84 years, 5-year survival was 60% in women, 51.7% in men. Mortality rates were probably underestimated since some patients died before the second dispensation of drugs and were not included in the study.

Conclusions: This nationwide registry study in Norway showed an increase in the prevalence of HF from 2011 to 2016. Since the incidence did not increase in the same period, this suggests improved survival. However, the long-term mortality in HF was still very high, especially in patients >75 years of age.

Invasive versus conservative strategy in elderly patients with non-ST-elevation myocardial infarction: a prospective cohort study

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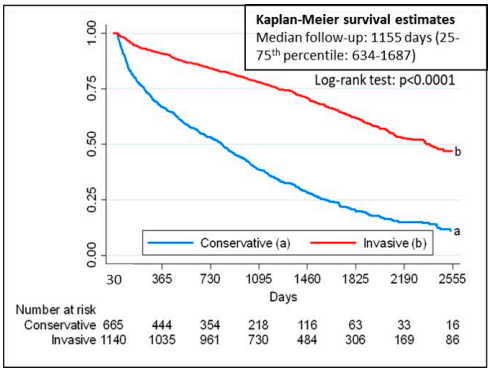
Background: It is debated whether an invasive strategy is associated with improved survival in elderly patients with non-ST-segment myocardial infarction (NSTEMI).

Purpose: We aimed to compare short- and long-term survival in NSTEMI patients ≥75 years managed with coronary angiography and revascularization if indicated (invasive strategy) versus a conservative strategy.

Methods: NSTEMI patients admitted to our hsopital during 2005–2011 were included consecutively in a prospective registry. Vital status until 31 December, 2013 was obtained from the Norwegian Cause of Death Registry. Survival at 30-days and 7-years were estimated using survival analyses. We used logistic- and Cox regression to estimate odds ratio (OR) and hazard ratio (HR) for death in the invasive versus conservative group, adjusted for known confounders.

Results: Among 5159 NSTEMI patients, 2064 patients (40.0%) were ≥75 years (48.2% women). Twelve hundred (58.1%) of these were treated with an invasive strategy; and were younger, more likely to be male and previously revascularized compared to patients treated conservatively. Survival at 30-days was 94.9% in the invasive versus 76.6% in the conservative group. For 30-day survivors, estimated 7-year survival was 47.4% and 11.6%, respectively. After multivariate adjustment, an invasive strategy was associated with lower risk of death at 30 days



Survival in elderly patients with NSTEMI

(adjusted OR 0.38 [95% CI 0.24–0.60]) and during 7 years follow-up (adjusted HR 0.45 [95% CI 0.38–0.54]).

Conclusion: In this real-life cohort of NSTEMI patients ≥75 years, an invasive compared to a conservative strategy was associated with improved short- and long-term survival, also after multivariate adjustment.

Low concentrations of circulating secretoneurin predict a favorable prognosis after cardiac surgery

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Background: Cardiac surgical patients have increased long-term mortality, and biomarker concentrations during surgery could identify patients at increased risk. Secretoneurin (SN) is a novel prognostic biomarker that seems to integrate information on systemic stress pathways and myocardial dysfunction. Accordingly, we hypothesized that SN would identify cardiac surgical patients at increased risk.

Methods: We measured SN, N-terminal pro-B-type natriuretic peptide (NT-proBNP), and high-sensitivity cardiac troponin T (hs-cTnT) concentrations before and on the morning after cardiac surgery in 619 patients. The prognostic value of SN was compared to established cardiac biomarkers and risk scores. We assessed the association to mortality within 961 days of follow-up in multivariate models that included the European System for Cardiac Operative Risk Evaluation (EuroSCORE) II risk model.

Results: SN concentrations were higher among non-survivors (n=59, 9.5%) compared to survivors, both before (median 168 pmol/L [quartile (Q) 1–3 147–206)] vs. 160 [131–193] pmol/L, p=0.039) and after cardiac surgery (173 [129–217] vs. 143 [111–173] pmol/L, p<0.001). Postoperative SN concentrations were significantly lower than preoperative values in long-term survivors (p<0.001), while patients who died during follow-up did not demonstrate significant change in SN concentrations after cardiac surgery (p=0.41; Figure). hs-cTnT and NT-proBNP concentrations increased after cardiac surgery in both survivors and non-survivors (p<0.001 for both; Figure). Lower preoperative NT-proBNP concentrations, higher preoperative SN concentrations, and short cardio-pulmonary bypass time were associated with decreasing SN concentrations after cardiac surgery in multivariate analysis. Postoperative SN concentrations were also associated with time to death in multivariate Cox regression analysis that adjusted for hs-cTnT, NT-proBNP, and EuroSCORE II; hazard ratio lnSN 2.96 (95% CI 1.46–5.99), p=0.003. Adding postoperative SN measurements to EuroSCORE II also improved risk stratification as assessed by the integrated discrimination index: 0.023 (95% CI 0.0043–0.041), p=0.016.

Conclusions: Patients with low circulating SN concentrations after cardiac surgery have a favorable prognosis and postoperative SN measurement improves risk assessment in cardiac surgical patients.

Markers of neutrophil extracellular traps as related to mortality in patients with ST-elevation myocardial infarction

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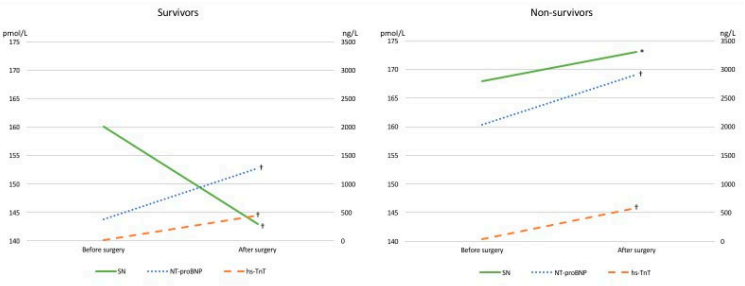


† p<0.001, * p=0.41. SN in pmol/L, NT-proBNP and hs-TnT in ng/L.

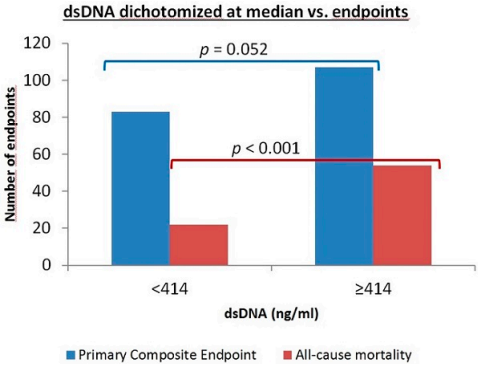
Background: Neutrophil extracellular traps (NETs) seem to be implicated in the pathophysiology of acute coronary syndromes (ACS) and have been associated with the severity of coronary atherosclerosis. The potential role of NETs

components as soluble biomarkers in ACS risk stratification is unclear.

Purpose: We aimed to investigate whether circulating NETs markers associated with clinical outcome in patients with ST-elevation myocardial infarction (STEMI). Secondarily, any relation to myocardial injury was assessed.

Methods: Patients with STEMI admitted for primary PCI (n=956) were included. Blood sampling was performed at a median of 18 hours post-PCI, and clinical outcomes were censored after a median of 4.6 years. Patients using oral anticoagulants were excluded. The primary endpoint was defined as a composite of reinfarction, unscheduled revascularization after more than three months, stroke, rehospitalisation for heart failure, or death, whichever occurred first. All-cause mortality was also recorded. As markers of NETs, double-stranded deoxyribonucleic acid (dsDNA) and myeloperoxidase-DNA (MPO-DNA) complexes were quantified in serum by use of a fluorescent nucleic acid stain and an ELISA technique, respectively.

Results: Levels of dsDNA and MPO-DNA did not differ significantly between groups with (n=190) or without a primary composite endpoint. Amongst the 76 patients who died during follow-up, however, dsDNA levels (median (25th, 75th percentile)) were significantly higher (460 ng/ml (407, 508) vs. 411 ng/ml (370, 466), p<0.001). When dichotomizing dsDNA levels at median, patients with high dsDNA levels had significantly higher all-cause mortality (54 vs. 22 deaths, p<0.001). After adjusting for relevant covariates (age, sex, smoking, leukocyte count, LDL-cholesterol, peak troponin T, and NT-proBNP), patients with high dsDNA levels still had a significantly increased risk of death (OR 2.85 [95% CI 1.56–5.21], p=0.001). No significant association to clinical outcome was observed for MPO-DNA. DsDNA and MPO-DNA were both correlated with peak troponin T (r=0.17 and 0.12, respectively, p<0.001 for both), whereas only dsDNA correlated significantly with levels of NT-proBNP (r=0.19, p<0.001). Amongst patients with reduced left ventricular ejection fraction ≤40% (n=145), dsDNA and MPO-DNA levels were significantly elevated (439 ng/ml (397, 494) vs. 409 ng/ml (366, 464) and 0.196 OD (0.148, 0.312) vs. 0.175 OD (0.137, 0.254), respectively, p≤0.007 for both).



Conclusions: In this cohort of patients with STEMI, dsDNA and MPO-DNA levels did not associate with adverse clinical outcome as defined by the primary composite endpoint. Levels of dsDNA were, however, significantly associated with increased mortality. The underlying mechanism for the apparent link between extracellular nuclear material and death is unclear and in need of further exploration.

The association between apolipoprotein A1 and HDL-cholesterol with acute myocardial infarction is modified by plasma choline. A cohort study of patients with suspected stable angina pectoris

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Background: Choline is related to 1-carbon metabolism and essential for lipoprotein assembly. Higher plasma choline has been associated with an increased risk of cardiovascular events, whereas serum high density lipoprotein (HDL)-cholesterol (HDL-C) and apolipoprotein (apo) A1, the main apolipoprotein of HDL, is inversely related to cardiovascular risk. There is evidence suggesting that the choline metabolism and HDL metabolism are interconnected; however, their potential interactions according to future cardiovascular events are not known.

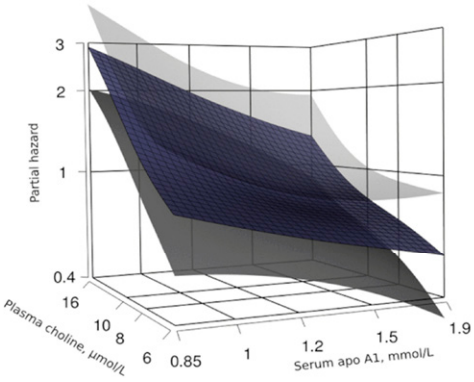
Purpose: To investigate the potential effect modification by plasma choline on the relationship between apo A1 and HDL-C with incident acute myocardial infarction (AMI).

Methods: We studied patients evaluated for suspected stable angina pectoris, and who were followed up for long-term cardiovascular events as identified according to regional health registries. By Cox regression, we investigated the associations between serum apo A1 and HDL-C with incident AMI according to median plasma choline concentration.

Results: Median (5th-95th percentile) age of the 4153 patients (2988 (71.9%) men) was 62 (44–78) years. During follow-up for median (5th-95th percentile) 4.6 (1.6–6.8) years, 344 (8.3%) patients suffered from at least one AMI.

As expected, we found inverse associations between serum apo A1 and HDL-C with subsequent AMI in the total population; however, the association for apo A1 was present only when plasma choline was ≥ median [age and gender adjusted HR (95% CI) 0.71 (0.61–0.83) vs. 1.06 (0.88–1.28) when plasma choline was < median; P for interaction=0.009], and a similar trend was also observed for HDL-C (P for interaction=0.09). Further adjusting for hypertension, smoking, diabetes and body mass index yielded similar results, and the 3-dimensional generalized additive model plot in Figure 1 suggests that the interaction is approximately linear.

Conclusion: Serum apo A1 and HDL-C were inversely related to risk of future AMI, with stronger associations observed among patients



with concomitant high plasma choline concentrations. Our results motivate further studies into potential ramifications between choline and lipid metabolism according to coronary heart disease.

Ventricular volume changes are more accurate markers of acute response to CRT than contraction indices

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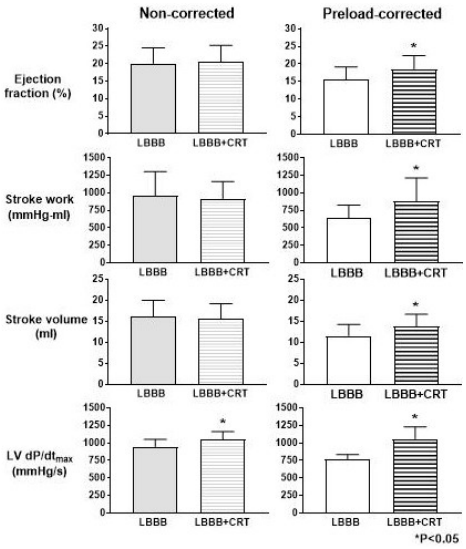
Background: Cardiac resynchronisation therapy (CRT) improves systolic function in left bundle branch block (LBBB). However, the magnitude of acute improvements in global ventricular contraction indices do not correlate consistently with long-term response to CRT.

Purpose: To determine the effect of CRT on contraction indices and ventricular volumes during LBBB by pressure-volume analysis.

Methods: In eight anaesthetised dogs, we measured left ventricular (LV) pressure by micromanometry and LV volume by sonomicrometry to calculate stroke work (SW), stroke volume (SV), peak rate of LV pressure rise (LV dP/dtmax) and ejection fraction (EF). LBBB was induced by radiofrequency ablation. Transient caval constrictions were performed to compare data at similar preloads.

Results: CRT decreased LV volumes significantly shown by a reduction in end-diastolic volume (EDV) from 83.2±21.4 to 79.5±21.1 (P<0.05) and end-systolic volume from 67.0±20.5 to 63.8±20.4 (P<0.05). There were negligible changes in SV, SW and EF whereas LV dP/dtmax increased moderately (Figure, left panels). When correcting for the reduction in preload, SV, SW and EF increased significantly (Figure, right panels). The magnitude of change in LV dP/dtmax was 3 times larger when using preload-corrected data.

Conclusions: CRT reduced preload shown by a significant reduction in EDV with little changes



in EF, SW and SV. These findings suggest that LV volume changes rather than conventional contraction indices should be used to evaluate acute CRT response. These observations may explain some of the apparent inconsistency between acute response and long-term response to CRT.

Associations of left atrial volume with cardiorespiratory fitness and indices of left ventricular diastolic function in a fit population sample

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On behalf: CERG (Cardiac Exercise Research Group)

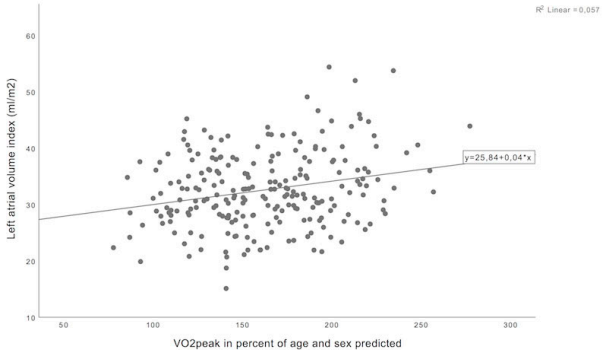
Background: Left atrial size is accepted as a strong predictor for future cardiovascular endpoints. Furthermore, it is related to diastolic dysfunction, and in recent recommendations it is included as one of the diagnostic criteria for diastolic dysfunction. Contrary, the left atrium is dilated in endurance athletes. Despite this paradox, little is known about the association of cardiorespiratory fitness (CRF), left atrial size and diastolic dysfunction in healthy and fit populations.

Purpose: To study the associations of left atrial size with CRF and diastolic dysfunction in a fit population.

Methods: In total, 243 participants (56% women, mean (SD) 48 (13) years) free from known pulmonary or cardiovascular disease, hypertension, antihypertensive medications, and diabetes included in a population study were examined with echocardiography and cardiopulmonary exercise testing of peak oxygen uptake (VO2peak). Echocardiography included assessment of left atrial volume and other indices of diastolic dysfunction. The inner border of left atrium was traced in apical 4- and 2-chamber views, and the left atrial volume indexed to body surface area (LAVI) was calculated. According to recent recommendations indices of left ventricular diastolic function included measurements of septal and lateral mitral annular early diastolic tissue velocity (septal and lateral e'), early (E) and late (A) mitral inflow velocity, E to A and E to e' ratio (E/e'), and peak tricuspid regurgitant jet velocity (TRV). VO2peak was measured using ventilator gas analysis during incremental treadmill exercise and expressed as percentage of published age and sex normal values for VO2peak (VO2%pred).

Results: In this fit healthy sample VO2%pred was mean (SD) 161 (38) %. LAVI was >34ml/m^2 in 39% of the study population and only three participants (1.2%) fulfilled the criteria for diastolic dysfunction. Of participants with VO2%pred above the average of 161%, 51 participants (57.3%) had LAVI >34ml/m^2. In linear regression analyses there was a significant association of larger LAVI with higher VO2%pred (β=0.041, R squared 0.057, p<0.001) and of VO2%pred and septal and lateral e' (both p=0.001). Furthermore, there was an association of higher VO2%pred with lower E/e' (p=0.012), but no significant association with TRV. There were no significant correlations of LAVI with the other indices of diastolic function.

Conclusions: In this fit and healthy population larger left atrium was associated with higher cardiorespiratory fitness and left atrial enlargement above the established cut-off was prevalent. Of special interest, left atrium volume index was not associated with other echocardiographic indices of diastolic dysfunction. The results indicate that left atrium volume index may not be a good predictor of adverse events in a fit population, which should be further studied.



The association between serum high-sensitivity cardiac troponin t and acute myocardial infarction in patients with suspected stable angina pectoris is modified by body mass index

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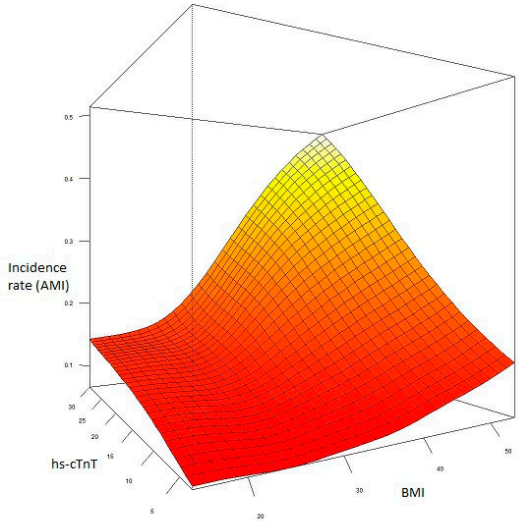
Purpose: High-sensitive cardiac troponin T (hs-cTnT) is associated with cardiovascular death and acute myocardial infarction (AMI). While overweight is an established risk factor for CVD, studies have suggested improved prognosis among overweight and obese patients with established CVD. We sought to explore the association between hs-cTnT and future AMI



Smooth surface spline estimate

according to BMI among patients with suspected stable angina pectoris (SAP).

Methods: A total of 3882 patients who underwent elective coronary angiography, and who had baseline hs-cTnT ≤30 ng/L, were followed to subsequent AMI or end of 2009. Endpoint data was obtained by linkage to national health registries. Risk associations were explored with Cox regression according to BMI categories <25kg/m^2, 25–30kg/m^2 and >30kg/m^2, and interactions tested in a model otherwise adjusted for age and gender. We also constructed generalized additive Cox models to explore any non-linear relationships in the potential hs-cTnT-BMI interactions.

Results: The population had a median (IQR) age of 61.7 (21–88) years and consisted of 2773 (71.4%) males. During median (IQR) 8 (2.3) years of follow-up, 460 (11.8%) patients experienced an AMI. Figure 1 suggests that hs-cTnT was more strongly associated with AMI among patients with higher BMI when adjusting for age, sex, hypertension, diabetes mellitus, smoking and left ventricular ejection fraction. Accordingly, the HRs (95% CIs) for incident AMI per 1SD log-transformed hs-cTnT were 1.06 (1.04–1.09), 1.04 (1.03–1.08) and 1.33 (1.25–1.41) in the BMI categories <25kg/m^2, 25–30kg/m^2 and >30kg/m^2, respectively (P for interaction = 0.02).

Conclusion: In a population of patients with suspected stable angina pectoris, the risk relationship of hs-cTnT with incident AMI was stronger in patients with higher BMI. Our results motivate further studies into potential pathophysiological mechanisms connecting hs-cTnT with increased cardiovascular risk among patients with stable coronary heart disease.

The feasibility, accuracy and reliability of fully automatic analyses of left ventricular systolic longitudinal function by pocket-size imaging device

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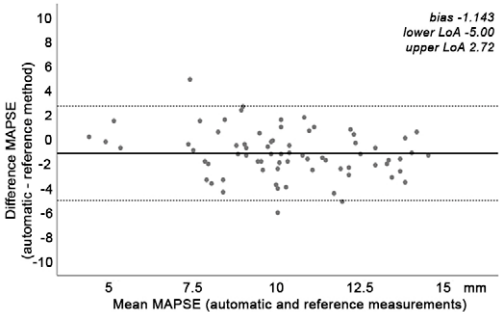
Background: Mitral annular systolic plane excursion (MAPSE) is an easy and reliable measure of global longitudinal left ventricular (LV) function. We have developed an algorithm that automatically measures MAPSE from live grey scale recordings that can be implemented on pocket-size imaging devices (PSID). Automatic measurements and interpretations of findings can assist inexperienced users when evaluating LV function. This has never been evaluated on PSID, which so far have not been able to provide quantitative assessment of LV function.

Purpose: We aimed to study the feasibility, accuracy and reliability of automatic measurements of MAPSE on recordings performed by PSID.

Methods: 20 consecutive patients at a university hospital's echocardiographic laboratory were examined first with standard echocardiography by a sonographer or cardiologist using a high-end scanner. Four separate grey scale recordings, each consisting of 3 cardiac cycles, of the LV 4-chamber view were included. Immediately after the standard echocardiography, the same user recorded the LV 4-chamber view in grey scale four separate times using a PSID.

A cardiologist experienced in echocardiography blinded to all other data, measured MAPSE in the septal and lateral mitral annulus using anatomical motion mode on the reference images, and by the fully automated algorithm in the pocket-size imaging recordings. In total, 80 pairs of recordings of the average of the lateral and septal measurements from the 20 cases were used in the analyses. The measurements of the automatic method were compared to the reference measurements by the cardiologist using high-end equipment.

Results: The automatic method failed in two patients, leaving 72 pairs of measurements for comparison of the methods. The fully automated method underestimated MAPSE of mean±SD 9.7±2.3 mm vs reference measurements of mean±SD 10.8±2.7 mm, respectively. There was a highly significant difference of mean±SD 1.1±1.9 mm. The lower and upper limits of agreement were -5.0 and 2.7 mm, and intraclass correlation for the absolute agreement between automatic analyses and reference method was 0.78. The within measurements coefficient of variation was mean±SD 9.6±7.6% and 7.4±4.1% for the automatic method and reference, respectively (p-value for difference 0.24). As seen in Figure 1 the absolute value of the measurements did not



influence the accuracy.

Conclusion: Fully automated quantification of LV systolic longitudinal function by grey scale recordings using PSID was feasible and reliable. The novel method yielded a small underestimation compared to reference imaging. This may allow for future quantification of LV function at the patient's point-of-care using PSID.

Lipoprotein subclasses and their associations with physical activity, cardiorespiratory fitness and adiposity in Norwegian schoolchildren: the active smarter kids study

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Background: Physical activity (PA), cardiorespiratory fitness (CRF) and adiposity are associated with certain lipoproteins. Research in adults has shown that these associations are not consistent across lipoprotein subclasses.

Purpose: To examine cross-sectional associations in children between objectively measured PA and sedentary time (SED), CRF and adiposity with a number of biomarkers of lipoprotein metabolism.

Methods: We included 1055 healthy fifth-grade (mean age 10.2 yrs) Norwegian schoolchildren (47.4% females). Total PA (tPA), PA intensity (light (LPA); moderate-vigorous (MVPA)), and SED were assessed using triaxial accelerometery. We used the 20-m shuttle run test to assess CRF, and waist circumference to measure abdominal adiposity. We quantified 31 measurements of lipoprotein metabolism including subclass concentrations, and particle size of three major classes (VLDL, LDL, HDL) using nuclear magnetic resonance spectroscopy. We used linear regression (median regression for skewed data) models adjusted for age, sex, sexual maturity and socioeconomic status (standard model). Additional tPA, PA intensity and CRF models were adjusted for adiposity, and additional adiposity models were adjusted for moderate-vigorous PA (MVPA) and CRF separately. An isotemporal substitution regression model quantified associations of replacing 30 minutes LPA or SED with 30 minutes MVPA. We applied a false discovery rate (FDR) adjustment to p-values of each regression model.

Results: Adiposity was significantly associated with all 31 biomarkers in the tPA and MVPA-adjusted models, and 29 biomarkers following adjustment for CRF. CRF was associated with each of the 31 biomarker measures in the standard model and 22 in the adiposity-adjusted model. Total PA, MVPA, LPA and SED were associated with 10, 18, 0 and 5 of the 31 biomarkers, respectively (standard model). The number of significant associations were attenuated after adjusting for adiposity (10, 12, 0, and 0), respectively. Substituting 30 minutes of SED or LPA for MVPA revealed significant associations with 22 and 21 biomarkers, respectively. Following adjustment for adiposity, 10 and 12 associations, respectively remained statistically significant ($p<0.05$).

Conclusion: CRF is associated with a number of markers of lipoprotein metabolism independent of adiposity. PA, especially of higher intensity, is associated with some of these biomarkers independent of adiposity. Substituting time spent sedentary or in LPA for MVPA shows favourable associations with these biomarkers. This suggests that improving cardiorespiratory fitness and increasing physical activity of at least moderate intensity may favourably affect lipoprotein metabolism in healthy children. Future work should replicate these findings in other cohorts and determine the clinical significance of differences in these biomarkers.

Septal rebound stretch is a tug of war between septum and left ventricular lateral wall

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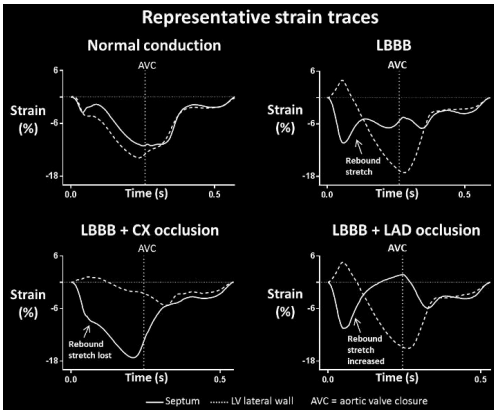
Introduction: The echocardiographic hallmark of left bundle branch block (LBBB) is abnormal motion of the interventricular septum. This includes marked preejection shortening and subsequent paradoxical systolic lengthening named rebound stretch. Since septal rebound stretch was suggested as predictor of response to cardiac resynchronization therapy (CRT) it is important to determine its mechanism and modifiers.

Purpose: To test the hypothesis that presence and extent of septal rebound stretch in LBBB is determined by the relative contractility in the septum and left ventricular (LV) lateral wall.

Methods: In 10 anaesthetized dogs we induced LBBB by radiofrequency ablation. The circumflex coronary (CX) artery was temporarily occluded (n=10) to reduce LV lateral wall contractility and the left anterior descending (LAD) artery was temporarily occluded (n=6) to reduce septal contractility. Septal and LV lateral wall segment lengths were measured by sonomicrometry before and during occlusions.

Results: Induction of LBBB caused the characteristic septal contraction pattern with preejection shortening, rebound stretch and reduced septal systolic shortening in all animals. CX occlusion reduced LV lateral wall systolic shortening from 5.0±1.2 (mean±SD) to 0.5±1.0 mm (p<0.01). This was followed by loss of septal rebound stretch from 1.4±0.6 to 0.2±0.2 mm (p<0.01) (figure) and increased septal systolic shortening from 2.1±1.4 to 4.2±1.3 mm (p<0.01).

LAD occlusion, on the other hand, caused an increase in septal rebound stretch to 2.7±1.2 mm (p<0.05 vs. no ischaemia) and a reduction in septal systolic shortening to 0.3±1.5 mm (p<0.05 vs. no ischaemia) (figure).



Conclusions: Septal ischaemia aggravated septal dysfunction in LBBB by increasing rebound stretch, whereas LV lateral wall ischaemia normalized septal contraction pattern by abolishing rebound stretch. These results imply that abnormal septal motion in LBBB reflects a tug of war between septum and LV lateral wall. This interaction should be taken into account when using abnormal septal motion to identify responders to CRT.

Septal work is a more sensitive marker of myocardial dysfunction in dyssynchrony than strain

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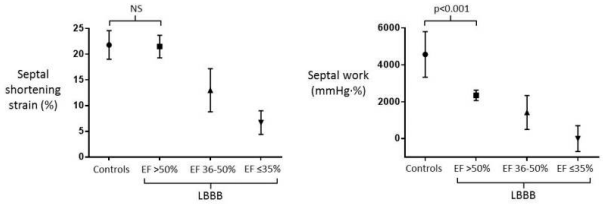
Introduction: Regional myocardial work by echocardiography was recently introduced as a clinical method. Since work incorporates load it may be superior to strain imaging to identify myocardial dysfunction. We hypothesized that myocardial work identifies preclinical myocardial dysfunction in patients with left bundle branch block (LBBB).

Purpose: To compare the echocardiographic modalities myocardial work and strain in the evaluation of systolic function in patients with LBBB.

Methods: 28 non-ischaemic LBBB patients were divided into three groups based on left ventricular (LV) ejection fraction (EF): Group EFnormal (n=8) with EF>50%, group EFmid (n=10) with EF 36–50% and group EFlow (n=10) with EF≤35%. Furthermore, we included a group of 10 healthy control subjects. All subjects were examined by speckle-tracking echocardiography to calculate peak longitudinal strain in the septum and LV lateral wall. Using a previously validated method for non-invasive estimation of LV pressure, segmental work was calculated by pressure-strain analysis.

Results: There were no significant differences in LVEF between controls and EFnormal LBBB patients (60±4 vs. 58±5%, NS) suggesting normal systolic function. This was also true for septal shortening (21.8±2.8 in controls vs. 21.5±2.2% in EFnormal, NS). Septal work, however, was substantially reduced (2346±280 in EFnormal vs. 4565±1233 mmHg·% in controls, p<0.001). This indicates markedly reduced septal function in LBBB patients despite normal EF (figure). There were further reductions in septal work in the



EFmid and EFlow groups consistent with gradually increasing dysfunction. LV lateral wall shortening and work did not change between controls, EFnormal and EFmid, which indicates preserved LV lateral wall function in LBBB patients despite reduced global systolic function.

Conclusions: Myocardial work was more sensitive than strain to identify myocardial dysfunction in patients with LBBB and normal LVEF. This probably reflects that work incorporates loading conditions which are often abnormal in the septum of LBBB patients. These results suggest a role for myocardial work to identify preclinical LV dysfunction. Future studies should investigate whether reduced myocardial work has prognostic value on top of strain.

Left and right ventricular deformation in preadolescent athletes assessed by speckle-tracking strain echocardiography

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On behalf: Center for Cardiac Innovation

Table 1

	Athletes (n=76)	Controls (n=25)	P-value
VO_2 max indexed, mL/kg/min	62±7	44±5	<0.001
RV basal diameter/BSA, mm/m²	28±3	25±4	<0.001
RV mid-cavity diameter/BSA, mm/m²	24±3	22±3	<0.01
RV end-diastolic area/BSA, cm²/m²	14.7±2.9	13.1±1.3	<0.01
RV end-systolic area/BSA, cm²/m²	8.5±1.8	7.5±0.9	<0.01
RV global longitudinal strain, %	28±4	31±3	<0.01
RV fractional area change, %	42±6	43±4	0.52
LV global longitudinal strain, %	23±2	23±2	0.36
LV ejection fraction, %	58±3	58±3	1.00

Data expressed as mean ± SD. Right column shows P-values for Student's t-test. BSA, body surface area; LV, left ventricular; RV, right ventricular.

Background: Studies in adult athletes have found irreversible reduction in right ventricular (RV) deformation with signs of fibrosis in a subset of the athletes. Reduced RV function in athletes has been found to be a pro-arrhythmic substrate.

Purpose: This study aims to improve our understanding of how endurance exercise in preadolescent athletes impacts the LV and RV function.

Methods: Seventy-six cross-country skiers aged 12.1±0.2 years were compared to a control group of 25 non-competing individuals aged 12.1±0.3 years. Echocardiography was performed in all subjects including 2D speckle-tracking strain echocardiography of both ventricles. Left ventricular (LV) global longitudinal strain (GLS) and RV GLS were calculated by averaging 16 LV and 3 RV free wall segments, respectively. All participants underwent cardiopulmonary exercise testing to assess oxygen-uptake and exercise capacity.

Results: While there was no difference in LV GLS, the controls had higher RV GLS than the athletes (Table). There was no difference with regards to LV ejection fraction and RV fractional area change. Athletes had greater indexed RV basal and mid-ventricular diameter, as well as greater RV end-diastolic and end-systolic area (Table). Athletes had greater VO2 max.

Conclusion: Increasing attention is being paid to the potential consequences of the remodeling seen in the heart of endurance athletes. This study supports the notion that cardiac changes are occurring as early as in preadolescent athletes, and that RV function might be key in evaluating and monitoring this growing population.

Risk factors for atrial fibrillation at the age of 40 years: 24-year follow-up data from the Norwegian Age 40 program and the Akershus cardiac examination (ACE) 1950 Study

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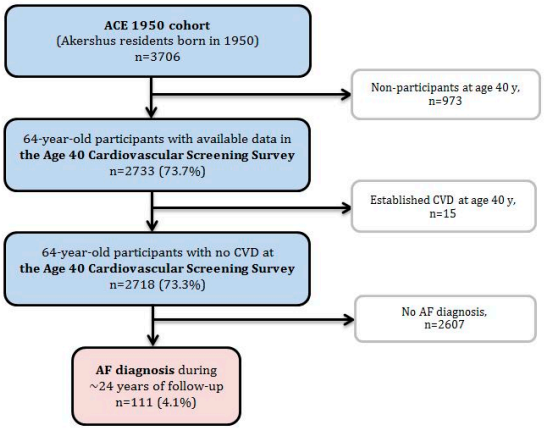
On behalf: ACE 1950 study group

	Univariate OR (95% CI)	p	Multivariate OR (95% CI)	p
Male sex	3.31 (2.13–5.14)	<0.001	0.79 (0.39–1.59)	0.51
Height per 10 cm	2.30 (1.84–2.89)	<0.001	2.32 (1.64–3.27)	<0.001
BMI, per unit	1.14 (1.08–1.19)	<0.001	1.15 (1.08–1.23)	<0.001
Systolic BP, per 10 mmHg	1.38 (1.22–1.57)	<0.001	1.27 (1.02–1.58)	0.03
Diastolic BP, per 10 mm Hg	1.37 (1.13–1.65)	0.001	0.86 (0.62–1.18)	0.33
Heart rate, per 10 beats/min increase	0.83 (0.71–0.98)	0.03	0.91 (0.76–1.08)	0.28
Triglycerides, per mmol/l increase	1.13 (1.01–1.25)	0.03	0.87 (0.71–1.07)	0.18
Total cholesterol, per mmol/l increase	1.18 (0.99–1.42)	0.07	1.05 (0.85–1.31)	0.65
Current daily smoking	0.65 (0.42–1.00)	0.05	0.78 (0.49–1.24)	0.29
1 first degree relative with AF	1.82 (1.18–2.81)	<0.01	1.97 (1.24–3.12)	<0.01
≥2 first degree relatives with AF	2.89 (1.28–6.50)	0.01	3.59 (1.51–8.54)	<0.01
Higher education	1.06 (0.72–1.55)	0.77	–	
Physical activity (low/medium as ref.)				
Inactive	0.93 (0.56–1.54)	0.77	–	
High level of physical activity	1.79 (0.63–5.06)	0.27	–	

Risk factors for prevalent AF Variables with p<0.20 in univariate logistic regression analysis are included in the multivariate analysis.



Flow chart

Background: Identification of early adulthood risk factors for atrial fibrillation (AF) is important to improve primary prevention. Various measures of body size, most importantly body mass index (BMI), have been associated with increased risk for AF. In this study, we evaluated the association between known AF risk factors at age 40 years and prevalent AF at age 64 years.

Methods: The Akershus Cardiac Examination (ACE) 1950 Study was conducted between 2013 and 2015. All women and men born in 1950 in Akershus county, Norway, were invited to undergo an extensive cardiovascular examination at age 64 years. In total, 3,706 individuals (48.8% women) participated in the study. Among these, 2,733 (73.7%) had been examined 24 years earlier, at the Age 40 Cardiovascular Screening Survey. We excluded fifteen individuals, who had known cardiovascular disease at age 40. Self-reported AF was validated with electrocardiograms or review of hospital records. Multivariate logistic regression models were constructed to assess independent risk factors associated with prevalent AF.

Results: Prevalent AF at age 64 years was identified in 4.1% (women 2.0%, men 6.2%; p<0.001). Independent risk factors associated with prevalent AF are presented in Table.

Conclusion: Family history of AF and increased body height, BMI and systolic blood pressure, at the age of 40 years, are associated with increased risk of prevalent AF at age 64. Any effect of preventive measures in early adulthood should be studied in specifically designed studies.

Cardiac remodelling in preadolescent endurance athletes assessed by traditional and three-dimensional echocardiography

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On behalf: Center for Cardiac Innovation

Background: Athlete's heart (AH) is a term used to describe exercise-induced cardiac remodelling in athletes. Recent studies suggest that these changes may occur even in preadolescence, but little is known of the initial morphological changes.

Purpose: This study aims to further describe the early morphological and functional changes in the hearts of endurance athletes by examining the hearts of preadolescent athletes

Table 1

	Athletes (n=76)	Controls (n=25)	P-value
VO_2 max indexed, mL/kg/min	62±7	44±5	<0.001
IVSd, mm	8±1	7±2	<0.05
LVIDd/BSA, mm/m²	21±3	18±2	<0.001
LVPWd, mm	7±1	6±1	<0.05
2D LV Mass/BSA, g/ m²	69±12	57±13	<0.001
3D LV EDV/BSA, mL	75±7	70±6	<0.01
3D LV ESV/BSA, mL	33±4	30±4	<0.01
3D LV Mass/BSA, g/m²	69±6	64±7	<0.01
Relative wall thickness	0.35±0.05	0.29±0.07	<0.001
LV ejection fraction, %	58±3	58±3	1.00

Data expressed as mean ± SD. Right column shows P-values for Student's t-test. BSA, body surface area; EDV, end-diastolic volume; ESV, end-systolic volume; IVSd, interventricular septum in diastole; LV, left ventricular; LVIDd, left ventricular internal diameter in diastole; LVPWd, left ventricular posterior wall in diastole; RWT, relative wall thickness

using traditional and three-dimensional (3D) echocardiography.

Methods: Seventy-six cross-country skiers aged 12.1±0.2 years were compared to a control group of 25 non-competing individuals aged 12.1±0.3 years. Echocardiography was performed in all subjects, including 3D acquisitions of the left ventricle (LV). Relative wall thickness (RWT) was calculated by multiplying the LV posterior wall by two and dividing it by the LV internal diameter.

Results: The cross-country skiers had a significantly greater indexed VO2 max, septal thickness, posterior wall thickness and LV mass (Table). Athletes also had greater indexed LV diameters and higher RWT. Ejection fraction did not differ between the two groups.

Conclusion: Athletes had greater LV mass and LV chamber volumes, and also higher RWT compared to the controls. This supports the notion that there is early physiological, adaptive remodelling in preadolescent athlete's heart. Furthermore, remodelling in preadolescent athletes seems to be primarily concentric in nature.

High aortic stiffness and myocardial ischemia in non-obstructive coronary artery disease (the MicroCAD project)

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Background: High aortic stiffness may reduce myocardial perfusion pressure and contribute to development of myocardial ischemia. Whether high aortic stiffness is associated with myocardial ischemia in patients with stable angina and non-obstructive coronary artery disease (CAD) is less explored.

Purpose: Assess if high aortic stiffness is associated with myocardial ischemia in patients with stable angina and non-obstructive CAD.

Methods: We assessed aortic stiffness as carotid-femoral pulse wave velocity (PWV) by applanation tonometry in 125 patients (62±8 years, 58% women) with stable angina and non-obstructive CAD participating in the Myocardial Ischemia in Non-obstructive CAD (MicroCAD) project. Non-obstructive CAD and coronary calcium score were assessed by coronary computer tomography angiography. Patients were grouped in PWV tertiles, and the highest tertile (>8.7 m/s) was taken as high aortic stiffness. Stress induced myocardial ischemia was detected as delayed contrast replenishment by myocardial contrast stress echocardiography. The number of left ventricular (LV) segments with delayed contrast replenishment was regarded as the extent of ischemia.

Results: Patients with high aortic stiffness were older with higher LV mass index and lower prevalence of obesity (all p<0.05), while there were no difference in symptoms, sex, prevalence of hypertension, diabetes, smoking, lipid profile, LV ejection fraction or coronary artery calcium

Table 1. Covariables of stress induced myocardial ischemia in multivariable logistic regression analysis

	Odds ratio	95% Confidence interval	p-value
High aortic stiffness	3.41	1.36–8.55	0.009
Age (years)	1.02	0.97–1.07	0.504
Left ventricular mass index (g/m²)	1.05	1.00–1.10	0.037
Obesity	2.50	0.97–6.42	0.057

score. Stress induced myocardial ischemia was more common (46% vs. 19%, p=0.001) and the extent of ischemia was larger (4±3 vs. 2±3 LV segments, p=0.005) in patients with high aortic stiffness. In multivariable logistic regression analysis, high aortic stiffness was associated with stress induced myocardial ischemia independent of age, LV mass index and obesity (Table).

Conclusions: In patients with stable angina and non-obstructive CAD, high aortic stiffness was associated with stress induced myocardial ischemia. This suggests that assessment of aortic stiffness may add to the diagnostic evaluation in patients with non-obstructive CAD.

Multimodality prediction of life-threatening ventricular arrhythmia in patients with arrhythmogenic cardiomyopathy; a prospective cohort study

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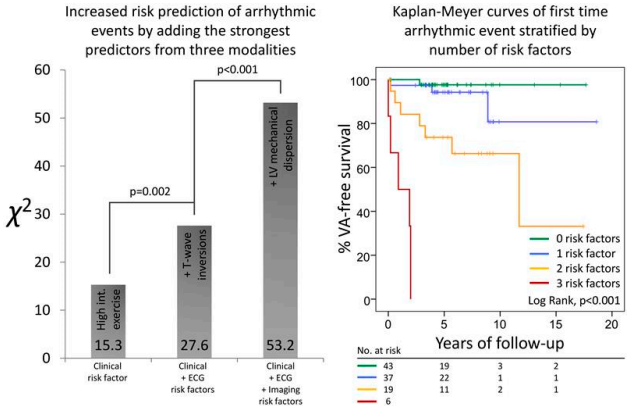
Background: Electrocardiogram (ECG) and cardiac imaging play key roles in the diagnostic criteria for arrhythmogenic cardiomyopathy (AC), but their roles in risk stratification of patients presenting without life-threatening ventricular arrhythmia are unclear.

Purpose: To identify predictors of first-time life-threatening ventricular arrhythmia by assessing clinical characteristics, ECG and cardiac imaging in a prospective cohort study of patients with AC.

Methods: We included consecutive AC probands and mutation positive family members with no previous life-threatening arrhythmic events, and followed them prospectively from time of diagnosis. The endpoint was the first life-threatening ventricular arrhythmia, defined as aborted cardiac arrest, appropriate ICD-shock or sustained ventricular tachycardia. At baseline, we assessed possible risk predictors from three categories; (1) clinical parameters, (2) ECG and (3) cardiac imaging (echocardiography and cardiac magnetic resonance imaging) according to the Task Force Criteria of 2010. In addition to traditional imaging criteria, we assessed left ventricular (LV) and echocardiographic strain parameters. LV mechanical dispersion was defined as the standard deviation of time from onset Q/R on ECG to peak negative strain in 16 LV segments. We recorded exercise habits, and defined high intensity exercise as >6 metabolic equivalents.

Results: We included 117 patients (29% probands, 50% female, age 40±17 years). During 4.2 (IQR 2.4 to 7.4) years of follow-up, 18 (15%) patients experienced life-threatening ventricular arrhythmia. The 1, 2 and 5 year incidence was 6%, 9% and 22%, respectively. History of high intensity exercise was the strongest clinical predictor, T-wave inversions ≥V3 was the strongest ECG predictor and greater LV mechanical dispersion by echocardiography was the strongest predictor from cardiac imaging (adjusted HR; 4.9 [95% CI 1.3–18.3], p=0.02, 5.8 [95% CI 2.1–16.1], p=0.001, and 1.4 [95% CI 1.2–1.6] by 10 ms increments, p<0.001, respectively). These parameters had incremental risk predicting value (Figure, left panel). Arrhythmia free survival in patients with all three risk factors was only 1.2 (95% CI 0.4–1.9) years, compared to 17.4 (95% CI 16.6–18.2) years in patients without any risk factors (Figure, right panel).

Conclusions: History of high intensity exercise, T-wave inversions ≥V3 on ECG and greater echocardiographic LV mechanical dispersion were strong and independent predictors of life-threatening ventricular arrhythmias. AC patients without any of these risk factors had minimal arrhythmic risk, while having more than one risk factor increased the risk dramatically. This may guide decisions on primary preventive ICD implantation in these patients.



Risk prediction model

Neutrophil extracellular traps (NETs) assessed by dsDNA and PAD4 mRNA in patients with ST-elevation myocardial infarction are associated with plasma glucose

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Background: Neutrophil extracellular traps (NETs) have recently been acknowledged to be implicated in atherothrombosis, holding proinflammatory and -thrombotic properties. An early event during NETs release is decondensation of nuclear chromatin by the enzyme peptidylarginine deiminase (PAD4). NETosis is suggested to be glucose dependent, but whether this is also the case in coronary artery disease (CAD) is unclear.

Purpose: Assess whether plasma glucose associate with the NETs marker double stranded DNA (dsDNA) in the acute phase and in a stable state after 3 months in patients with acute ST-elevation myocardial infarction (STEMI). Secondly, investigate whether an acute glucose load by an oral glucose tolerance test (OGTT) leads to upregulated NETosis by evaluation of dsDNA and PAD4 mRNA levels.

Methods: In this prospective observational cohort, 224 patients with STEMI treated with primary percutaneous coronary intervention (PCI) were included. Blood samples were collected in the acute phase (median 16.5 hours after PCI) and after 3 months at the time of performing the OGTT. Glucometabolic status was defined as normal glucose tolerance, impaired fasting glucose, impaired glucose tolerance or type 2 diabetes mellitus in the acute phase and after 3 months. DsDNA was measured in serum by Quant-iT Picogreen dsDNA, while PAD4 mRNA was measured in circulating leukocytes (PAXGene tubes) by RT-PCR with relative quantification (RQ).

Results: Levels of dsDNA were significantly higher in the acute phase than after 3 months (395 (344, 438) vs. 339 (313, 376) ng/ml, p<0.01) and correlated significantly to plasma glucose at both times (r=0.12–0.17, p<0.02, both). Glucometabolic status did not affect dsDNA levels at any time. During the course of OGTT, dsDNA remained unchanged (339 (313, 376) vs. 337 (308, 372) ng/ml, p=0.39) while PAD4 mRNA increased significantly (RQ 0.836 (0.620, 1.070) vs. 0.920 (0.670, 1.226), p=0.02). DsDNA and PAD4 mRNA levels did not correlate at any times.

Conclusions: In this cohort of patients with STEMI, plasma glucose associated significantly with levels of dsDNA both in the acute phase and after 3 months. The acute glucose load by an OGTT at 3 months led to increased PAD4 mRNA levels suggestive of enhanced NETosis. However, this was not reflected in corresponding dsDNA levels, possibly due to a delayed time course of NETs release.

Reference values for automatic measurements of tissue doppler indices

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Background: Tissue Doppler imaging is widely used to quantify global left ventricular (LV) longitudinal function. We have developed an algorithm that automatically measures the mitral annular peak velocities in systole (S'), early diastole (e') and late diastole (a'). This algorithm can be implemented on most available echocardiographic scanners, and also future handheld scanners. Automatic measurements and interpretation of findings can speed up work flow for cardiologists and assist inexperienced users when evaluating LV function. Normal reference values of automatic measurements are needed.

Purpose: To estimate age- and gender-specific reference values of the automatic measurements.

Methods: The study population included 1032 Caucasian volunteers (53% females, mean age (standard deviation (SD)) 49 (14) years), all free from cardiovascular disease, hypertension and

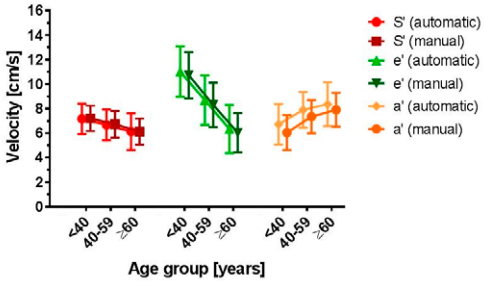

Figure 1. Error bars indicate standard deviations.

Table 1. Reference values for automatic measurements of tissue Doppler indices

	Females (n=547)			Males (n=485)		
Index	**<40 y**	**40–59 y**	**≥60 y**	**<40 y**	**40–59 y**	**≥60 y**
S' [cm/s]	7.0 (1.2)	6.6 (1.1)	6.0 (1.6)	7.4 (1.2)	6.8 (1.4)	6.3 (1.4)
e' [cm/s]	11.1 (2.1)	9.0 (2.0)	6.7 (2.2)	10.9 (2.0)	8.4 (2.0)	6.0 (1.7)
a' [cm/s]	6.6 (1.7)	7.9 (1.5)	8.1 (2.0)	6.8 (1.7)	7.9 (1.4)	8.6 (1.6)

Data are presented as mean (standard deviation). Abbreviations: S' = mitral annular peak systolic velocity, e' = mitral annular peak early diastolic velocity, a' = mitral annular peak late diastolic velocity, y = years.

diabetes. An experienced cardiologist examined all patients conventionally using a high-end scanner. Apical four-chamber color tissue Doppler recordings were analyzed manually and by the automatic algorithm, and then compared. All measurements were calculated as the average of septal and lateral measurements from three cardiac cycles.

Results: Normal reference ranges (mean (SD)) are presented by gender and age in Table 1. Figure 1 shows automatic and manual measurements according to age. There was no significant interaction effect between gender and age on any of the automatic indices (all p≥0.21). There were highly significant differences by age. S' and e' were lower, and a' higher, with higher age (all p≤0.001).

Conclusion: Age influenced all indices considerably. The agreement between automatic and manual measurements is comparable to what has been shown in interobserver studies, which suggests that the automatic measurements could assist both experienced and inexperienced users.

Factors associated with prolonged increase in cardiac troponin following strenuous physical exercise in recreational athletes - a NEEDED 2014 sub-study

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Risk of prolonged cTn increase

	cTnI >26 ng/L (n=166)	p-value	cTnT >14 ng/L (n=292)	p-value
	Adjusted odds ratio (95% CI)		Adjusted odds ratio (95% CI)	
Race duration	0.59 (0.43–0.82)	0.002	0.43 (0.32–0.57)	<0.001
SBP	1.02 (1.01–1.03)	0.006	1.02 (1.01–1.03)	<0.001
BMI	1.07 (1.00–1.14)	0.048	1.07 (1.01–1.13)	0.015
Sex	1.52 (0.97–2.67)	ns	0.83 (0.50–1.38)	ns
Age	1.01 (0.98–1.03)	ns	1.01 (1.00–1.04)	ns
SCORE	1.00 (0.85–1.18)	ns	0.99 (0.85–1.15)	ns
LDL	1.17 (0.95–1.44)	ns	0.97 (0.81–1.16)	ns

Logistic regression analysis on the risk of having prolonged increase in cTn (>99th percentile of the assay) 24h after strenuous exercise. (SCORE = ESC risk score, BMI = body mass index, SBP = systolic blood pressure, LDL = low density lipoprotein, ns = non-significant).

On behalf: the North Sea Race Endurance Exercise Study Group (NEEDED)

Background: Cardiac troponins (cTn) concentrations increase following strenuous physical exercise, but usually return to normal range within 24 hours. Factors associated with prolonged release of cTn remains to be determined.

Purpose: To assess determinants of cTn above the 99th percentile 24h after strenuous exercise.

Methods: 991 healthy, recreational cyclists without CV treatment or known CV disease, who participated in a 91 km mountain bike race, were included in this analysis. Clinical status, blood samples, ECGs, blood pressure and demographics were obtained 24h prior the race, and at 3h and 24h after the race. Values are reported as median and interquartile range (IQR).

Results: Subjects were: 46.7 (40.1–52.4) years old, 774 (78.1%) males. Race duration: 3.8 (3.4–4.3) hours. At 3h after the race 831 subjects (83.9%) had cTnI values above the 99th percentile of the assay (26 ng/mL), and 914 (92.2%) subjects had cTnT values above the 99th percentile of the assay (14 ng/mL). At 24h after the race 166 (16.8%) still had cTnI values above the 99th percentile, and 292 (29.5%) had cTnT values above the 99th percentile. Multiple logistic regression analysis found lower race duration (cTnI: p=0.002, cTnT: p<0.001), higher systolic blood pressure at baseline (cTnI: p=0.006, cTnT: p<0.001) and higher body mass index (cTnI: p=0.048, cTnT: p=0.015) to increase the probability of prolonged elevation of cTn (>99th percentile of the assay) at 24h after the race (Table).

Conclusion: Higher blood pressure, higher body mass index, and a high degree of physical strain were associated with prolonged increase of cTn after strenuous exercise. The clinical implications of this finding remain to be determined.

A new score for assessing bleeding risk in patients with atrial fibrillation treated with NOACs

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Background: Atrial fibrillation (AF) significantly increases the risk of embolic

stroke and death. Treatment with oral anticoagulants (OAC) effectively reduces risk of stroke, but this effect comes at a cost of significantly increased risk of bleeding. Non-vitamin K oral anticoagulants (NOACs) are gradually replacing vitamin K antagonists as the drugs of choice. Studies on risk factors for bleeding have mainly been performed on warfarin- treated patients. In the current era, information is needed on bleeding risk factors specifically for patients on NOACs.

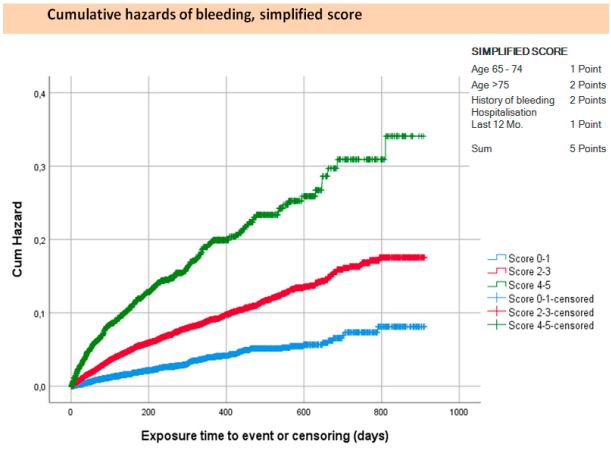
Purpose: The aim of this study was to identify risk factors for bleeding in patients with atrial fibrillation being treated with NOACs, and to create a simple bedside tool to assess bleeding risk in these patients.

Methods: Using nationwide registries (Norwegian Patient Registry and Norwegian Prescription Database), we identified AF patients with a first prescription of a NOAC between January 2013 and June 2015. Patients were followed until discontinuation or switching of oral anticoagulants, death, or end of follow-up (June 30, 2015). The primary endpoint was major or clinically relevant non-major (CRNM) bleeding. Cox proportional hazards analyses were used to identify risk factors for bleeding, and a bleeding score was developed based on the ten strongest risk factors.

Results: A total of 21 248 patients were included in the cohort; 7925 were treated with dabigatran, 6817 with rivaroxaban, and 6506 with apixaban. The median age was 73 years and 57.4% of patients were male. After a median follow-up time of 183 days, 1257 (5.9%) patients experienced a major or CRNM bleeding. The strongest prediction model included the variables age, male sex, history of stroke/TIA, history of bleeding, history of anaemia, hypertension, heart failure, non-bleeding related hospitalisation within the last 12 months, chronic kidney disease, and chronic obstructive pulmonary disease, and showed good discriminative ability, with a Harrell's c – index of 0.68. A bleeding risk score was then created with weights proportional to the model coefficients. From our cohort we also calculated a modified HAS-BLED score, which achieved a c - index of 0.59.

A simplified score was finally derived from the full score, including only age, history of bleeding, and non-bleeding related hospitalisation within the last 12 months, that reached a Harrell's c – index of 0.66.

Conclusions: In this nationwide cohort study of real-life AF patients being prescribed NOACs, a bleeding risk score was created that showed a high c- index, requiring no blood sampling or imaging for its calculation. The simplified version of the bleeding risk score would help clinicians quickly assessing bleeding risk bedside, aiding in planning anticoagulation in patients with AF.



Simplified Bleeding Score

Circulating notch ligand DLL1 is elevated in pulmonary hypertension and associated with mortality

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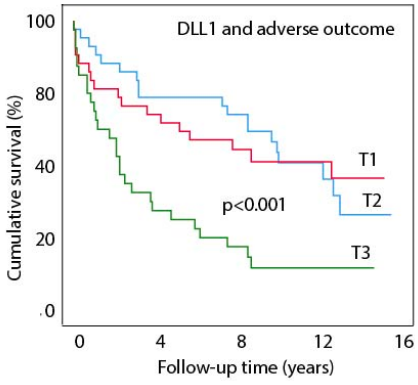
Introduction: Pulmonary arterial hypertension (PAH) is characterised by increased proliferation of smooth muscle cells in small pulmonary arteries, increased pulmonary vascular resistance and right heart failure, which may lead to death. The Notch signalling system, which consists of four Notch receptors (Notch 1–4) and five ligands (Jagged 1 and 2, Delta-like ligand 1, 3 and 4) promotes the development of PAH experimentally and has been shown to be activated in clinical PAH. Circulating Delta-like Notch ligand 1 (DLL1) is elevated in chronic heart failure, associated with disease severity and adverse outcome, but little is known about circulating DLL1 in PAH.

Purpose: We wanted to study DLL1 in clinical PAH and hypothesised that circulating DLL1 would be regulated and associated with disease severity and outcome.

Methods: We measured plasma DLL1 by enzyme immunoassay in a prospectively recruited cohort of 100 adult patients (mean age 48 yrs, 31% men) referred to our tertiary hospital for evaluation of pulmonary hypertension. DLL1 levels were determined in samples achieved from the pulmonary artery by right heart catheteriza-

tion and from puncture of the femoral artery. Association with adverse outcome (death or transplantation, median follow-up 7.4 yrs, 62% with outcome) was assessed by multivariable Cox-regression adjusting with the strongest demographic (age, gender), haemodynamic [pulmonary artery (AP) oxygen saturation, cardiac index] and biochemical (NT-proBNP) predictors of mortality.

Results: In PAH, no differences in DLL1 obtained from pulmonary or femoral artery were noted. Pulmonary levels are reported throughout. Plasma DLL1 was elevated in PAH (median 13.9 [IQR 11.6,17.5] ng/mL) compared to healthy controls (n=40, 11.8 [9.5,13.4] ng/mL, p<0.001) with particularly high levels in PAH related to risk factors or associated conditions (n=42, 15.9 [12.9,19.5] ng/mL compared to idiopathic (n=27, 12.4 [10.2,17.3] ng/mL, p=0.038) and thromboembolic (n=31, 13.8 [11.4,15.6] ng/mL, p=0.011). No correlations between DLL1 and clinical, haemodynamic, or biochemical measures were found. For the total study population, Kaplan-Meier analysis revealed a higher mortality in patients with DLL1 in the top tertile (>16.5 ng/mL). Evaluated as a continuous variable and expressed as log/SD gave a HR (95% CI) of 2.00 (1.47,2.69), p<0.001, which was unmodified in adjusted analysis (HR 2.00 [1.41,2.83] p<0.001).



Plasma DLL1 and outcome

DLL1 was a markedly stronger predictor compared to the other variables with a Wald-score of 15.2 compared to AP oxygen saturation as the second strongest predictor (Wald-score 10.8).

Conclusion: In pulmonary hypertension circulating DLL1 is elevated and associated with adverse outcome. DLL1 seems to reflect pathophysiology in PAH related to poor prognosis not mirrored by conventional measures. More research is needed to study DLL1 as a potential biomarker for pulmonary hypertension and the prognosis of the disease.

Left ventricle systolic dysfunction in young survivors after allogeneic haematopetic stem cell transplantation

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Introduction: Allogeneic haematopetic stem cell transplantation (allo-HSCT) is a potential curative therapy for young sufferers of hematological malignant and non malignant diseases. This intensive proceedure usually involves pretransplantation myeloablative chemotherapy and / or radiation therapy, both well documented to cause adverse effects to the heart. In addition, allo-HSCT patients are at risk of graft-versus-host-disease (GVHD).

Purpose: In the last decade there has been increasing awareness of heart related disease in survivors of cancer therapy. The main aim of this study is to describe the total burden of the cardiovascular late effects in young survivors of allo-HSCT.

Methods: This cross sectional, multidisciplinary survey was conducted between 2013 and 2016. The study included, 104 individuals, of whom 53.8% were female. Age at allo-HSCT was (mean±SD) 17.8±9.6 years. Age at follow-up was 35.0±11.7 years, and follow-up time from allo-HSCT was 17.2±5.6 years. The majority (98,1%) of individuals received myeloablative chemotherapy, 12.5% received radiation therapy and 1.9% received neither. Cardiovascular function was evaluated by comprehensive echocardiography (GE E9), including Speckle Tracking (2DSTE) and three dimensional echocardiography (3D). Left ventricular systolic dysfunction was defined by left ventricular ejection fraction (2D EF) ≤53% and Global Longitudinal Strain (GLS) ≤-17 (as recommended by the EACVI).

Results: LV systolic dysfunction defined by either by 2D EF ≤53% or GLS≤-17 or both was observed in 48.1%. The average 2D EF was 55.2±5.8%. 2D EF ≤53% was found in 35.6% of patients. Evaluation with GLS gave an average of -17.5±2.2% and 32.7% of the patients had a GLS ≤-17%. In 21.2%

2D EF	2D LVEDV index	2D LVESV index	3D EF	Fractional shortening	LVIDd index	GLS mean
%	(ml/m²)	(ml/m²)	%	%	(cm/m²)	%
55.2±5.8	63.1±13.9	28.6±8.5	54.0±5.0	30.6±5.7	2.7±0.32	-17.5±2.2

of the patients, a combination of GLS ≤-17% and 2D EF ≤53% was found.

Conclusion: Left ventricle systolic dysfunction is highly prevalent in long term survivors after allo-HSCT. These patients may be asymptomatic and unaware of their potential risk. Monitoring and screening regimes including echocardiography are important in allo-HSCT patients to ensure early detection of heart disease, early medical intervention and prevention against progressive heart failure.

Neutrophil extracellular traps are associated with myocardial injury, left ventricular function and future adverse clinical events in patients with ST-elevation myocardial infarction

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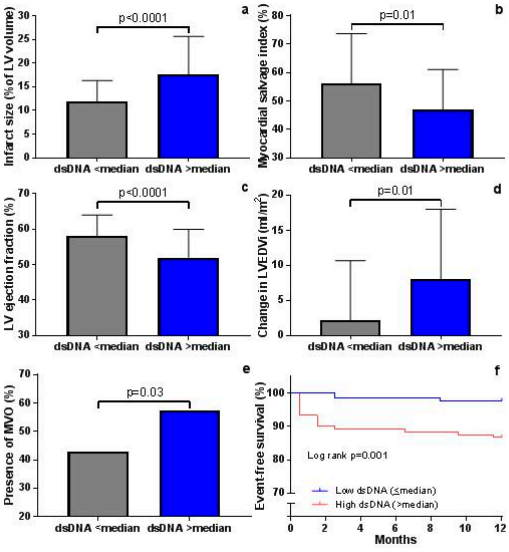
Background: Neutrophil extracellular traps (NETs) are complex structures of nuclear chromatin and cellular proteins released from neutrophils following activation or apoptosis, and are thought to have prothrombotic properties. Experimental models have implicated NETs in ischaemia-reperfusion (IR) injury. Very little is known about the role of NETs in myocardial infarction (MI), but both high levels of circulating NETs and increased burden of NETs in coronary thrombi have been reported to be associated with larger infarct size in patients with ST-elevation MI (STEMI).

Purpose: We hypothesized that NETs measured in the acute phase of STEMI are associated with IR-injury, infarct size and left ventricular (LV) function, and used serial measurements of the NETs marker double-stranded DNA (dsDNA) as well as repeated cardiac magnetic resonance imaging (CMR), to evaluate: 1) the temporal profile of dsDNA during STEMI, 2) possible associations between dsDNA and microvascular obstruction (MVO), myocardial salvage, infarct size, and LV function and remodeling, and 3) possible associations with adverse clinical events.

Methods: 258 patients with first-time STEMI, treated with primary percutaneous coronary intervention (PCI) were included. Blood samples for measurement of dsDNA were drawn before and immediately after the PCI procedure, at Day 1 and at 4-month follow-up. dsDNA was quantified in serum by use of a fluorescent nucleic acid stain. CMR was performed in the acute phase and after 4 months. Clinical events were registered during 12 months' follow-up.

Results: There was a gradual and significant decrease in dsDNA levels from admission to Day 1 with a subsequent decline to 4-month follow-up. Patients with high (>median) levels of dsDNA measured at Day 1 had significantly higher frequency of MVO in the acute phase, and larger final infarct size, decreased myocardial salvage, lower LV ejection fraction (LVEF), and larger increase in indexed LV end-diastolic volume (LVEDVi) at 4-month follow-up, compared to patients with low levels of dsDNA (Figure 1, panels a-e). In multivariable linear regression analyses dsDNA remained associated with infarct size, LVEF, myocardial salvage and change in LVEDVi after adjustment for relevant clinical variables, but not after adjustment for peak troponin T. A total of 19 adverse clinical events were registered during 12 months of follow-up.



Patients with high levels of dsDNA at Day 1 had significantly more adverse events compared to patients with low levels (Figure 1, panel f). No significant associations were observed between dsDNA levels measured during PCI and at 4-month follow-up, and the different outcome variables determined by CMR or adverse clinical events.

Conclusions: High circulating levels of dsDNA measured the following day after admission with STEMI were associated with MVO, large infarct size, decreased myocardial salvage, LV remodelling and adverse clinical outcome.

Combining the European Society of Cardiology troponin algorithms and HEART Score for ruling out acute coronary syndrome in unselected patients presenting with acute chest pain: The WESTCOR study

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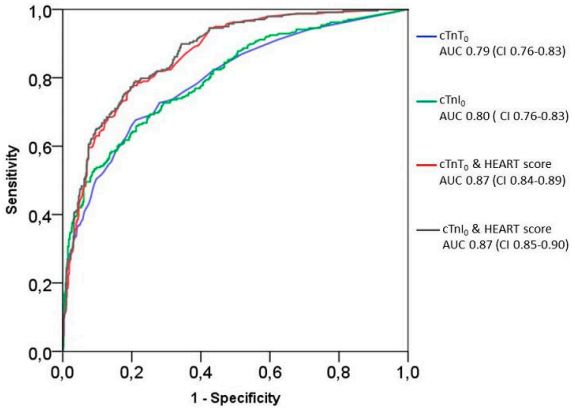
Background: If not interpreted in a correct clinical context, the ESC troponin algorithms for ruling out NSTEMI may potentially rule out patients with NSTE-ACS.

Purpose: To assess the diagnostic accuracy of the ESC rule out algorithms combined with a standardized clinical judgement (HEART-Score) for NSTE-ACS patients in the Emergency Department.

Methods: 990 patients with suspected NSTE-ACS were consecutively included from Sept. 2015 to Feb. 2017. Serum samples were collected at 0 (cTn0), 1 (n=481; results were not reported to clinical care), 3 and 8–12 hours. The final diagnosis was adjudicated by two independent cardi



Effects of statin treatment on coronary plaques in patients with inflammatory joint diseases

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Background: Statins have an established preventive effect on coronary artery disease in the general population, but the statin effect on coronary plaque progression in patients with inflammatory joint diseases (IJD) is unknown.

Purpose: Our aim was to evaluate the change in coronary atherosclerosis in long-term statin-treated patients with IJD.

Methods: Sixty-eight patients with IJD and carotid artery plaque, underwent coronary computed tomography angiography before and after 4.7 (range 4.0–6.0) years of statin treat-

Table 1

	NSTEMI	UAP	Non-ACS cardiac disease	Non-cardiac chest pain	Other diseases	Total
Complete Cohort	N=130	N=110	N=79	N=574	N=97	N=990
cTnT <5 ng/L	2 (1.5)	19 (17.3)	6 (7.6)	246 (42.9)	28 (28.9)	301 (30.4)
cTnI <2 ng/L	3 (2.3)	10 (9.1)	3 (3.8)	189 (32.9)	18 (18.6)	223 (22.5)
cTnT <5 ng/L & HEART Score ≤3	1 (0.8)	5 (4.5)	5 (6.3)	212 (36.9)	23 (23.7)	246 (24.8)
cTnI <2 ng/L & HEART Score ≤3	1 (0.8)	3 (2.7)	2 (2.5)	151 (26.3)	13 (13.4)	170 (17.2)
1 Hour Cohort	N=67	N=56	N=30	N=283	N=45	N=481
cTnT*	1 (1.5)	32 (57.1)	8 (26.7)	243 (85.9)	28 (62.2)	312 (64.9)
cTnI**	1 (1.5)	31 (55.4)	6 (20.0)	212 (75.2)	19 (42.2)	269 (55.9)
cTnT* & HEART Score ≤3	1 (1.5)	3 (5.4)	3 (10.0)	178 (62.9)	19 (42.2)	204 (42.4)
cTnI** & HEART Score ≤3	1 (1.5)	3 (5.3)	1 (3.3)	154 (54.4)	10 (22.2)	169 (35.1)

**cTnT0 <5 ng/L or cTnT0 <12 ng/L and Δ0–1h <3 ng/L. **cTnI0 <2 ng/L or cTnI0<5 ng/L and Δ0–1h <2 ng/L.*

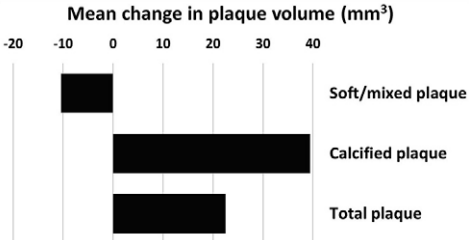
LDL-c goal and change in plaque

	LDL-c <1.8 mmol/L	LDL-c >1.8 mmol/L	p-value
	n=34	n=34	
LDL-c baseline, mean ± SD	3.7±0.9	4.4±1.0	<0.01
LDL-c follow-up, mean ± SD	1.5±0.2	2.4±0.7	<0.01
Change in LDL-c, mean ± SD	-2.2±0.9	-1.9±1.3	0.38
Change in Calcium score, median (IQR)	21 (2, 143)	69 (16, 423)	<0.01
Change in soft/mixed plaque, median (IQR)	0 (-3.5, 0.0)	0 (-15.7, 0.0)	0.71
Change in calcified plaque, median (IQR)	1.7 (0.0, 17.3)	13.4 (1.5, 107.6)	0.02
Change in total plaque volume, median (IQR)	0.08 (-1.0, 13.9)	13.0 (0.0, 60.8)	0.02

LDL-c: low density lipoprotein cholesterol, SD: standard deviation, IQR: interquartile range.

ment. LDL-c goal was ≤1.8 mmol/L. Changes in coronary artery calcification (CAC) and coronary artery plaque volume (calcified, mixed/soft and total) were assessed using the 17-segment model of the American Heart Association. Linear regression analysis was used to identify predictors of atherosclerotic progression.

Results: Coronary plaques were present in 42% of the patients at baseline and in 51% at follow up. Mean CAC score increased with 173±284, calcified plaque volume with 39.4±78.3 mm^3



and total plaque volume with 22.8±54.6 mm^3 (p≤0.01, for all) (Figure). Mean mixed/soft plaque volume decreased with -10.4±27.5 mm^3 (p≤0.01). At follow-up, 51% of the patients had obtained LDL-c goal. Compared to patients above LDL-c target, patients with an LDL-c <1.8 mmol/L experienced reduced median progression of both CAC and total plaque volume (Table).

Conclusions: We revealed a progression of atherosclerotic plaque volume in statin-treated patients with IJD, mainly due to calcifications. However, soft, unstable plaques were reduced, probably as a result of an alteration in plaque composition from mixed/soft plaques into calcified plaques. Patients with recommended LDL-c levels at follow-up experienced a reduced atherosclerotic progression compared to patients with LDL-c levels above the treatment target. Our results support the importance of treatment to guideline recommended lipid targets in IJD patients.

Prediction of subclinical myocardial injury and left ventricular dysfunction: data from the Akershus Cardiac Examination (ACE) 1950 Study

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Background: Concentrations of cardiac troponin I (cTnI) are strongly associated with the risk of incident heart failure (HF) and myocardial infarction (MI) in the general population. The associations between cTnI, left ventricular structure and preclinical stages of left ventricular dysfunction do however remain unclear.

Methods: We measured cTnI with a high-sensitivity assay in 1237 women and 1157 men participating in the prospective observational ACE 1950 Study, which invited all subjects born in 1950 residing in Akershus county, Norway. All study participants were free from known coronary heart disease and underwent echocardiography at baseline. Analyses were performed on the

Table 1. Associations between cTnI and indices of left ventricular structure and function

		Odds ratio (95% CI)		
	Cardiac troponin I	Model 1	Model 2	Model 3
GLS (n=2394)	Continuous	1.14 (1.00–1.30)	1.23 (1.07–1.40)	1.18 (1.02–1.36)
	Sex specific cutoffs*	1.73 (1.12–2.69)	1.85 (1.18–2.88)	1.82 (1.14–2.89)
LVEF (n=2382; 1231 women)	Continuous	0.95 (0.82–1.09)	1.03 (0.89–1.20)	0.99 (0.84–1.17)
	Sex specific cutoffs*	1.15 (0.70–1.89)	1.28 (0.77–2.13)	1.23 (0.73–2.06)
LV mass (n=2370; 1223 women)	Continuous	1.35 (1.19–1.53)	1.50 (1.31–1.71)	1.49 (1.30–1.71)
	Sex specific cutoffs*	2.11 (1.38–3.23)	2.29 (1.49–3.53)	2.30 (1.29–3.56)

**cTnI ≥7.0ng/L for men and cTnI ≥4.7ng/L for women. Model 1, unadjusted. Model 2, adjusted for sex and age. Model 3, adjusted for sex, age, BMI, eGFR, total and HDL cholesterol, CRP, education, hypertension, diabetes mellitus and smoking status.*

upper sex specific deciles of global longitudinal strain (GLS) and left ventricular mass (LVm), and on the lower sex specific decile of left ventricular ejection fraction (LVEF).

Results: cTnI was measurable in 60.2% of study participants, and was positively associated with male sex, BMI, higher education, HDL cholesterol, and hypertension, and negatively associated with current smoking. Study participants exhibiting left ventricular dysfunction, as assessed by GLS, were more frequently older with higher body mass index and prevalent diabetes mellitus, as well as increased concentrations of CRP, fasting blood glucose, HbA1c, and triglycerides, and lower eGFR and concentrations of HDL cholesterol. In the total cohort, concentrations of cTnI were significantly associated with GLS (OR 1.14 [1.00–1.30]), and this association persisted also in multivariate analysis (OR 1.18 [1.02–1.36]). cTnI was also strongly associated with LVm, but not LVEF (Table).

Conclusion: Subclinical left ventricular dysfunction is associated with several indices of metabolic dysregulation. Concentrations of cTnI are strongly predictive of GLS and LVm but not LVEF. GLS may be an earlier and more specific marker of the subclinical left ventricular remodeling possibly preceding overt HF.

Classic mechanical dyssynchrony is rare in TAVR-induced left bundle branch block

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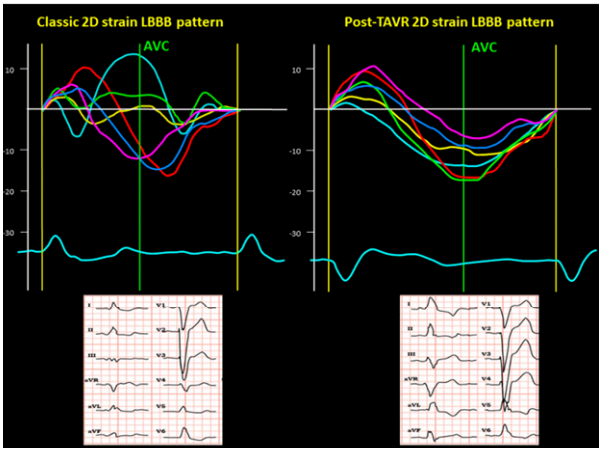
Background: Conduction abnormalities, especially left bundle branch block (LBBB), frequently complicate transcatheter aortic valve replacement (TAVR). Acute effects of altered conduction on ventricular mechanics after TAVR have not previously been described.

Purpose: We aimed to investigate how TAVR procedure related conduction abnormalities influence ventricular mechanics with particular focus on new-onset persistent LBBB.

Methods: Patients with severe aortic stenosis undergoing transfemoral TAVR were included in a repeated measures cross-sectional study. ECG and echocardiography with speckle tracking strain analysis were performed before and after the procedure. LBBB was defined by strict ECG criteria. Mechanical contraction patterns were assessed by longitudinal strain in apical 4-chamber view and classified as classical, dyssynchronous LBBB contraction pattern (Figure, left panel) or non-classical patterns.

Results: We included 140 consecutive patients undergoing TAVR (83±8 years old, 49% women) with severe AS (valve area 0.7±0.2 cm^2, mean pressure gradient 54±18 mmHg, peak velocity 4.5±0.7 m/s) and relatively preserved LVEF (52±11%). Compared to baseline, GLS improved after TAVR in all patients (-15.1±4.3 vs -16.1±3.9%, p<0.01, n=140), and all subgroups, regardless of, pre-existing (n=27) or procedure-acquired conduction abnormalities (n=32), including in the 28 patients with new-onset LBBB fulfilling strict ECG criteria (-14.5±3.9% vs -15.6±3.0%, p=0.03). Despite significant conduction delay in ECG, the vast majority of new-onset LBBB patients (n=26, 93%) had a non-classical homogenous contraction pattern with segmental synchronous peak shortening timed at aortic valve closure (AVC) and relatively sparse lateral wall pre-stretch (Figure, right panel). Classical dyssynchronous LBBB contraction pattern was only observed in 2 patients (7%) with new-onset LBBB.

Conclusions: Longitudinal function improved in all patients after TAVR, irrespective of conduction abnormalities. Classical dyssynchronous LBBB contraction pattern was absent in the majority of patients with new-onset post-TAVR LBBB, even when applying strict ECG criteria for LBBB. These findings raise a question of whether TAVR-induced LBBB may be functionally and prognostically different from traditional LBBB.



Increase in cardiac biomarkers during exercise stress test in patients with angiographically verified coronary artery disease

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Background: In stable patients with chest pain or angina equivalent symptoms, exercise stress test has a moderate sensitivity and specificity. Adding a reliable cardiac biomarker to the exercise test could potentially improve the accuracy of the test. We therefore compared the change of NT-proBNP and hs-cTnT during exercise stress test in patients with angiographically verified CAD and in those without CAD. We hypothesized that NT-proBNP and hs-cTnT would increase to a higher extent in CAD patients.

Method: In 297 patients presenting with symptoms suggestive of stable CAD, venous blood samples were taken at rest and within 5 min of termination of a maximal exercise stress test on a bicycle ergometer. All study participants underwent coronary angiography. Significant CAD was defined as having >75% stenosis in one or more segments of the coronary arteries. Patients included did not have clinical heart failure, arrhythmias, valvular disease or renal failure.

Results: Out of the 297 participants, significant CAD was found in 121 (41%) patients. The CAD and no CAD groups, were similar with regards to exercise duration and workload.

Baseline levels of NT-proBNP (74.18 vs 55.60 ng/L) and hs-cTnT (7.92 vs 4.98 ng/L) were significantly higher in patients with CAD compared to patients without CAD ($p=0.004$ and $p\leq0.001$ respectively). During exercise there was an increase in levels of both biomarkers in the total population ($p\leq0.001$ for both). The increase in NT-proBNP was not significantly different between the two groups (8.43 vs 9.18 ng/L, $p=0.389$). However, patients with CAD had a higher exercise induced increase in hs-cTnT compared to those without CAD (0.50 vs 0.27 ng/L, $p=0.005$).

Among patients with negative exercise test results (n=190), CAD was angiographically verified in 58 patients, yielding a false-negative rate of 20% in the total population. These patients had a significantly higher increase in hs-cTnT during exercise than the 132 patients without CAD and negative exercise test (0.58 vs 0.31ng/L respectively, $p=0.001$).

Conclusion: We found significantly higher baseline levels and almost a two-fold increase in hs-cTnT during exercise in patients with CAD compared to those without CAD. This was also true for patients with false-negative compared to true-negative exercise test results. Our results may indicate a beneficial value of taking exercise induced change in hs-cTnT, but not NT-proBNP, into account in diagnosis of CAD in patients suspected of stable CAD.

Inhibitory g protein and phosphodiesterases 3,4 regulate compartmentation of beta-1 and beta-2 adrenoceptor-evoked inotropic responses elicited through activation of either adenylyl cyclase 5 or 6

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Background: Both beta-1 and beta-2 adrenergic receptor (βAR) activation increases heart contractile force that is amplified by inactivation of inhibitory G protein (Gi), despite only the β2AR directly coupling with both Gi and stimulatory G protein (Gs). Our data suggest that intrinsic Gi activity constitutively inhibits adenylyl cyclase (AC) activity independent of receptor activation. Further, studies indicate that subcellular localization of the AC5/6 subtypes differs contributing to compartmentation of β1AR versus β2AR signaling.

Purpose: Determine: 1) if intrinsic Gi inhibition is AC subtype selective, 2) whether there is a differential role of AC5 and AC6 to mediate β1AR- and β2AR-evoked increases in contractile force of the heart and 3) the role of phosphodiesterases 3 and 4 (PDE3,4) to regulate β1AR and β2AR signalling and function.

Methods: We measured β1AR- and β2AR-mediated increases in contractile force in left ventricular muscle strips. cAMP levels were measured by radioimmunoassay or with a FRET biosensor in cardiomyocytes from wild type (WT), AC5 or AC6 knockout (KO) mice, with or without pertussis toxin (PTX) pretreatment to inactivate Gi and/or after selective inhibition of PDE3 or PDE4.

Results: Noradrenaline potency to evoke a β1AR-mediated inotropic response (IR) was increased in AC6KO versus WT and AC5KO. PDE4 inhibition significantly increased noradrenaline potency at β1AR in WT and AC5KO but not AC6KO, whereas PDE3 inhibition had a modest effect in all groups. PTX increased noradrenaline potency only in WT but increased the maximal IR in all groups. PTX also potentiated the effect of both PDE3 and PDE4 inhibition alone in WT and AC5KO only. β1AR-evoked cAMP levels were increased by PDE4 or Gi inhibition in WT and AC5KO. In contrast, PDE3 inhibition alone or in combination with Gi inactivation did not increase β1AR-evoked cAMP accumulation. An adrenaline-evoked β2AR-IR was observed only after combined PDE3,4 inhibition in WT and

AC5KO, whereas in AC6KO, PDE3 or PDE4 inhibition alone was sufficient. A β2AR-IR was also observed after PTX treatment in all groups.

Conclusion: These data are consistent with constitutive receptor independent Gi inhibition upon AC since PTX inactivation of Gi enhanced both β1AR and β2AR responses despite β1AR not coupling to Gi. The β1AR and β2AR can activate and elicit an IR through activation of either AC5 or AC6 indicating that neither receptor is dependent upon a specific isoform for its functional effect. PDE4 seems to be the primary PDE regulating the β1AR-IR when signaling through AC6. Inhibiting Gi and/or PDE3 and PDE4 synergistically enhances the ability of adrenaline to evoke a β2AR-IR. We propose β2AR-mediated signalling is so constrained by Gi and PDEs in mouse ventricle, eliciting a β2AR-IR requires a breakdown in compartmentation, with cAMP leaking into the β1AR "contractile compartment".

Left ventricular ejection fraction and adjudicated, cause-specific hospitalizations after myocardial infarction complicated by heart failure or left ventricular dysfunction

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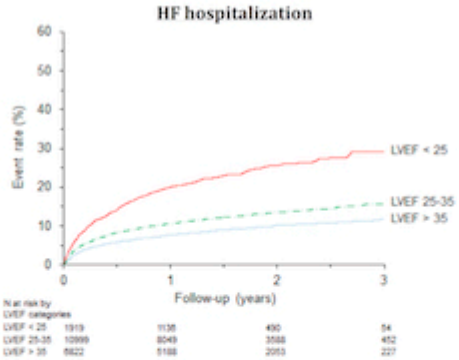
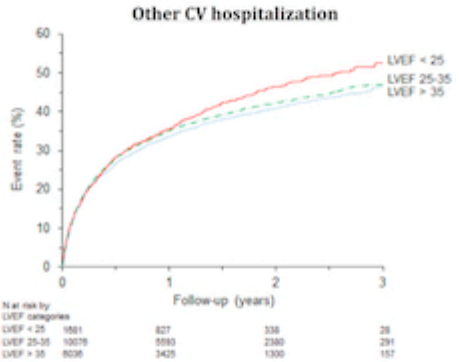
Introduction: Patients with heart failure (HF) or left ventricular (LV) dysfunction after acute myocardial infarction (AMI) are at high risk of subsequent hospitalization. Identifying prognostic factors for hospitalization may reduce morbidity and improve effective healthcare expenditure. Low LV ejection fraction (LVEF) is an established predictor of adverse outcome after AMI, but its ability to forecast cause-specific hospitalization in a high-risk population is less well defined.

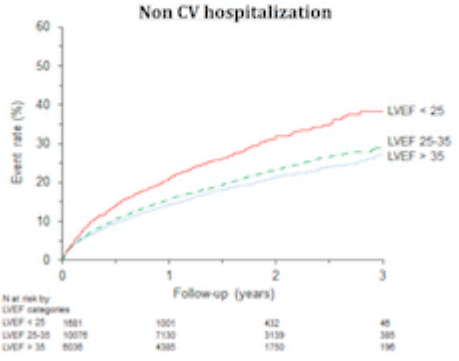
Purpose: We aimed to investigate the association between LVEF and adjudicated, cause-specific hospitalizations for HF, other cardiovascular (CV) and non CV causes in patients with a high risk for hospitalizations following complicated AMI.

Methods: In an individual patient data meta-analysis of three large randomized trials that included and followed subjects with high risk AMI (CAPRICORN, EPHESUS and VALIANT), Cox proportional hazards modeling was performed to study the association between LVEF sampled during the index AMI and the cause of subsequent hospitalizations during follow-up.

Results: 19,740 patients were included with a median follow-up of 707 (484–974) days, during which 2,368 HF hospitalizations, 6,952 other CV hospitalizations and 3,703 non CV hospitalizations occurred. The event rates for all types of







hospitalizations increased with decreasing LVEF (Figure 1). In multivariable models adjusted for age, gender, Killip class, systolic blood pressure, comorbidities (diabetes, hypertension, renal insufficiency, chronic obstructive pulmonary disease, peripheral artery disease), medication use (beta blockers, angiotensin converting enzyme inhibitors/angiotensin receptor blockers, diuretics), estimated glomerular filtration rate <60 mL/min/1.73m^2, hemoglobin and sodium, each 5-point decrease in LVEF was associated with a 22% increased risk of HF hospitalization (hazard ratio [HR] 1.22, 95% confidence interval [CI] 1.16–1.28), a 4% increased risk of other CV hospitalization (HR 1.04, 95% CI 1.01–1.08) and an 8% increased risk of non CV hospitalization (HR 1.08, 95% CI 1.04–1.13).

Conclusion: In a high-risk population following complicated AMI, LVEF was a strong and independent predictor of HF hospitalization, with a more modest ability to predict CV hospitalization and non CV hospitalization.

Prediction of subclinical atherosclerosis using an ultra-sensitive cardiac troponin I assay: data from the Akershus Cardiac Examination (ACE) 1950 Study

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Background: Concentrations of cardiac troponin I (cTnI) are strongly associated with risk of incident myocardial infarction (MI) in the general population, and this association is particularly pronounced in women. The association between cTnI and subclinical stages of atherosclerosis in men and women does however remain unclear.

Methods: We measured cTnI with a novel ultra-sensitive assay (us-cTnI) on the Singulex Clarity System in 1745 women and 1666 men participating in the prospective observational Akershus Cardiac Examination (ACE) 1950 Study, which invited all subjects born in 1950 residing in Akershus county, Norway. All study participants were free from known coronary heart disease and underwent extensive cardiovascular phenotyping at baseline, including carotid ultrasound (common-, external-, and internal carotid artery on both sides). Significant subclinical atherosclerosis was defined as being in the upper decile of quantitative carotid plaque burden.

Results: Concentrations of us-cTnI were measurable in 99.8% of study participants. Participants with subclinical atherosclerosis were more frequently male with prevalent hypertension, diabetes mellitus, and COPD, and more frequently current smokers without higher education. us-cTnI concentrations were also higher in this patient group (1.24 [0.79–1.94] vs. 1.01 [0.69–1.57] ng/L; p<0.001). In the total cohort, concentrations of us-cTnI were significantly associated with subclinical atherosclerosis (OR 1.34 [1.16–1.54]), this association was barely attenuated in multivariate analysis (OR 1.17 [0.99–1.39]). In separate sex specific analyses, no association with us-cTnI was found for women. For men, however, significant associations were found even in multivariate analyses (Table).

Conclusion: Cardiac troponin I measured with the us-cTnI assay is independently associated with subclinical atherosclerosis in men, but not in women.

Table 1. Associations between us-cTnI and subclinical atherosclerosis

		Odds ratio (95% CI)		
Cardiac troponin I		**Model 1**	**Model 2**	**Model 3**
Continuous	Both	1.34 (1.16–1.54)	1.19 (1.02–1.39)	1.17 (0.99–1.39)
	Female	1.14 (0.84–1.55)	1.14 (0.84–1.55)	1.05 (0.73–1.50)
	Male	1.22 (1.01–1.46)	1.21 (1.01–1.45)	1.22 (1.01–1.48)
Q4 vs Q1	Both	1.56 (1.08–2.25)	1.55 (1.07–2.25)	1.52 (1.02–2.25)
	Female	1.58 (0.85–2.94)	1.58 (0.85–2.94)	1.28 (0.66–2.49)
	Male	1.55 (0.98–2.46)	1.55 (0.98–2.46)	1.76 (1.07–2.92)

Model 1, unadjusted. Model 2, adjusted for sex (analysis for both sexes only) and age. Model 3, adjusted for sex (analysis for both sexes only), age, BMI, eGFR, total and HDL cholesterol, CRP, education, hypertension, diabetes mellitus and smoking status. Q, sex specific quartiles of us-cTnI.

High prevalence of known and unknown type 2 diabetes mellitus among middle-aged Norwegians: Data from the Akershus cardiac examination (ACE) 1950 study

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On behalf: ACE 1950 study group

Background: The prevalence of type 2 diabetes mellitus (T2DM) is increasing worldwide. More knowledge on the proportion of undiagnosed diabetes in the population may be useful for future prevention strategies. Accordingly; we aimed to

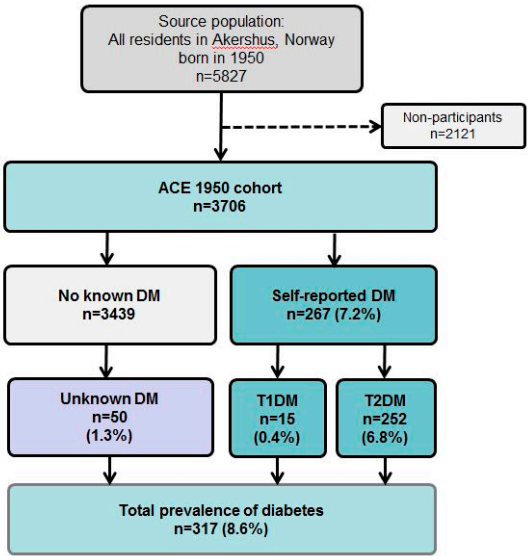
Risks associated with unknown T2DM

	Univariate OR (95% CI)	p	Multivariate OR (95% CI)	p
Male sex	2.90 (1.54–5.47)	0.001	1.92 (0.95–3.86)	0.07
Body mass index	1.17 (1.11–1.23)	<0.001	1.10 (1.04–1.17)	<0.01
Systolic blood pressure (per 10 mmHg)	1.22 (1.07–1.40)	<0.01	1.18 (1.01–1.38)	0.03
Fasting triglycerides	1.89 (1.56–2.29)	<0.001	1.45 (1.16–1.80)	0.001
HDL-cholesterol	0.08 (0.03–0.19)	<0.001	0.24 (0.08–0.69)	<0.01
History of CVD	0.75 (0.23–2.42)	0.63	–	
Impaired kidney function-	1.14 (0.27–4.74)	0.86	–	
Daily smoking	0.82 (0.35–1.93)	0.65	–	
Higher education	0.75 (0.42–1.32)	0.32	–	
Sedentary lifestyle	1.76 (0.94–3.29)	0.08	1.18 (0.61–2.29)	0.63
1 first degree relative with diabetes	2.99 (1.62–5.51)	<0.001	2.62 (1.39–4.95)	<0.01
≥2 first degree relatives with diabetes	10.54 (4.41–25.17)	<0.001	9.31 (3.63–23.88)	<0.001

All variables with p<0.20 in univariate analyses are included in the multivariate analysis.

report prevalence of known and unknown T2DM, as well as risk factors associated with unknown T2DM, in a middle-aged Norwegian population.

Methods: All women and men born in 1950, residing in Akershus county, Norway, were invited in the Akershus Cardiac Examination (ACE) 1950 study. All participants underwent a clinical examination including fasting blood glucose (FBG) and HbA1c. Known T2DM was defined as self-reported history of T2DM or daily use of antidiabetic drugs, and unknown T2DM was defined as the absence of any of these combined with FBG ≥7.0 mmol/L and HbA1c ≥6.5%. Risk factors associated with unknown T2DM were assessed by multivariate logistic regression.



Flow chart

Results: A total of 3706 among 5827 eligible subjects were included. Mean age was 63.9±0.7 years, 48.8% were women. Known diabetes was reported in 7.2% (9.6% men, 4.6% women; p<0.001). Unknown T2DM was found in 1.3% (1.9% men, 0.7% women; p=0.001), and the total prevalence of diabetes was 8.6% (11.6% in men, 5.4% women; p<0.001). Variables associated with unknown T2DM are presented in Table.

Conclusion: In a contemporary Norwegian population cohort aged 64 years, we identified a considerable proportion of previously unknown T2DM in both sexes, but particularly in men. Elevated BMI, systolic blood pressure, triglycerides, low HDL-cholesterol and a family history of diabetes were associated with unknown T2DM.

Estimation of filling pressure by E/e' in left bundle branch block: why is it so difficult?

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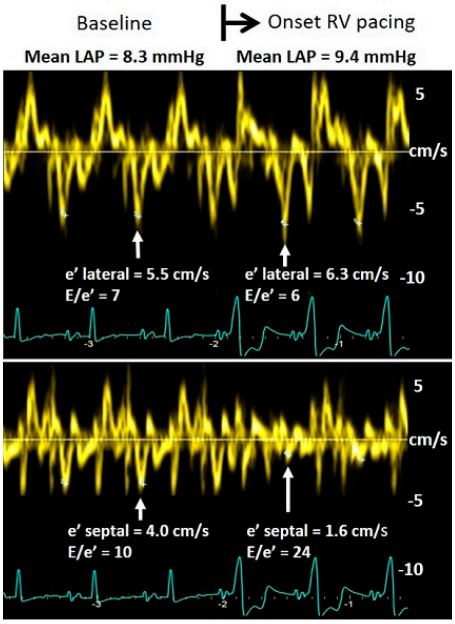
Introduction: Current guidelines recommend the ratio between early-diastolic mitral flow velocity and mitral annular velocity (E/e') as a key parameter for noninvasive estimation of left ventricular (LV) filling pressure. It is debated, however, if E/e' should be used in patients with left bundle branch block (LBBB).

Purpose: To determine how LBBB modifies the relationship between E/e' and LV filling pressure.

Methods: Heart failure patients with wide QRS due to LBBB or right ventricular (RV) pacing (n=13) were compared to heart failure patients with narrow QRS (n=82). Mitral annular velocities were measured at septal (e'septal) and lateral (e'lateral) locations, and average (e'average) was calculated. LV filling pressure was measured as pulmonary capillary wedge pressure (PCWP). In 6 anaesthetized dogs we induced LBBB activation pattern by RF ablation and by RV pacing, measured pressures by micromanometers and E and e' by echocardiography.

Results: In heart failure patients with narrow QRS there was good correlation between E/e' and PCWP with r values 0.54 and 0.46, for e'average and e'septal, respectively (p<0.0001.) In heart failure patients with LBBB, however, neither e'average nor e'septal correlated with PCWP



(r=0.32 and 0.28 respectively, NS).

In the dog model, induction of LBBB and RV pacing caused QRS widening and septal motion similar to patients with LBBB. Septal e' decreased from 6±2 to 3±2 cm/s (mean±SD) (P<0.05), but e'lateral was unchanged at 6±1 cm/s. Septal E/e' increased from 8±2 to 15±6 (p<0.05), whereas E/e'average showed no significant change (8±2 and 9±2, respectively). There was no significant change in mean left atrial pressure (7.4±3.2 vs. 9.0±2.8 mmHg, respectively).

Conclusions: Induction of LBBB markedly increased septal E/e' due to reduction in septal e', but this did not reflect elevation of LV filling pressure.

As suggested by the clinical data and strongly supported by the experimental study, septal E/e' should not be used for estimation of LV filling pressure in patients with LBBB. Whether the average of septal and lateral E/e' is useful, should be explored further in larger patient populations with LBBB.

Asymptomatic coronary artery disease in type 2 diabetes (T2D), a prospective invasive coronary angiographic (ICA) study with intravascular ultrasound (IVUS) evaluation

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Background and aims: The prevalence of asymptomatic CAD in T2D is unclear. We investigated 1) the CAD burden cross-sectionally using IVUS in an asymptomatic T2D-cohort compared to a reference population without T2D and 2) whether the disease progression of CAD in the T2D cohort, evaluated by ICA, could be modulated with a program to reduce cardiovascular (CV) risk.

Methods: Patients with T2D and ≥1 CV risk factor were randomized to 2 years of a hospital based multi-intervention (MULTI, n=30), or standard care by general physicians (STAND, n=26), with a pre-planned follow-up at year 7. ICA was performed at baseline (BL) whereas at year 7 both ICA and IVUS. Angiograms were scored as: grade 0:<25% diameter stenosis (st), 1:<50% st, 2: <75% st, 3: >75% st, 4: occlusion. CAD burden was described conventionally by the extent score (number of segments graded ≥1, adjusted to 16 segments) and severity score (average grade of

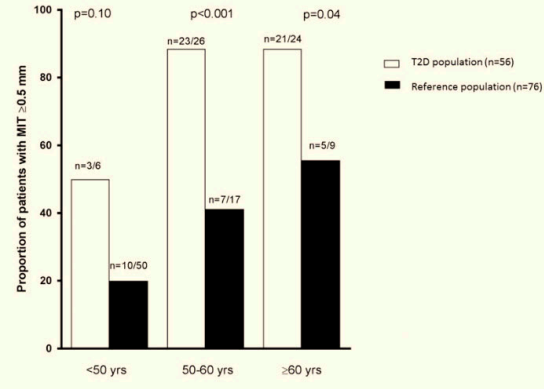

Figure: Age-stratified prevalence of coronary artery disease (defined as MIT ≥0.5 mm) in the T2D study population (n=56) and the reference non-T2DM population (heart transplant donors) (n=76). Abbreviations: T2D: type 2 diabetes, MIT: maximal intima thickness

Table 1. Progression of CAD from baseline to 7 years in the two treatment groups, and atheroma burden in the T2D population compared to the reference population

		T2D population					Reference population	
		Baseline		7 years		p	7 years	p
		MULTI	STAND	MULTI	STAND			
CAD progression	Extent score	0.038±0.067	0.078±0.12	0.050±0.081	0.10±0.11	0.30*	NA	
	Severity score	0.47±0.84	0.83±1.11	0.67±0.98	1.18±1.06	0.20*	NA	
Atheroma burden	MIT (mm)	NA	NA	0.72±0.25	0.78±0.29	0.43†	0.44±0.18	<0.001#
	PAV (%)	NA	NA	32.1±8.6	35.6±10.9	0.19†	20.1±	<0.001#
	Normalized TAV (mm^3)	NA	NA	265.1±131.9	290.7±144.5	0.49†	139.0±110.0	<0.001#

**p for between-group difference in change from baseline to 7 years by ANCOVA. †p for difference between groups at 7 years by Student's T-test. #p for difference between the total T2D population and the reference population at 7 years. Abbreviations: CAD: coronary artery disease, T2D: type 2 diabetes, MULTI: multi-intervention, STAND: standard care, MIT: Maximal intimal thickness, PAV: Percent atheroma volume, TAV: total atheroma volume*

the diseased segments graded ≥1). IVUS was described by maximal intimal thickness (MIT), percent atheroma volume and total atheroma volume and compared with individuals without T2D and CAD (heart transplant donors) who had IVUS performed 7–11 weeks post transplantation (n=76).

Results: At year 7, atheroma burden was significantly greater (Table) and the age-stratified prevalence of CAD defined by MIT significantly higher (Figure) in T2D than in the reference population.

The 2 year multi-intervention reduced CV risk factors (HbA1c, blood pressure, lipids) in MULTI, but did not result in long-term between-group differences in CAD progression by ICA or in atheroma burden, by IVUS, at year 7 (Table).

Conclusion: Our data suggest that asymptomatic T2D patients have extensive CAD, that progresses over time and is not modulated by a 2 year multi-intervention, suggesting a need for more durable residual CV risk management using alternative approaches.

Autoimmune diabetes in adults and the risk of incident heart failure: The HUNT study in Norway

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Background/Introduction: Autoimmune diabetes in adults (AIDA) is a common form of autoimmune diabetes, yet there are few studies on the risk of long term adverse cardiovascular outcomes and factors contributing to poor prognosis.

Purpose: We aimed to investigate the risk of heart failure (HF) in AIDA compared to type 2 diabetes, taking into account sociodemographic, lifestyle, metabolic, and glycemic risk factors.

Methods: We followed 64,449 participants including 2,695 with adult (≥35 years) onset diabetes in the population-based Norwegian HUNT study for incident HF in hospital records during 1995–2016. Individuals with AIDA were anti-GAD positive (n=211) and those with type 2 diabetes anti-GAD negative (n=2,484).

Table 1. Risk of heart failure

	Events/ Person-Time	Model 1	p	Model 2	p	Model 3	p	Model 4	p
No diabetes	2.190/1.081456	Reference		Reference		Reference		Reference	
Type 2 diabetes	281/36.570	2.13 (1.88–2.42)	<0.001	1.82 (1.59–2.09)	<0.001	1.75 (1.52–2.01)	<0.001	1.68 (1.46–1.93)	<0.001
AIDA	18/2.910	1.67 (1.05–2.66)	0.03	1.64 (1.03–2.62)	0.04	1.62 (1.02–2.59)	0.04	1.72 (1.08–2.74)	0.02
LADA	14/2.036	1.72 (1.02–2.91)	0.04	1.72 (1.02–2.92)	0.04	1.70 (1.00–2.88)	0.05	1.80 (1.06–3.05)	0.03

HRs (95% CIs) for heart failure (N=2,489) in adult-onset autoimmune diabetes, type 2 diabetes, and LADA, compared to individuals without diabetes.

Results: We identified 2,489 incident HF events during a mean follow-up of 17.7 (± 5.0) years. The risk of HF was increased in AIDA (Hazard ratio (HR) 1.72, 95% confidence interval (CI) 1.08- 2.74) and type 2 diabetes (HR 1.68, 95% CI 1.46- 1.93), after adjustment for age, sex, socio-demographic and lifestyle factors, the metabolic syndrome, family history of diabetes, and previous history of myocardial infarction. Compared to type 2 diabetes, those with AIDA had more favorable metabolic profile but worse glycemic control (mean HbA1c 8.3 vs. 7.7, p<0.001). In AIDA, but not in type 2 diabetes, excess risk of HF was only seen in individuals with HbA1c ≥7%, did not differ depending on insulin treatment and was more pronounced in individuals with low insulin secretion.

Conclusion: Participants with AIDA had increased risk of HF and poor glycemic control seem to play a major role for this risk increment. This highlights the preventive potential and need for improved management of these patients.

Exercise testing in asymptomatic patients with moderate or severe aortic stenosis

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On behalf: valve study group

Purpose: To assess the safety and tolerability of treadmill exercise testing and the association of revealed symptoms with outcome in apparently asymptomatic moderate to severe aortic stenosis (AS) patients.

Methods: A retrospective cohort study of 316 patients (age 65±12 years, 67% men) with moderate and severe AS who underwent echocardiography and modified Bruce exercise treadmill tests (ETT) at a specialist valve clinic. The outcome measures were exercise-revealed symptoms, aortic valve replacement (AVR), and cardiovascular and all-cause mortality.

Results: At baseline there were 210 (66%) patients with moderate and 106 (34%) with severe AS. There were 264 (83%) events. 234 (74%) patients reached an indication for AVR, 145 (69%) with moderate and 88 (83%) with severe AS (p<0.05). Of the 30 (9%) deaths recoded during follow-up, 20 (6%) were cardiovascular related. In total 797 exercise tests (mean 2.5±2.1 per patient) were performed. No serious adverse events were observed. The prevalence of revealed symptoms at baseline ETT was 29% (n=91) and was significantly higher in severe AS compared to moderate AS (38% vs. 23%, p=0.008). Symptoms were revealed in 18–59% of patients during serial ETT conducted over a follow up period of 34.9 (SD35.1) months. The event-free survival at 24 months with revealed symptoms was 46±4% and without revealed symptoms was 70±4%.

Conclusions: ETT in patients with moderate or severe AS is safe and tolerable. Serial exercise testing is useful to reveal symptoms not volunteered on the history, and adds incremental prognostic information to baseline testing.

Graft versus host disease and left ventriclular function in long-term survivors after allogeneic haematopetic stem cell transplantation at young age

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Introduction: Allogeneic haematopetic stem cell transplantation (allo-HSCT) is a complex therapy involving myeloablative chemotherapy and/or radiation therapy, both well documented to cause adverse effects to heart function. These patients are also at risk of the detrimental effects of graft-versus-host-disease (GVHD).

Purpose: GVHD has previously been attributed to left ventricular (LV) dysfunction, LV remodeling, and pericardial disease. This study aims to describe cardiac function in long term survivors of allo-HSCT and to investigate the influence of GVHD.

Methods: This cross sectional study included 104 individuals (53.8% female). Age at allo-HSCT was (mean±SD) 17.8±9.6 years, age at follow-up was 35.0±11.7 years, and time to follow-up was 17.2±5,6 years. The majority (98,1%) received myeloablative chemotherapy and 12.5% received radiation therapy. Acute (aGVHD) and chronic GVHD (cGVHD) were graded by the Glucksberg and Schulman scale, respectively. The cumulative incidence of GVHD was 64.4% (52.9% aGVHD, 38.5% cGVHD and 26.9% both). Echocardio-

	Total (n=104)	GVHD (n=67)	No GVHD (n=37)	p value
2D EF %	55.2±5.8	55.8±5.6	54.1±6.2	0.16
2D LVEDVindex (ml/m²)	63.1±13.9	61.2±12.6	66.2±15.8	0.80
2D LVESVindex (ml/m²)	28.6±8.5	27.5±7.6	30.6±9.7	0.07
GLS mean %	-17.5±2.2	-17.5±2.0	-17.5±2.5	0.92
LVIDindex (cm/m²)	2.7±0.32	2.7±0.32	2.7±0.32	0.98
RWT	0.30±0.06	0.30±0.05	0.30±0.06	0.82

Values indexed to body surface area.

graphy (GE E9) was performed following the EAVI recommendations. LV ejection fraction (EF) and global longitudinal strain (GLS) were used to evaluate LV systolic function. LV cardiac mass and relative wall thickness (RWT) were used to determine LV geometry. Pericardial fluid or thickening were classified as pathological. Groups were compared by t-test and Fishers exact test as appropriate.

Results: EF≤53% was found in 35,6% and GLS≤-17% was found in 32.7% of patients. No statistical significant difference ($p<0.05$) was found between groups for EF, GLS or RWT. Pericardial pathology was observed in 7 patients in the GVHD group and in only 1 patient without GVHD ($p=0.25$).

Conclusion: LV systolic dysfunction was found to be highly prevalent in allo-HSCT patients. Cause of which was found not to be associated with GVHD. Furthermore, no significant evidence of LV remodeling was observed in GVHD. Pericardial pathology was more prevalent in GVHD, however did not reach statistical significance.

Deaths and vascular outcomes with non-vitamin k oral anticoagulants versus warfarin in patients with heart failure in the food and drug administration adverse event reporting system

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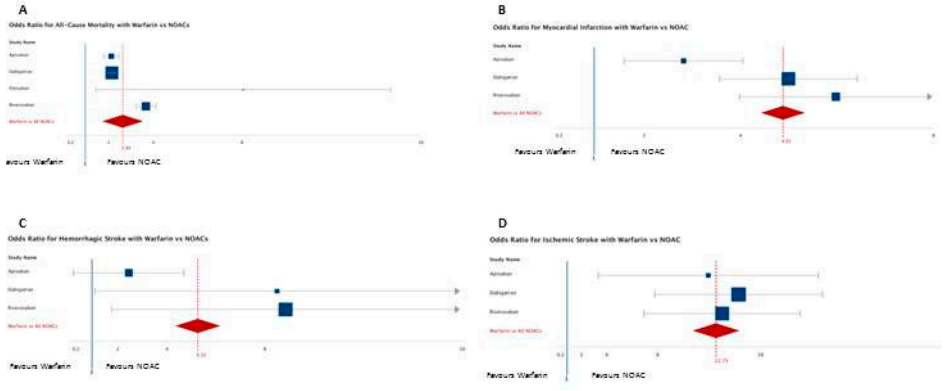
Background: Many patients with heart failure (HF) are prescribed warfarin or non-vitamin K antagonist oral anticoagulants (NOACs). We sought to identify any potential clinical benefit of NOACs relative to warfarin in HF in a large real world database.

Methods: Using the US Food and Drug Administration Adverse Event Reporting System (FAERS) database, we investigated the endpoints of all-cause mortality, myocardial infarction, and stroke for warfarin and NOACs in subjects with HF during 2015. Adverse event reports in subjects on warfarin, dabigatran, rivaroxaban, apixaban, or edoxaban were extracted and stratified according to the absence or presence of HF. We computed odds ratios (OR; 95% confidence interval, CI) for warfarin relative to NOACs.

Results: FAERS reported 137,026 HF cases, with mortality in 42,942 (31.3%). Among HF patients 11,278 (8.2%) were on anticoagulants, with more prescribed warfarin (n=8,260; 73%) than the four NOACs combined (n=3,018; 23%). The odds ratios (OR; 95% CI) for the composite of mortality, myocardial infarction and stroke with warfarin were 1.91 (1.76–2.07) versus apixaban, 1.92 (1.81–2.03) versus dabigatran, 1.80 (1.27–2.56) versus edoxaban and 4.09 (3.38–4.37) versus rivaroxaban (all $P<0.01$). Warfarin, compared to all NOACs combined demonstrated higher rates of mortality (OR=2.69; fig.1 A), myocardial infarction (OR=4.91; B), hemorrhagic stroke (OR=5.32; C) and ischemic stroke (OR=12.73; D; all $P<0.001$).

Conclusions: Annual 2015 FAERS profiles in HF patients reveal that warfarin was associated with higher risk of mortality, myocardial infarction and stroke compared to NOACs. These observational data provide real-world insight into a potential benefit of NOACs over warfarin in the setting of HF.



Odds ratios for adverse events

Association between ventricular arrhythmogenicity and myocardial mechanical dispersion assessed by strain echocardiography in chagas cardiomyopathy

A.C.A. Azevedo[1], M.V. Barros[2], L.G. Klaboe[3], T. Edvardsen[4], M.C.P. Nunes[1], H.S. Costa[1], G.M.M. Paixao[1], J.P.P. Martins[2], H.R. Bernardes[2], O.R. Santos Junior[1], M.O.C. Rocha[1], [1]Federal University of Minas Gerais - Belo Horizonte - Brazil, [2]Faculdade de Saúde e Ecologia Humana - Vespasiano - Brazil, [3]Center for Cardiological Innovation - Oslo - Norway, [4]Oslo University Hospital - Oslo - Norway,

Introduction: Endemic Chaga's disease is a major health concern in Latin America. Ventricular arrhythmias (VA) is a hallmark of Chagas cardiomyopathy (ChD) associated with worse prognosis. Myocardial mechanical dispersion (MD) by speckle tracking echocardiography reflects heterogenous ventricular contractions and is a sensitive marker of ventricular arrhythmias in several cardiomyopathies. We aimed to verify the possible association between ventricular arrhythmias and mechanical dispersion in patients with chronic Chagas cardiomyopathy (ChD).

Methods: We included otherwise healthy patients with chronic ChD in a cross sectional echocardiographic study. MD was defined as the standard deviation of time from onset of Q/R on ECG to peak longitudinal strain in 16 segments. Non-sustained ventricular tachycardia (NSVT) by Holter monitoring was defined as complex ventricular arrhythmia. Included patients were split into two groups according to absence (GROUP 0) or presence (GROUP 1) of NSVT by Holter.

Results: We included 76 ChD patients (55±10 years, 60% men). GROUP 0 had 44 patients and GROUP 1 had 32 patients. Patients with NSVT (GROUP 1) had more pronounced MD (59±15ms vs. 87±49ms, p=0.006) and worse GLS (-14.4±2.9% vs. -12.5±4.2, p=0.02) than patients without NSTV (GROUP 0), while LVEF (44±6% vs 42±9%, p=0.57), end-diastolic diameter (61±6 mm vs 62±7 mm, p=0.9) and diastolic function (E/e' 10.2±4.4 vs. 11.7±4.9, p=0.19) were similar. Both MD and GLS were univariate predictors of CVA (P<0.01). MD was independently associated with non-sustained ventricular tachycardia (OR 1.04; 95% CI, 1.00–1.20; p=0.031) in a multivariate analysis

Conclusion: MD was the only echocardiography parameter associated with NSVT in Chagas disease cardiomyopathy and may add important information in the risk stratification of those patients. Better knowledge of pathophysiological and pathogenetic mechanisms, through new methodologies, should allow better therapeutic management and knowledge of earlier risk factors to worse prognosis and stratification of patients.

Effects of the PAR-1 receptor antagonist vorapaxar on platelet activation and coagulation biomarkers in patients with stable coronary artery disease

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Introduction: Vorapaxar is a selective antagonist of protease-activated receptor 1 (PAR-1), thereby blocking thrombin-mediated platelet activation. Although vorapaxar is likely not to affect the coagulation process directly, inhibition of platelet activation and thereby reducing the availability of a procoagulant platelet surface for the assembly of coagulation factors, might reduce the formation of thrombin and fibrin indirectly. While standard coagulation tests, like prothrombin time (PT) and activated partial thromboplastin time (aPTT), are not influenced by vorapaxar use, the effect on more specific biomarkers of coagulation is currently unknown. A reduction in platelet activation can be measured by soluble P-selectin, a plasma biomarker of in vivo platelet activation. Next to thrombin-antithrombin (TAT) complex levels, the complexes of factor IXa-antithrombin (IXa-AT) and factor Xa-antithrombin (Xa-AT) are new biomarkers of upstream coagulation activity.

Purpose: To investigate the effect of vorapaxar on biomarkers of platelet activation and coagulation activity in patients with stable coronary artery disease (CAD).

Methods: Soluble P-selectin and TAT were measured following manufacturer's instructions. Factor IXa-AT and factor Xa-AT were determined with in-house developed enzyme-linked immunosorbent assays (ELISAs). Samples were taken while on long-term treatment in a subgroup of patients with stable CAD randomized to vorapaxar or placebo on top of standard antiplatelet therapy participating in the TRA2°P-TIMI-50 trial. For this analysis, we excluded patients using anticoagulant medication during follow-up. Student's t-test and Mann-Whitney

U test were used for comparison of biomarker levels between groups.

Results: Baseline characteristics including comorbidity, prior cardiovascular disease, concomitant aspirin and clopidogrel use (99.3% and 56.3%, respectively), and other concomitant medication were well balanced between the vorapaxar-group (n=73) and placebo-group (n=62). Samples were taken after a mean study drug exposure of 904 (± 149) days. As anticipated, platelet activation was reduced in the vorapaxar-group, according to soluble P-selectin levels (ng/mL) (mean ± SD); 26.12±7.81 in the vorapaxar-group vs. 29.39±9.16 in the placebo-group (p=0.027). However, coagulation activity as measured by TAT, IXa-AT and Xa-AT was comparable in vorapaxar vs placebo group: TAT (µg/L) (median, [IQR]) 4.08 [3.20–5.01] vs. 3.88 [3.26–4.92], p=0.71; IXa-AT (pM) (median, [IQR]) 86,7 [77.2–101.3] vs. 85,5 [77.7–97.6], p=0.95; X-AT (pM) (mean ± SD) 282.1±57.4 vs. 296.4±54.6, p=0.14.

Conclusion: On top of standard antiplatelet therapy, vorapaxar reduced platelet activation as measured by a reduction in soluble P-selectin levels. We did not find an additional effect of vorapaxar on TAT, IXa-AT and Xa-AT levels in patients with stable CAD, indicating that vorapaxar does not further reduce thrombin generation via intensified platelet inhibition.

Factors associated with guideline adherence - Results from ESC CRT survey II with 11 088 patients

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On behalf: CRT Survey II Scientific Committee

Introduction: Cardiac Resynchronization Therapy (CRT) reduces morbidity and mortality in selected patients with heart failure and electrical dyssynchrony. Guidance on which patients should be selected for implantation with CRT devices is provided by recommendations in ESC guidelines. However, several studies suggest that implanters explore indications outside guideline recommendations.

Purpose: The purpose of this analysis is to assess adherence to ESC guidelines for CRT implantation and identify factors associated with guideline adherence in the large cohort of patients included in CRT Survey II.

Methods: In 2016, HFA and EHRA conducted CRT Survey II, a survey of CRT implantations in 11,088 patients in 42 ESC member states. The majority of these patients were implanted prior to the release of the 2016 HFA heart failure guidelines. We used the data collected to group these patients according to the recommendation levels under which they were implanted according to the 2013 EHRA guidelines on CRT. These guidelines were the most recent ESC guidelines at the start of CRT Survey II.

Results: From 1. Oct 2015 to 20. May 2016 5214 patients were recruited in the survey and there was sufficient data available to include them in the guidelines adherence analysis. Women, patients <75 years, patients with non-ischaemic heart failure aetiology and those admitted electively were more likely to be implanted under the strongest recommendation levels. There were no significant differences in number of patients implanted under recommendation level I as far as hospital size or type of hospital (university versus non-university) were concerned.

Conclusions: Implanters are more likely to consider CRT implantations with weaker recommendation levels and less strong evidence in men, patients ≥75 years, patients with ischaemic aetiology and those admitted non-electively. A large number of patients are being implanted with CRT devices outside recommendation level I.

Patients implanted with recommendation I

Patient Characteristic	Yes	No	p-value
Male	64% (2500/3917)	78% (1011/1295)	<0.00001
Age ≥75 years	62% (942/1520)	70% (2570/3693)	<0.00001
Ischaemic heart failure aetiology	63% (1506/2392)	71% (2000/2814)	<0.00001
Elective admission	71% (2904/4112)	55% (607/1099)	<0.00001
Implanted in a hospital which implants ≥100 CRTs per year	65% (1488/2295)	69% (1993/2876)	0.0007
Implanted in university hospital	67% (2158/3206)	68% (1335/1979)	0.91
Implanted in a hospital with ≥600 beds	67% (1900/2835)	68% (1581/2336)	0.61
Referal from another centre	67% (962/1430)	67% (2543/3774)	0.94

Impact of estimated left atrial volume on prognosis in patients with initially asymptomatic mild to moderate aortic stenosis

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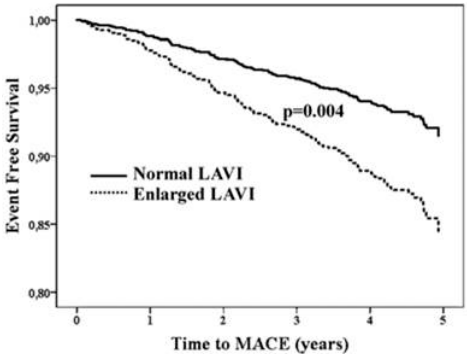
Background: The prognostic impact of increased left atrial (LA) volume in

Variable	Hazard Ratio (95% CL)	p
LAVI enlargement	1.88 (1.21–2.93)	0.005
LV hypertrophy	1.49 (1.04–2.11)	0.031
Age (≥65 years)	2.17 (1.42–3.31)	<0.0001
Sex (male)	1.31 (0.91–1.90)	0.146
Obesity	1.12 (0.75–1.70)	0.582
Randomized treatment	1.10 (0.78–1.54)	0.596
Hypertension	0.91 (0.56–1.48)	0.705
LV ejection fraction (%)	0.97 (0.96–0.99)	0.021
Peak aortic jet velocity (m/s)	2.23 (1.59–3.12)	<0.0001
AVR before MACE (%)	0.58 (0.38–0.89)	0.012

AVR = aortic valve replacement; LAVI = estimated left atrial volume; LV = left ventricular.



mild-to-moderate aortic valve stenosis (AS) is unclear.

Purpose: We investigated the association of estimated LA volume with prognosis in a large prospective study of patients with asymptomatic mild-to-moderate AS

Methods: The association of estimated LA volume with major cardiovascular events (MACE, cardiovascular death, hospitalization for heart failure and non-hemorrhagic stroke) was assessed in 1543 patients with initially mild-to moderate asymptomatic AS, participating in the Simvastatin Ezetimibe in Aortic Stenosis (SEAS) study for a median of 4.3 years. LA volume was estimated from LA diameter applying a validated equation and indexed to body height in meter squared (LAVI). Estimated LAVI was considered enlarged if ≥18.5 in men, and ≥16.5 ml/m² in women, reflecting the 95th percentile in healthy European population.

Results: Patients with enlarged LAVI (13%) were older, more likely to be female and obese, and had higher systolic blood pressure and left ventricular (LV) mass index (all p<0.05). During follow-up, MACE occurred more often in patients with enlarged LAVI (19% vs. 8%, p<0.001). In Cox regression, enlarged LAVI at baseline predicted increased hazard of MACE (Hazard Rate 1.91 [95% confidence interval 1.22–2.98], p=0.009) in univariable analysis (Figure) and after adjustment for age, LV hypertrophy, ejection fraction, peak aortic jet velocity and aortic valve replacement (Table).

Conclusion: Presence of enlarged LAVI estimated by a validated equation was independently associated with increased risk of MACE in patients with initially mild to moderate AS.

Longitudinal changes in troponin concentrations from mid- to late-life and left ventricular structure and function in late-life: The Atherosclerosis Risk in Community Study

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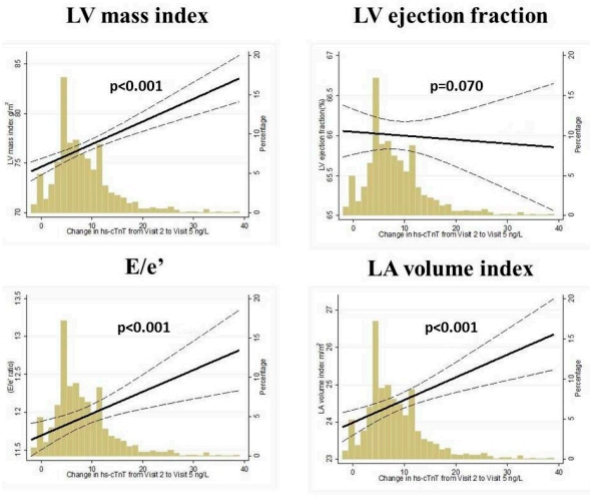
On behalf: ARIC study group

Background/Introduction: Cardiac troponins predict incident heart failure (HF) and death and associate with left ventricular (LV) mass in the general population, but the relationship between



Fitted restricted cubic spline models of echocardiographic measurements as a function of change in hs-cTnT from Visit 2 (1990-1992) to Visit 5 (2011-2013). Models are adjusted for age, sex, race, hypertension, diabetes, smoking, blood pressure, heart rate, estimated glomerular filtration rate and NT-proBNP at Visit 5 and p is for linear trend.

changes in concentration and cardiac structure and function is unclear.

Purpose: To define the association between longitudinal change in high-sensitivity cardiac troponin T (hs-cTnT) over ~20 years from mid- to late-life and cardiac structure and function in late-life.

Methods: The relationship between hs-cTnT at Visit 2 (1990–1992), Visit 4 (1996–1998) and Visit 5 (2011–2013) to LV structure, and systolic and diastolic function assessed at Visit 5 was assessed in 3,573 elderly participants (mean age 75±5 years, 63% female, 20% black) free of overt cardiovascular (CV) disease in the Atherosclerosis Risk in Communities (ARIC) Study.

Results: Median increase in hs-cTnT from Visits 2 and 4 to Visit 5 was 7 (IQR 4–11) ng/L and 6 (3–9) ng/L, respectively. After adjusting for demographics, comorbidities, vital parameters and renal function, greater increase in concentrations of hs-cTnT from both Visit 2 and Visit 4 to Visit 5 was associated with greater LV mass ($p<0.001$ for both) and with worse diastolic indices: higher E/e' ratio ($p<0.001$ and $p=0.007$), and greater left atrial volume index ($p<0.001$ for both) (Figure). Longitudinal change in hs-cTnT was not associated with LV ejection fraction ($p=0.07$ and $p=0.09$) or circumferential strain ($p=0.14$ and $p=0.98$), but with longitudinal strain ($p=0.02$ and 0.005). Each 10 ng/L increase in hs-cTnT concentration from Visit 2 to Visit 5 was associated with a 21% higher odds of diastolic dysfunction (OR 1.21 [95% CI 1.08–1.35], $p=0.001$) and with the risk of incident HF or death (HR 1.27 [95% CI 1.13–1.43], $p<0.001$) after adjusting for demographics, comorbidities, vital parameters and renal function at Visit 5. 33% of participants increased ≥10 ng/L from Visit 2 to 5. Participants with ≥10 ng/L increase in hs-cTnT and diastolic dysfunction demonstrated higher risk of incident HF or death at a mean follow-up of 2.6 years (incidence rate 4.0 [95% CI 3.0–5.5] /100 person-years) compared to participants without diastolic dysfunction (2.6 [2.1–3.2], $p<0.001$; Figure).

Conclusions: Greater increase in hs-cTnT concentrations from mid- to late-life are associated with worse LV mass and diastolic function in late-life, but not with measures of systolic function. A large increase in hs-cTnT in addition to the presence of diastolic dysfunction at late-life seems to reflect a particularly malignant phenotype.

Biomarkers in heart failure patients with and without diabetes

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Introduction: Heart failure patients with type 2 diabetes have an even worse prognosis than heart failure patients without diabetes. The explanation for this excess risk is uncertain and does not seem to be fully explained by the greater prevalence of coronary artery disease and renal dysfunction in individuals with diabetes. We have measured an array of biomarkers to gain insight to potential additional pathophysiological processes active in heart failure patients with diabetes compared to those without.

Methods: We measured a panel of biomarkers reflecting a range of pathophysiological processes in the Controlled Rosuvastatin Multinational Trial in Heart Failure trial (CORONA) which enrolled patients with HFrEF of ischaemic aetiology.

Results: Levels of many biomarkers were higher in patients with diabetes compared to those without, including those reflecting myocyte stress/injury such as high-sensitivity (hs) troponin T (median [IQR] 16.5 [8.5, 32.5] vs 13.0 [6.0, 23.2] pg/ml, P=0.0001) and biomarkers reflecting inflammation e.g.

Table 1. Biomarker levels according to history of diabetes

	Patients, n (%)	No diabetes	Diabetes	P-values
Myocyte stress/injury				
NTproBNP (pmol/L)	3664 (73)	172.2 [72.0, 363.3]	177.7 [75.6, 377.1]	0.3519
ST2 (ng/mL)	1449 (29)	17.6 [12.8, 24.6]	18.8 [13.7, 25.6]	0.0285
Troponin T (pg/mL)	1245 (25)	13.0 [6.0, 23.2]	16.5 [8.5, 32.5]	0.0001
Inflammation				
hsCRP (mg/L)	4961 (99)	3.3 [1.5, 7.2]	4.0 [1.8, 8.2]	0.0001
IL6 (pg/mL)	1480 (30)	2.9 [1.8, 5.3]	3.2 [1.9, 5.8]	0.0852
TNF-α (ng/mL)	1480 (30)	3.7 [3.7, 3.7]	3.7 [3.7, 3.7]	0.1071
ECM remodeling				
Galectin-3 (ng/mL)	1462 (29)	18.8 [15.4, 23.7]	19.6 [15.8, 23.9]	0.0739
Endostatin (ng/mL)	1391 (28)	154.5 [124.3, 195.6]	160.4 [129.9, 209.5]	0.0211
IGFBP7 (ng/mL)	1442 (29)	54.2 [45.7, 65.1]	57.0 [47.9, 69.7]	0.001
Kidney function				
NGAL (ng/mL)	1415 (28)	296.0 [215.0, 431.0]	302.0 [209.5, 453.5]	0.8651
Creatinine (µmol/L)	5011 (100)	110.5 [97.0, 128.5]	110.5 [97.0, 133.0]	0.0011

hs CRP (4.0 [1.8, 8.2] vs 3.3 [1.5, 7.2] mg/l, P=0.0001) [Table]

Conclusions: Biomarkers reflecting myocyte stress/injury, inflammation and remodelling were higher in HF patients with diabetes. It is possible that these differences contribute to the worse outcomes in HF patients with diabetes.

Alcohol consumption and risk of atrial fibrillation - results from the BiomarCaRE Consortium

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On behalf: BiomarCaRE

Background: Atrial fibrillation (AF) is an arrhythmia with high impact on public health. Among modifiable risk factors for the disease the role of alcohol consumption (AC) has remained inconsistent.

Purpose: To assess the association between AC and incident AF across European cohorts.

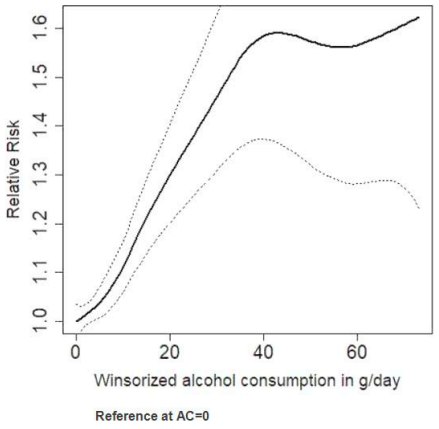

Figure 1. Age and sex-adjusted, cohort-stratified relative risk of incident AF for right-winsorized AC in grams per day. The results are from a multivariable-adjusted Cox regression analysis with non-linear effect of AC

Methods: To study the association between self-reported AC and incident AF in N=107,845 community-based individuals from the BiomarCaRE consortium, 106,915 individuals free of AF at baseline were followed up for AF and stroke after AF. We assessed AC using validated questionnaires. Biomarkers N-terminal pro B-type natriuretic peptide (Nt-proBNP) and high sensitivity troponin I (hsTnI) were measured.

Results: The median age of individuals was 47.8 years, 48.3% were men. The median of right-winsorized AC was 3 g/day. N=6,055 individuals developed AF (median follow-up time: 13.9 years). In a linear multivariable-adjusted Cox regression analyses, AC was linearly and positively associated with incident AF (Figure), hazard ratio (HR) per g/day 1.009, 95% confidence interval (CI) 1.007- 1.012, P<0.001. For one drink (12g) per day the HR was 1.15, CI 1.12–1.18, P<0.001. There was a high heterogeneity in associations across cohorts.

No significant interactions of the association by Nt-proBNP and hsTnI were observed. AC was positively related to stroke risk after diagnosis of AF (HR 1.18, 95% CI 1.04–1.34, P=0.012).

Conclusions: In contrast to other cardiovascular diseases, we did not observe a U-shaped association of alcohol with incident AF in the community, but a rather linearly increasing relation.

Empagliflozin reduces mortality and hospitalisation for heart failure irrespective of cardiovascular risk score at baseline

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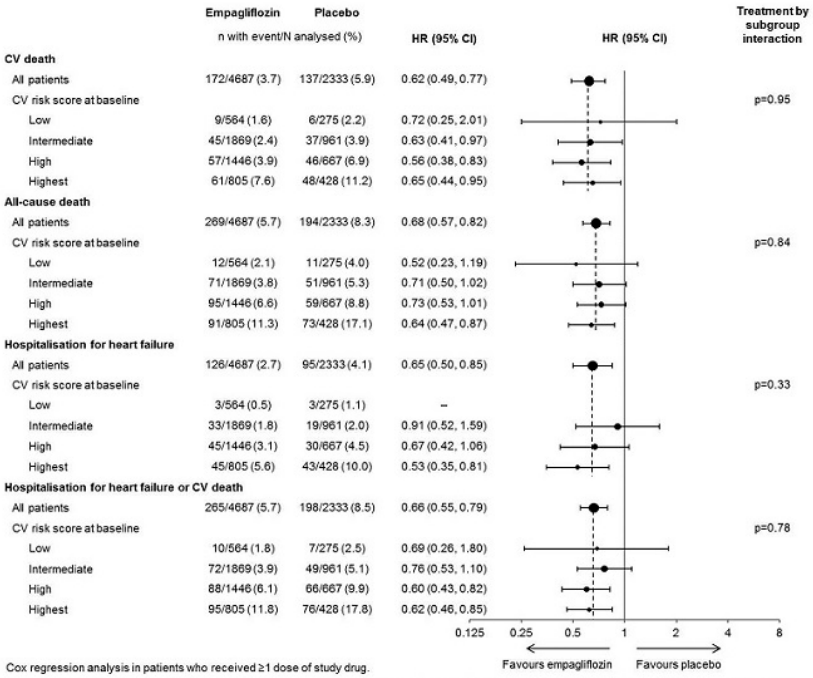
Background: In the EMPA-REG OUTCOME trial in patients with type 2 diabetes and established cardiovascular (CV) disease, empagliflozin added to standard of care reduced CV death vs placebo by 38% (HR 0.62 [95% CI 0.49, 0.77]), all-cause death by 32% (HR 0.68 [95% CI 0.57, 0.82]) and hospitalisation for heart failure (HHF) by 35% (HR 0.65 [95% CI 0.50, 0.85]). We investigated whether residual CV risk at baseline



Cox regression analysis in patients who received ≥1 dose of study drug.

The 10-point TRS 2°P included (1 point each): heart failure; hypertension; age ≥75 years; diabetes; prior stroke; prior coronary artery bypass graft surgery; peripheral artery disease; eGFR <60 ml/min/1.73m²; current smoking; prior myocardial infarction.

Residual CV risk: low = ≤2 points; intermediate = 3 points; high = 4 points; highest = ≥5 points.

influenced the effect of empagliflozin on these outcomes.

Methods: We investigated CV death, all-cause death, HHF and the composite of HHF or CV death with empagliflozin vs placebo in subgroups by degree of CV risk at baseline based on the 10-point TIMI Risk Score for Secondary Prevention (TRS 2°P). P-values for treatment-by-subgroup interaction were obtained from tests of homogeneity of treatment group differences among subgroups with no adjustment for multiple testing.

Results: Based on the TRS 2°P risk score, of 7020 patients who received study drug in the EMPA-REG OUTCOME trial, 12%, 40%, 30% and 18% were at low, intermediate, high and highest residual CV risk, respectively, at baseline. In the placebo group, from low to highest predicted risk, the proportion of patients with CV death increased from 2.2% to 11.2% and the proportion of patients with HHF increased from 1.1% to 10.0%. Effects of empagliflozin on CV death, all-cause death, HHF and HHF or CV death were consistent across subgroups by baseline CV risk score (Figure).

Conclusion: The benefits of empagliflozin on key clinical outcomes in the EMPA-REG OUTCOME trial occurred irrespective of residual CV risk at baseline.

Cardiac troponin T concentrations are lower in women than men with atrial fibrillation but have similar prognostic value regardless of sex - insights from the ARISTOTLE trial

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Background: Sex seems to influence absolute concentrations and the prognostic ability of cardiac troponin in several clinical settings. Whether sex influences cardiac troponin T concentrations and its prognostic value in patients with atrial fibrillation (AF) is not known.

Methods: We measured cardiac troponin T concentrations with a high-sensitivity assay (hs-TnT) in plasma samples obtained at randomization in 14897 patients with AF in the ARISTOTLE trial. Patients were stratified according to sex and the associations between hs-TnT concentrations

Table 1. Associations between baseline cardiac troponin T value and outcomes. The hazard ratio for troponin is between the first (7.5) and third quartile (16.7) based on all troponin values regardless of sex

Outcome		n	Events	Hazard ratio (95% CI)			P for interaction by sex (Model 3)
				Model 1*	Model 2*	Model 3*	
Cardiac death	Both	14897	542	3.29 (2.68–4.03)	3.22 (2.60–3.98)	2.45 (1.94–3.10)	0.58
	Female	5305	154	3.01 (2.37–3.83)	2.99 (2.34–3.83)	2.36 (1.81–3.08)	
	Male	9592	388	3.42 (2.73–4.29)	3.40 (2.69–4.29)	2.52 (1.95–3.26)	
MI	Both	14897	149	3.38 (2.27–5.02)	3.12 (2.07–4.71)	2.56 (1.64–3.99)	0.10
	Female	5305	46	4.03 (2.49–6.50)	3.75 (2.30–6.10)	3.13 (1.87–5.24)	
	Male	9592	103	3.04 (2.00–4.63)	2.78 (1.80–4.29)	2.22 (1.39–3.55)	
Stroke/ SEE	Both	14897	397	1.63 (1.38–1.92)	1.60 (1.34–1.91)	1.38 (1.13–1.68)	0.50
	Female	5305	156	1.52 (1.22–1.90)	1.46 (1.17–1.84)	1.31 (1.03–1.68)	
	Male	9592	241	1.82 (1.48–2.25)	1.74 (1.39–2.16)	1.45 (1.14–1.84)	

**Model 1, unadjusted. Model 2, adjusted for age and sex (sex only included for analysis in the total cohort; n=14897). Model 3, adjusted for age, systolic blood pressure, hypertension, smoking status, diabetes, eGFR, prior myocardial infarction, CRP, BNP, GDF-15 and ApoA1 concentrations, and sex (only for the total cohort; n=14897).*

and cardiovascular outcomes were assessed in multivariate Cox models.

Results: hs-TnT concentrations were higher in men (n=9649) compared to women (n=5331) with AF: median 11.8 (Q1–3 8.1–18.0) vs. 9.6 (6.7–14.3) ng/L, p<0.001. This difference was significant also in adjusted analyses: β (SE) for loghs-TnT 0.34 (0.02), p<0.001. hs-TnT concentrations were associated with the same clinical variables in men and women, but the hs-TnT difference between patients with permanent vs. persistent AF was more marked in women (p=0.036 for interaction). During median 1.9 years follow-up, 542 patients died from cardiac cause, 149 patients suffered a new MI and 397 patients suffered a stroke or systemic embolism. hs-TnT concentrations were significantly associated with all clinical outcomes, in both men and women (Table 1).

Conclusion: Men with AF have higher hs-TnT concentrations than women with AF. Regardless of sex, hs-TnT concentrations remains similarly associated with adverse clinical outcomes.

Genetic variant score predicts cardiac events in arrhythmogenic right ventricular cardiomyopathy

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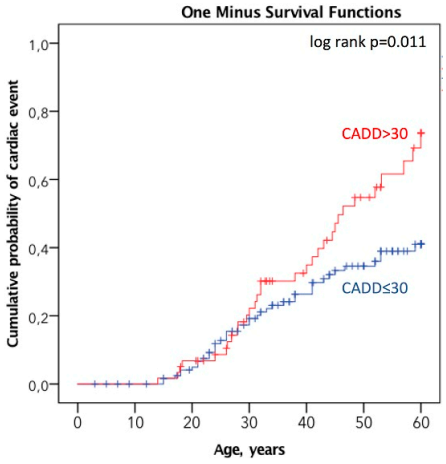
Background: Whether genetic information may contribute to risk stratification of patients with arrhythmogenic right ventricular cardiomyopathy (ARVC) remains uncertain. The Combined Annotation Dependent Depletion (CADD) score, a bioinformatic tool that measures the pathogenicity of genetic variants, has not been tested for its association with clinical manifestations of ARVC.

Objective: We aimed to assess whether CADD score is associated with cardiac events in individuals carrying pathogenic variants of plakophilin-2 (PKP-2) gene.

Methods: In this retrospective study, all individuals enrolled in the Nordic ARVC Registry and

the North American Multidisciplinary ARVC Study carrying PKP-2 variants that according to the American College of Medical Genetics and Genomics (ACMG) were classified as pathogenic or likely pathogenic were included. In total, 36 unique genetic variants were reported in 187 patients (93 males, 75 probands, 101 with definite ARVC diagnosis by Task Force 2010 and median age of 38 [IQR 24–52] years). No individuals had a pathogenic genetic variant in any other ARVC-related gene. CADD scores were calculated and their association with age at (1) first ventricular tachycardia/ventricular fibrillation (VT/VF) defined as ventricular tachycardia, appropriate ICD therapy or aborted cardiac arrest or (2) cardiac event (VT/VF or syncope) evaluated. Kaplan–Meier analysis and



CADD score and risk of cardiac events

Cox regression analysis adjusted for gender were used to assess relationship between CADD score and the risk of cardiac events before the age of 60 years.

Results: Cardiac events were reported in 81 patients (43%) and VT/VF in 63 (34%). CADD score was higher in patients with cardiac events than in those without (30.9 vs. 28.7, p=0.023) and Kaplan-Meier analysis indicated higher frequency of cardiac events in those with CADD score >30 (log rank p=0.011, Figure). In the Cox regression analysis, CADD >30 (upper tertile) was significantly associated with the risk of cardiac events (HR=1.80, 95% CI 1.12–2.88, p=0.014). No association between cardiac event rates and the most common genetic variant types (splice site, deletion, nonsense) was observed.

Conclusions: We are the first to report a significant correlation between PKP-2 mutation characteristics assessed using CADD-score and the age at first clinical manifestations of ARVC, thus indicating the potential of genetic information for risk stratification.

LDL cholesterol, apolipoprotein B, lipoprotein(a), apolipoprotein CIII and triglyceride lowering by MGL-3196, a thyroid hormone beta selective agonist, in a 12 week study in HeFH patients

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Background and aims: MGL-3196 is a liver-directed, orally active, selective THR-beta agonist studied in a Phase 2 clinical trial in 116 patients with proven heterozygous familial hypercholesterolemia (HeFH). In Phase 1 studies MGL-3196 reduced LDL-cholesterol (LDL-C), triglycerides (TG) and lipoprotein(a) (Lp(a) and reduced ALT at 12 weeks in Phase 2 NASH patients with baseline elevated ALT. The primary endpoint was reduction in LDL-C compared with placebo and secondary endpoints included effects on additional lipids and lipoproteins.

Methods: MGL-3196-06 is a 12 week multicenter, randomized, double blind, placebo controlled trial in HeFH patients not at LDL-C target on maximally tolerated statins. Patients received MGL-3196 100 mg or placebo once daily (in a 2:1 ratio) in addition to their LDL-C lowering regimen. Based on blinded Week 2 PK, MGL-3196

Lipid lowering by MGL-3196

	Week	Placebo n=37	MGL-3196 n=76	Optimal MGL-3196 n=39
LDL-C (mg/dL), (SD)	BL	132.6 (51)	131.5 (48)	135.8 (59)
	W12	142.4 (68)	114.5 (35)	114.0 (41)
% CFB LDL-C compared to placebo			-18.8% (4.5)	-21.2 (5.2)%
			p<0.0001	p<0.0001
Lp(a) (nmol/L), (SD)	BL	68.9 (111)	86 (143)	73.7 (126)
	W12	71.2 (117)	70.8 (125)	51.9 (84)
% CFB Lp(a) compared to placebo			-26.3 (5.0)%	-33.2 (5.7) %
			p<0.0001	p<0.0001

BL, baseline; W12, week 12. CFB, change from BL; Optimal MGL-3196, prespecified group at exposure target, confirmed by Sex Hormone Binding Globulin biomarker level

patients continued on 100 mg or a dose of 60 mg from Week 4–12.

Results: Baseline characteristics: age 57.3; male 52.3%; atorvastatin 80mg, 37.1%; rosuvastatin 20/40 mg 37.1%; moderate or no statin, 25.9%; ezetimibe, 71.6%. MGL-3196 treated patients (intention-to-treat) achieved highly significant (p<0.0001) LDL-C and Lp(a) lowering compared with placebo (Table). LDL-C lowering reached 28.5% compared to placebo in the prespecified group of MGL-3196-treated patients on moderate dose/no statins. Triglyceride (TG) (25–31%) apolipoprotein CIII (Apo CIII) (24%) and ApoB (18.0–20.3%) lowering were observed (p<0.0001). MGL-3196 was well-tolerated. Seven patients did not complete the study, 5 withdrew for mild/moderate AEs (placebo, 2; MGL-3196, 3). AEs, mild to moderate, were balanced (placebo, 28; MGL-3196, 63) with five severe AEs, placebo, 3; MGL-3196, 2. Two SAEs occurred, one in a placebo and one in a drug-treated patient (unrelated).

Conclusions: MGL-3196 lowers LDL-C in HeFH, a difficult-to-treat genetic dyslipidemia, especially in HeFH patients intolerant to high intensity statins. MGL-3196 also robustly decreases TGs, ApoB, ApoCIII and Lp(a) making it an excellent candidate to lower cardiovascular risk in NASH patients and dyslipidemic patients on moderate statin doses or intolerant to statins.

Benefit of LDL-C lowering with evolocumab on cardiovascular outcomes by age & sex: an analysis of the FOURIER trial

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On behalf: FOURIER Trial

Background: In trials of lipid-lowering with statins, uncertainties remain on the efficacy and safety in the elderly population and by patient sex. The FOURIER trial compared evolocumab, a monoclonal antibody against PCSK9, with placebo in patients with established atherosclerotic cardiovascular (CV) disease. We conducted prespecified analyses of the trial outcomes according to age at randomisation and in men versus women.

Methods: The effects of evolocumab (either 140 mg subcutaneously every 2 weeks or 420 mg subcutaneously monthly) were compared with matching placebo over a median 2.2 years follow-up, on LDL-cholesterol reductions, CV outcomes and adverse safety events, among all 27,564 FOURIER participants, according to quartiles of age and by sex.

Results: Older patients were more likely to be female and have a background history of stroke or peripheral artery disease rather than myocardial infarction (MI). Reductions in LDL-cholesterol differed only marginally by age and sex. For the primary endpoint, women had a lower event rate than men (KM at 3 years 11.2 vs 14.4%) with slightly fewer MIs, more strokes and fewer CV deaths. Relative risk reductions in the primary endpoint (PEP: CV death, MI, stroke, hospitalization for unstable angina, coronary revascularization) and in the key secondary endpoint (SEP: CV death, MI, stroke) were greater in women (HR 0.81 [95% CI 0.69–0.95] and HR 0.74 [0.61–0.90] respectively) than in men (0.86 [0.80–0.94] and 0.81)[0.73–0.90]) as were the absolute risk reductions (2.66% [0.59–4.62] and 2.69% [0.82–4.55] vs 1.82% [0.47–3.17] and 1.78% [0.61–2.96]) respectively, but tests for heterogeneity were negative.

Comparing quartiles of age, there were no differences in relative risk reductions for the PEP (Q1 [age <56] vs Q4 [age >69], 0.83 [0.72–0.96] vs 0.86 [0.74–1.00]), or the SEP (Q1 vs Q4, 0.74 [0.61–0.89] vs 0.82 [0.69–0.98]); P interaction = NS. Subdivision by age <65>, or <75> years gave similar results.

Adverse events were more common in women and the elderly (Q3 and Q4) but there were no differences between those reported on evolocumab and placebo.

Conclusions: These analyses show that the benefits of evolocumab are maintained throughout the age range with no diminution of efficacy in the elderly. Similar benefits are seen in both men and women. No safety issues were observed.

Clinical and electrocardiographic dynamics during exercise after STEMI in patients with a concomitant CTO either randomized to CTO PCI or no-CTO PCI

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Introduction: Chronic total coronary occlusions (CTOs) are frequently seen in the cathlab. In ST-elevated myocardial infarction (STEMI), cardiogenic shock and stable coronary artery disease

the presence of a CTO is associated with a higher mortality and more frequent ventricular arrhythmias (VAs), compared to patients without a CTO. We hypothesize that that mortality and VA events occur more frequently in these patients in the setting of stress or exercise. Whether percutaneous coronary intervention (PCI) of a CTO in STEMI patients reduces the arrhythmic substrate and improve complaints in these patients during exercise or stress, is unknown.

Purpose: To compare exercise capacity, complaints and X-ECG parameters in STEMI patients with a concomitant CTO, randomized to CTO PCI or no-CTO PCI.

Methods: We evaluated all available exercise stress tests (X-ECGs) of patients randomized in the EXPLORE trial. In short, in EXPLORE 302 STEMI patients were randomized to CTO PCI or no-CTO PCI after primary PCI. X-ECGs were performed at follow-up, and these were collected and analyzed retrospectively.

Results: In total, 155 X-ECGs at follow-up were available for analysis. Of these, 80 were randomized to CTO PCI and 75 to no-CTO PCI. Patient baseline characteristics and anti-arrhythmic medication use at follow-up (at the time of X-ECG) were well-balanced between groups. At 4 months follow-up, our preliminary results showed that the performed exercise was equal between randomization groups, but patients in the no-CTO PCI group experienced more chest pain during exercise compared to patients in the CTO PCI group (6.7% vs. 0%, p=0.025). Furthermore, there was a trend towards a higher systolic blood pressure in the CTO PCI group (185 (IQR 51) mmHg vs. 175 (33) mmHg, p=0.086). In addition, we observed a non-significantly higher prevalence of ventricular ectopy in the CTO PCI group (31% vs 13%, p=0.141).

At ESC 2018 we will be able to present more data regarding X-ECG parameters (i.e. QT duration, QRS duration, QTc duration, blood-pressures over time, ST-deviation), angiographic parameters and clinical follow-up.

Conclusion: Our preliminary results of exercise ECGs in STEMI patients with a concomitant CTO, randomized to either CTO PCI or no-CTO PCI, show that patients randomized to CTO PCI experience less chest pain during exercise and appear to be able to build-up a higher systolic blood pressure during exercise, but may also experience more ventricular ectopy.

Temporal relations between atrial fibrillation and ischemic stroke and their prognostic impact on mortality

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On behalf: BiomarCaRE investigators

Introduction: Atrial fibrillation (AF) and stroke are common diseases and AF is a well-established risk factor for stroke. The physiological mechanism of atrial dysfunction, disturbed hemodynamics and arterial thromboembolism links the pathologies. However, limited evidence is available on the temporal relationship between stroke and AF and the impact of subsequent disease onset on mortality in the community.

Methods and results: Across five prospective community cohorts (DanMONICA, FINRISK, Moli-Sani project, Northern Sweden MONICA study, The Tromsø Study) of the Biomarkers for Cardiovascular Risk Assessment in Europe (BiomarCaRE)-project we assessed baseline cardiovascular risk factors in 101164 individuals, median age 46.1 (25th, 75th percentile 35.8, 57.6) years, 48.4% men. We followed them for incident stroke and AF and determined the relation of subsequent disease diagnosis with overall mortality. Follow-up (FU) for stroke and AF was based upon linkage with national hospitalization registries or administrative registries for ambulatory visits to specialized hospitals.

Over a median FU of 16.1 years N=4556 individuals were diagnosed solely with AF, N=2269 had a stroke but no AF diagnosed, and N=898 developed both stroke and AF during FU. Participants who developed either AF or stroke as the index event revealed a similar baseline risk factor profile. Temporal relations showed a peak of the diagnosis of both diseases within the years around the diagnosis of the other disease. The highest incidence rates of stroke were observed within a five-year interval prior to AF diagnosis. Cox regression showed an association of baseline stroke with diagnosis of AF during FU (hazard ratio (HR) 1.29; 95% confidence interval (CI) 1.11–1.50; p<0.001).

In multivariable-adjusted Cox regression analyses with time-dependent covariates excluding individuals with diagnosis of both AF and stroke or death within 30 days, subsequent diagnosis of AF after stroke was associated with a higher

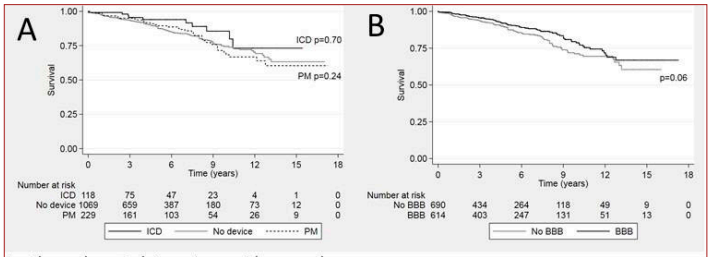
overall mortality (HR, 3.51; 95% CI 1.87–6.59; p<0.001); subsequent stroke after the diagnosis of AF was associated with a HR of 2.39 (95% CI 1.59–3.60; p<0.001).

Conclusions: Stroke and AF are common comorbidities in older adults with an overlapping risk factor profile. The temporal relations appear to be bidirectional, although uncertainty regarding disease onset remains due to the often paroxysmal and asymptomatic nature of AF. Stroke may precede detection of AF by years. The subsequent diagnosis of both diseases significantly increases mortality risk. Whether targeting modifiable risk factors or improved screening for AF after stroke would improve survival needs to be determined.

Table 1. Associations between bundle branch block and NYHA functional class 3–4 at latest clinical follow-up in patient treated with alcohol septal ablation

	Odds ratio	95% confidence limits	P
Post procedural BBB (right or left)	0,98	0.63–1.51	0.91
Pre-defined confounders			
Age	1.07	1.05–1.09	<0.001
Sex	1.08	0.68–1.73	0.73
Ejection fraction	0.97	0.95–0.99	0.001
Resting LVOT gradient	1.02	1.01–1.03	<0.001
Pre-ASA IVSd*	1.04	0.98–1.09	0.17

Overall p>0.001. ASA, Alcohol septal ablation; IVSd, Interventricular septum dimension; NYHA, New York Heart Association; LVOT, Left ventricular outflow tract.



A: Observed survival in patients with pacemaker (PM), implantable cardioverter defibrillator (ICD) and without device (No device) after ASA. P-values represent differences from patients without device adjusted for previously identified risk factors.

B: Observed survival in patients with and without bundle branch block (BBB) after ASA. The P-value represents analysis adjusted for previously identified risk factors.

Clinical significance of impaired cardiac conduction after alcohol septal ablation

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On behalf: the Euro-ASA registry

Objective: Impairment of cardiac conduction and need for pacemaker (PM) after alcohol septal ablation (ASA) in patients with obstructive hypertrophic cardiomyopathy (HCM) has been of major concern.

Methods: We analysed the impact of bundle branch block (BBB) and PM after ASA on symptoms and survival in 1416 HCM patients.

Results: Before ASA 58 (4%) patients had a PM and 64 (5%) patients had an implantable cardioverter defibrillator (ICD). At latest follow-up (5.0±4.0 years) after ASA, 118 (8%) patients had an ICD and 229 (16%) patients had a PM. In patients without implantable device before ASA 13% had a PM and 5% had an ICD implanted following ASA. New onset BBB was present in 44% (right BBB in 31%) of patients without previous BBB. At latest follow-up, we found no associations between BBB and New York Heart Association (NYHA) class 3–4 (OR 0.98, CI 0.63 - 1.51, p=0.91) (see Table) or Canadian Cardiovascular Society (CCS) class 3–4 (OR 1.5, CI 0.32–6.7, p=0.62), respectively, and no associations between PM and NYHA class 3–4 (OR 1.2, CI 0.70–2.0, p=0.52) or CCS 3–4 (OR 1.3, CI 0.24–6.6, p=0.79), respectively. The survival after ASA was not reduced in patients with BBB (HR 0.73, CI 0.53–1.01, p=0.06) or PM (HR 0.78, CI 0.52–1.17, p=0.24) (see Figure 1A and B).

Conclusions: Development of BBB or need for a PM after ASA was not associated with inferior symptomatic outcome or reduced survival, thus

concerns for the negative impact of impaired cardiac conduction on the clinical outcome after ASA were not confirmed.

Diabetes and acute aortic dissection: insights from the International Registry of Acute Aortic Dissection

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On behalf: International Registry of Acute Aortic Dissection

Background: The prevalence of diabetes in general adult population in developed countries is 7–11%. Studies have shown that diabetes is less prevalent in acute aortic dissection (AAD) or aortic aneurysm patients than in those with coronary artery disease or heart failure. Controversies exist about its impact on AAD outcome.

Purpose: The aim of this study is to better define patient characteristics and outcomes among both diabetic type A (TAAD) and type B acute aortic dissection (TBAD)

Methods: Patients enrolled in the international registry of acute aortic dissection (IRAD) were analyzed (n=6100, 1996–2017). Marfan patients were excluded. Diabetic and non-diabetic patients with either TAAD (n=3947, 8.5% diabetic) or TBAD (n=2153, 9.5% diabetic) were compared in this study.

Results: Both TAAD and TBAD diabetics were older, had higher prevalence of history of hypertension, prior cardiac surgery, aneurysm at initial imaging and were less frequently Caucasian (all p<0.05). TAAD diabetics were less likely to undergo surgery (82.1% vs. 87.0%, p=0.012), and were more often managed medically (16.4% vs. 9.4%, p<0.001). Both TAAD and TBAD diabetics experienced more hypotension (TAAD, 37.3% vs. 27.6%, p=0.001; TBAD, 14.4% vs. 9.5%) and acute renal failure (TAAD, 31.8% vs. 23.6%; TBAD, 26.5% vs. 17.6%) during hospitalization. Acute renal failure was more frequently associated with diabetes both in TAAD managed medically (31.3% vs. 18.4%, p=0.040) and surgically, (31.3% vs. 23.2%, p=0.003), while in TBAD patients, it was more frequently associated with diabetes only in patients managed medically (21.1% vs. 12.9%, p=0.016). In TAAD, in-hospital mortality was comparable for diabetics and non-diabetics (21.7% vs. 20.7%, p=0.650), while in TBAD it tended to be higher for diabetics (13.7% vs. 9.4%, p=0.054), becoming significant in the subgroup undergoing endovascular treatment (23.3% vs. 9.6% p=0.001). Diabetics demonstrated lower 5-year survival (TAAD, 73.5±6.3% vs. 83.2±1.4%, p=0.006; TBAD, 61.4±7.8% vs. 77.1±1.9%, p=0.016). After adjusting for age in multivariable Cox regression analysis, the presence of diabetes was independently correlated with late mortality for TBAD (age, p<0.001, HR 1.05, 95% CI 1.04–1.07 and diabetes p=0.050, HR 1.59, 95% CI 1.00–2.51) and did not reach statistical significance for TAAD (age p<0.001 HR 1.05, 95% CI 1.04–1.06 and diabetes p=0.057 HR 1.6, 95% CI 0.99–2.63).

Conclusion: This AAD cohort showed similar prevalence of diabetes compared to the normal population, and therefore diabetes might have a neutral role in the development of AAD. AAD patients with diabetes tend to have a more adverse outcome, in particular for TBAD.

Does concordance last over years? - From training exercise to practice in the SUCCOUR trial

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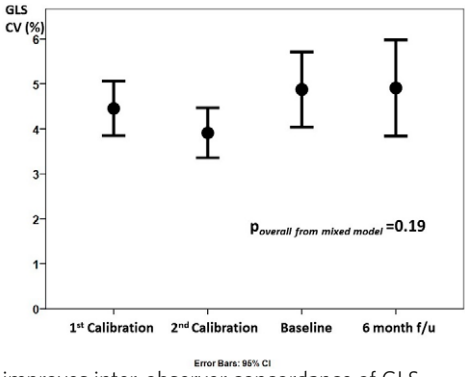
On behalf: SUCCOUR study

Background: Because global longitudinal strain (GLS) has shown greater sensitivity and lower variability than EF, the use of it is recommended in cardio-oncology guidelines. Previous work has documented that a quality control process



improves inter-observer concordance of GLS, which exceeds that of EF. However, it is unknown whether the concordance persists subsequently.

Purpose: To show the stability of training over time would be valuable in both research and practice

Methods: To standardise GLS measurement, we administered a two-stage baseline calibration session with tailored feedback to 18 independent strain readers at 17 different sites in a multi-national randomised controlled trial. This study involved the consistency of GLS between the sites and core lab (CL) over 6 month follow-up (6MFU). Coefficient of variance (CV) was used to determine concordance.

Results: 18 readers had completed the calibration and the CV of GLS at 1st and 2nd session were 4.5±3.1% and 3.9±2.9%. In the trial, 71 patients (54±13 years, 66 female) were enrolled. The time delay between training and initial analysis was 20±23 weeks. Baseline GLS of the overall group at CL and sites (-21.1±2.4% vs -20.3±1.9%, p=0.16) decreased at 6MFU (-19.8±2.5% vs -19.3±2.6%, p=0.85). The CV of GLS at baseline and 6MFU were 4.9±3.5% and 4.9±4.5% (p=0.96). In the whole period from 1st calibration to the 6MFU, the CV was stable and did not significantly change (p=0.19) (Figure). In contrast, the CV of EF at 1st session, baseline & 6MFU were 8.5±7.2, 4.7±3.3 & 6.1±5.0%, respectively and those tended to exceed that of GLS at each time-point (1st Cal: p<0.001, baseline: p=0.78, 6MFU: p=0.07, respectively).

Conclusion: Consistency of measurement of sequential GLS is critically important in clinical trials as well as in practice. The results of this study show that the benefits of an initial calibration process carry over to ongoing follow-up.

Feature-tracking cardiovascular magnetic resonance derived myocardial right ventricular strain parameters in patients with ST-segment elevation myocardial infarction patients and a con

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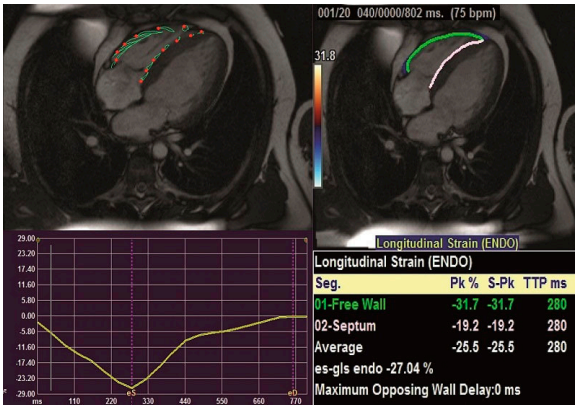


Example of RV strain analysis

Recovery and comparison of RV strain

	CTO-RCA (n=82)	IRA-RCA (n=55)	Control (n=34)	p-value CTO-RCA vs control	p-value IRA-RCA vs control	p-value CTO-RCA vs IRA-RCA
Global RV strain (%)						
Baseline (BL)	-21.3 (6.4)	-17.7 (7.6)	-21.6 (6.7)	0.81	0.01	0.005
Follow-up (FU)	-23.5 (6.3)	-22.6 (5.3)	-23.4 (4.2)	0.99	0.43	0.41
Change	-2.1 (7.7)	-4.9 (8.6)	-1.8 (7.2)	0.82	0.07	0.06
p-value (BL vs FU)	0.02	<0.001	0.16			
RV free wall strain (%)						
Baseline	-28.4 (8.2)	-23.8 (8.7)	-29.7 (6.9)	0.38	0.001	0.003
Follow-up	-30.3 (7.9)	-28.4 (7.8)	-30.5 (5.1)	0.84	0.14	0.19
Change	-1.9 (8.9)	-4.6 (10.5)	-0.8 (6.8)	0.49	0.04	0.11
p-value (BL vs FU)	0.06	0.002	0.49			

Introduction: The right ventricle (RV) is frequently involved in STEMI patients with concurrent CTO when the culprit or CTO is located in the right coronary artery (RCA). Identification of RV dysfunction has prognostic implications. Feature-tracking CMR (FT-CMR) strain is a novel technique to assess early myocardial deformation, however RV strain in STEMI patients with CTO has never been determined. The objective of this study was to investigate FT-CMR RV strain in STEMI patients with CTO and the effect of PCI CTO on strain recovery.

Methods: The EXPLORE trial included STEMI patients after primary PCI with concurrent CTO and randomized to PCI CTO (n=148) or no-PCI CTO (n=154). In this substudy, we analysed 171 EXPLORE patients with serial RV strain data (baseline and 4 month FU) and divided them in three groups: (1) CTO-RCA (patients with CTO in RCA and culprit in non-RCA; n=82), (2) IRA-RCA (culprit in RCA and CTO in non-RCA; n=55), and (3) control group (culprit and CTO in non-RCA; n=34). RV strain was measured off-line using the 4-chamber longitudinal axis (Fig. 1).

Results: Mean age was 60±10 years. Baseline RV strain was lower in IRA-RCA group compared to CTO-RCA and control group (-17.7±7.6% versus -21.3±6.4% and -21.6±6.7%; p=0.005 and p=0.01). RV strain parameters significantly improved in both CTO-RCA and IRA-RCA at follow-up, but not in controls. Strain recovery was the highest in IRA-RCA patients (from -17.7±7.6% to -22.6±5.3%; p<0.001) (table 1). However there was no treatment effect of PCI CTO on RV strain recovery in CTO-RCA patients.

Conclusions: This is the first study to report FT-CMR RV strain. We found that baseline RV strain was most impaired in culprit-RCA compared to CTO-RCA patients and controls. Furthermore, RV strain significantly improved from baseline to follow-up. However, PCI CTO of the RCA did not improve RV strain recovery.

Figure 1 Freedom from cardiac death in all patients

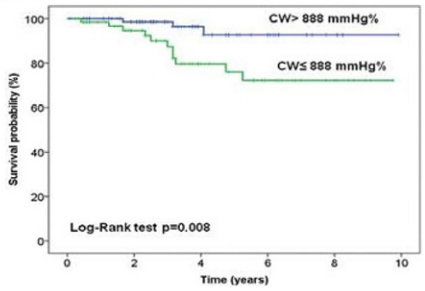
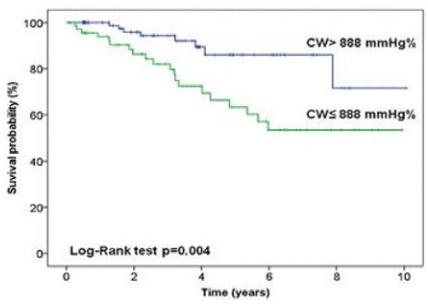


Figure 2 Freedom from all-cause death in all patients



	Univariable analysis			Multivariable analysis		
Cardiac death	**HR**	**95% CI**	**p-value**	**HR**	**95% CI**	**p-value**
Age, per year	1.08	(1.01-1.15)	0.02	1.07	(1.00-1.15)	0.04
Ischaemic disease	3.99	(1.34-11.94)	0.01	2.33	(0.71-1.15)	0.16
NYHA >2	1.39	(0.46-4.24)	0.56			
LBBB	0.87	(0.27-2.77)	0.81			
LVEF, per %	0.99	(0.92-1.08)	0.89			
Septal flash	0.19	(0.06-0.62)	0.006	0.48	(0.12-1.95)	0.30
CW, per mmHg%	0.99	(0.99-1.00)	0.04	0.99	(0.99-1.00)	0.04
CRT-response	0.26	(0.09-0.78)	0.02	0.68	(0.18-2.57)	0.58
All-cause death						
Age, per year	1.05	(1.01-1.09)	0.01	1.06	(1.01-1.10)	0.01
Ischaemic disease	2.69	(1.27-5.66)	0.009	1.94	(0.86-4.39)	0.11
NYHA>2	1.86	(0.80-4.30)	0.15			
LBBB	0.85	(0.34-2.12)	0.72			
LVEF, per %	0.98	(0.93-1.04)	0.50			
Septal flash	0.39	(0.19-0.83)	0.02	0.87	(0.34-2.22)	0.77
CW, per mmHg%	0.99	(0.99-1.00)	0.03	0.99	(0.99-1.00)	0.03
CRT-response	0.36	(0.17-0.76)	0.007	0.24	(0.24-1.43)	0.59

Myocardial constructive work is a predictor of long-term outcomes in patients with heart failure undergoing cardiac resynchronization therapy

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Background: Myocardial constructive work (CW) assessed by pressure strain loops (PSLs) is an independent predictor of cardiac resynchronization therapy response (CRT+).

Purpose of the study: To assess the role of CW in the prediction of long-term outcome in patients undergoing CRT.

Methods: 2D- and speckle-tracking echocardiography were performed in 166 CRT

candidates (mean age: 66±10 years, males: 69%) before CRT implantation and at 6-month follow-up. Left-ventricular (LV) end-systolic volume reduction >15% at 6-month follow-up defined CRT+ and occurred in 48 (29%) patients.

Results: After a median 4-year FU (range: 1.3–5 years), all-cause death occurred in 28 patients (17%), cardiac death in 14 (8%). At Cox-regression analysis, CW emerged as an independent predictor of outcome (Table 1). A CW cut-off of 888 mmHg% (AUC 0.71, p=0.007 and AUC 0.67, p=0.004 for cardiac and all-cause mortality) was associated with an increased mortality risk (Figures 1, 2).

Conclusions: The estimation of LV-CW is a relatively novel tool, which allows the prediction of long-term outcome in CRT candidates

Myocardial constructive work is additive to left ventricular dyssynchrony and volumetric response to CRT in the prediction of overall mortality after CRT implantation

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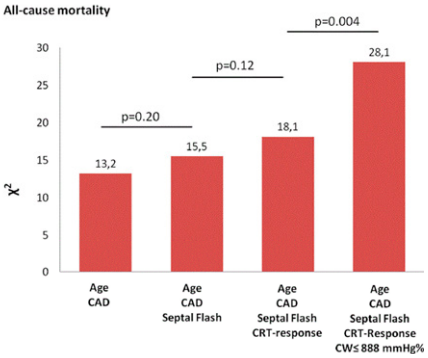
Background: Recent studies have shown that myocardial constructive work (CW) assessed by pressure strain loops (PSLs) is an independent predictor of the response to cardiac resynchronization therapy (CRT). Aim of our study is to assess if CW has an additive value in the prediction of long-term outcome of patients undergoing CRT, in addition to CRT response (CRT+) and left ventricular (LV) dyssynchrony.

Methods: 2D standard and speckle tracking echocardiography were performed in 166 CRT candidates (mean age: 66±10 years, males: 69%, QRS duration: 165±19 ms) before CRT implantation and at 6-month follow-up. Myocardial constructive work (CW) was assessed by PSLs. CRT+ was defined by a >15% reduction in left-ventricular end-systolic volume at 6-month

Table 1

Cardiac death	Univariable analysis			Multivariable analysis		
	HR	95% CI	p-value	HR	95% CI	p-value
Age, per year	1.08	(1.01–1.15)	0.02	1.07	(1.00–1.15)	0.04
Ischaemic disease	3.99	(1.34–11.94)	0.01	2.33	(0.71–1.15)	0.16
NYHA >2	1.39	(0.46–4.24)	0.56			
LBBB	0.87	(0.27–2.77)	0.81			
LVEF, per %	0.99	(0.92–1.08)	0.89			
Septal flash	0.19	(0.06–0.62)	0.006	0.48	(0.12–1.95)	0.30
CW, per mmHg%	0.99	(0.99–1.00)	0.04	0.99	(0.99–1.00)	0.04
CRT-response	0.26	(0.09–0.78)	0.02	0.68	(0.18–2.57)	0.58



follow-up and was observed in 48 (29%) patients. LV dyssynchrony was visually assessed by septal flash.

Results: After a median FU of 4 years (range: 1.3–5 years), all-cause death occurred in 28 patients (17%). At multivariable Cox-regression analysis, CW and age were the only prognostic predictors of cardiac death (Table 1). At ROC curve analysis, CW≤888 mmHg% was the best cut-off to predict all-cause mortality (AUC 0.67, p=0.004). Variables with a p-value <0.05 at univariable Cox-regression analysis were used to test the prognostic power of different nested models. Only the addition of CW≤888 mmHg% to a model including clinical variables (age and ischemic etiology for heart failure), SF, and CRT+ caused a significantly increase in model power for the prediction of prognosis cardiac (χ2: 13.2 vs 28.1, p=0.004) (Figure 1).

Conclusions: The estimation of myocardial CW has an additive value for the prediction of mortality in CRT candidates, over SF and volumetric CRT-response.

Myocardial constructive work is additive to volumetric response to cardiac resynchronization therapy in the prediction of mortality after CRT implantation

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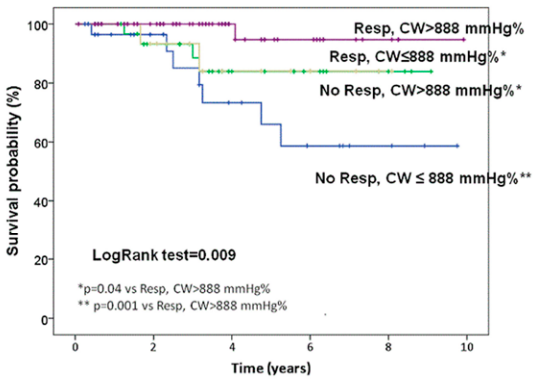
Background: Recent studies have shown that myocardial

Table 1

Predictors of cardiac death	Univariable analysis			Multivariable analysis		
	HR	95% CI	p-value	HR	95% CI	p-value
Age, per year	1.08	(1.01–1.15)	0.02	1.07	(1.00–1.15)	0.04
Male sex	1.75	(0.49–6.27)	0.39			
Ischaemic disease	3.99	(1.34–11.94)	0.01	2.33	(0.71–1.15)	0.16
NYHA >2	1.39	(0.46–4.24)	0.56			
QRS duration, per ms	0.99	(0.97–1.03)	0.81			
LBBB	0.87	(0.27–2.77)	0.81			
LVEF, per %	0.99	(0.92–1.08)	0.89			
LVEDV, per ml	1.02	(0.99–1.01)	0.49			
LVESV, per ml	1.00	(0.99–1.01)	0.53			
Septal flash	0.19	(0.06–0.62)	0.006	0.48	(0.12–1.95)	0.30
CW, per mmHg%	0.99	(0.99–1.00)	0.04	0.99	(0.99–1.00)	0.04
CRT-response	0.26	(0.09–0.78)	0.02	0.68	(0.18–2.57)	0.58

Freedom from cardiac death according to CW and CRT response



constructive work (CW) is an independent predictor of the volumetric response to cardiac resynchronization therapy (CRT).

Purpose of the study: To assess if CW is additive to volumetric CRT-response in the prediction of cardiac mortality in CRT-candidates.

Methods: 2D-standard and speckle-tracking echocardiography were performed in 166 CRT candidates (mean age: 66±10 years, males: 69%) before CRT implantation and at 6-month follow-up. Left ventricular (LV) CW was assessed by pressure-strain loops (PSLs). A reduction in LV end-systolic volume >15% at 6-month follow-up defined CRT-volumetric response and was observed in 48 (29%) patients.

Results: After a median 4-year FU (range: 1.3–5 years), cardiac death occurred in 14 patients (8%). CW and age were the only prognostic predictors of cardiac death (Table 1), independently from septal flash and CRT-volumetric response. At ROC curve analysis, CW≤888 mmHg% was the best cut-off to predict cardiac mortality (AUC 0.71, p=0.007). Among CRT responders, the presence of CW≤888 mmHg was associated with a dismal prognosis (log-rank test p=0.04). The concomitance of CW≤888 mmHg and absence of volumetric response to CRT identified patients with the worst prognosis (log-rank test p=0.001) (Figure 1)

Conclusions: Left ventricular CW allows the prediction of cardiac death in CRT candidates. A CW≤888 mmHg is associated with a increased cardiac mortality in both CRT responders and non-responders.

Right ventricular free wall strain predicts low cardiac output syndrome in patients left ventricular ejection fraction >35% undergoing open aortic valve replacement

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Background: Low cardiac output syndrome (LCOS) after surgical aortic valve replacement (SAVR) leads to increased mortality and health care related costs. Right ventricular free wall longitudinal strain (RVFWS) may be a risk factor in patients without severely reduced left ventricular ejection fraction (LVEF). All had LVEF >35%.

Purpose: To evaluate the role of RVFWS to predict the occurrence LCOS after surgical aortic valve replacement in patients without severely reduced LVEF.

Methods: We prospectively recruited patients with severe aortic stenosis, with class I indication for SAVR. Clinical, hemodynamic and echocardiographic data was collected. Conventional right

ventricular function parameters and RVFWS were measured using speckle tracking echocardiography. Univariate and multivariate linear regression analysis was used to analyze variables related with the occurrence of LCOS.

Results: Eighty-one patients (63 years ±8 were included and LCOS occurred in 19 (23%). Patients with LCOS had more frequently diabetes (35.5 vs 10.5%, p=0.037), underwent more mitral valve replacement (3% vs 16%, p=0.046), had longer aortic clamping time (72 (85–116 min) vs 96 (79–136 min), p<0.0008), cardiopulmonary bypass time (99 (85–116 min) vs 120 (102–184 min) p<0.001), lower LV global longitudinal strain (GLS) (-17±4% vs 14±5%, p=0.001) and RVFWS (-14±4 vs -18±4%, p=0.0001). Interestingly LVEF (p=0.065), tricuspid annular plane systolic motion (p=0.28) right ventricular fractional area change (p=0.57) and right ventricular systolic pressure (p=0.062) did not differ. In the multivariate analysis, RVFWS was the only independent predictor of LCOS (Table). On ROC curve analysis a RVFWS with an absolute value lower than 15.1% had a sensitivity of 72% and a specificity of 79% (AUC=0.78) for LCOS occurrence.

Conclusions: RVFWS is a strong independent predictor of LCOS after aortic valve replacement in patients without severely reduced LVEF. RVFWS can improve risk stratification for LCOS in this patient subset. Future studies to confirm our findings are needed.

Multivariate linear logistic regression analysis for LCOS

Variable	Odds Ratio (CI 95%)	p value
Diabetes	0.37 (0.05–2.69)	0.32
Mitral valve replacement	1.4 (0.09–20.5)	0.80
CPB	1.029 (0.95–1.07)	0.44
Aortic clamping time	1.12 (0.92–1.08	0.78
LV GLS	1.046 (0.84–1.29)	0.68
RVFWS	1.49 (1.13–1.78)	0.002

Role of cardioversion in the management of non-valvular atrial fibrillation: insights from the GARFIELD-AF registry

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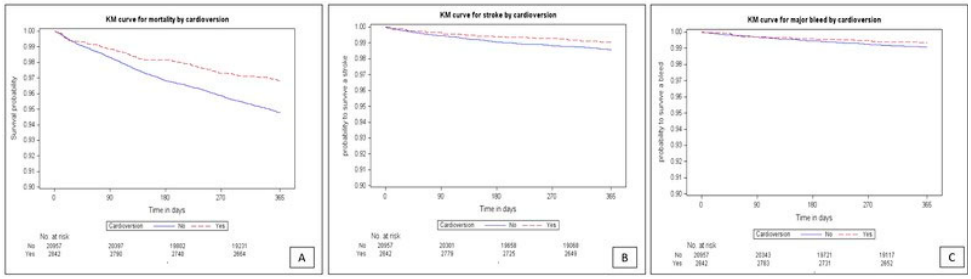
On behalf: the Garfield-AF Investigators

Introduction: In atrial fibrillation (AF), a strategy of rhythm control based on cardioversion, by restoring sinus rhythm, may reduce the risk of stroke/systemic embolization (SE) and improve quality of life. However, randomized trials conducted so far have failed to show a benefit of cardioversion on hard endpoints. This study aims to investigate the prevalence of cardioversion and its association with clinical outcomes in patients from GARFIELD-AF registry.

Methods: GARFIELD-AF is a prospective, global registry of patients with recent-onset (<6 weeks) non-valvular AF (NVAF). Patients were enrolled in 32 countries between 2010 and 2016, patients with paroxysmal AF were excluded from the analysis. Comparisons were made between those receiving cardioversion at baseline and patients who had no cardioversion. Clinical endpoints, evaluated over 1 year, were: all-cause mortality, stroke or systemic embolism (SE) and major bleeding. An adjusted Cox proportional hazard model was utilized.



Results: The study cohort consisted of 23,919 patients; 2856 received cardioversion (11.9%). Patients who were treated with cardioversion were younger (65.5±11.7 years vs 70.6±11.3 years; p≤0.001), had a shorter time since AF diagnosis (1.7±1.6 weeks vs 2.0±1.7 weeks; p≤0.001), and were more often treated in a cardiology setting (73.9% vs 63.5%; p≤0.001). Event rates per 100 person years (95% CI) for all-cause mortality were 3.26% (2.65–4.01) (n=89) for cardioversion vs 5.40% (5.09–5.76) (n=1072) for no cardioversion, (Fig.1); stroke/SE rate 0.96% (0.65–1.40) (n=26) for cardioversion and 1.48% (1.32–1.65) (n=291) no cardioversion and major bleed 0.66% (0.42–1.05) (n=18) cardioversion vs 0.93% (0.80–1.07) (n=183) no cardioversion. Adjusted hazard ratios (95% CI) for cardioversion were 0.69 (0.53–0.90) for all-cause mortality, 0.92 (0.58–1.44) for stroke/SE and 0.82 (0.46–1.47) for major bleed.

Conclusion: Data from GARFIELD-AF show that cardioversion is used in a minority of patients with recent onset, non-paroxysmal NVAF. Patients who receive cardioversion have a lower risk of major events than those who did not. Our results, after adjustment, support the findings from randomized clinical trials, which suggest that there is no additional risk associated with cardioversion.

Segmental strain predicts functional recovery incremental to infarct in patients with a concurrent chronic total occlusion after primary percutaneous coronary intervention for stemi

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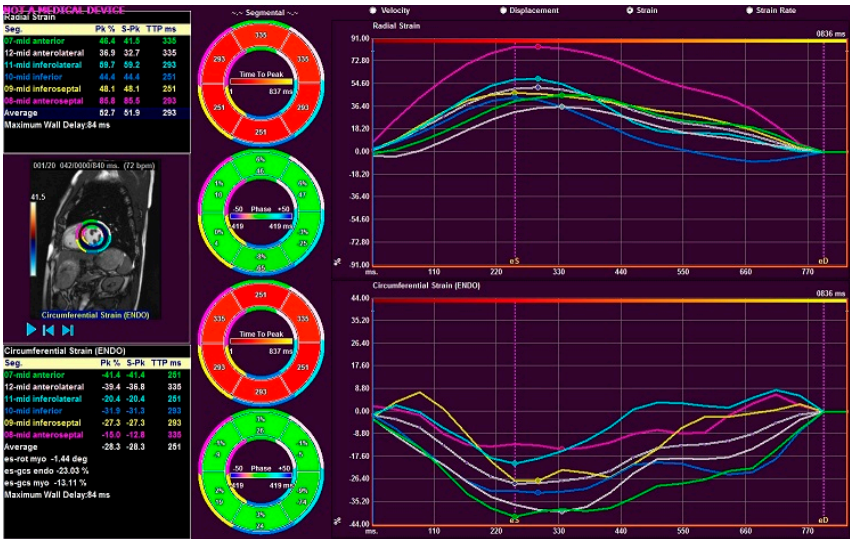
On behalf: EXPLORE investigators

Background: In the randomized EXPLORE trial in ST-segment elevation myocardial infarct (STEMI) patients percutaneous coronary intervention (PCI) of the concurrent chronic total occlusion (CTO) compared to CTO-No PCI did not result in improved global left ventricular function. Currently myocardial strain is gaining more interest as it able to identify subtle but important regional myocardial deformation.

Purpose: We aimed to determine the recovery and prognostic value of segmental circumferential strain (CS) measured with cardiovascular magnetic resonance (CMR) featuring-tracking (FT).

Methods: In the current study 2560 segments were available for serial segmental CS analysis (n=160 patients). Segmental CS was calculated from core lab quantified 3 short axis views (basal, mid and apical) according to the 16-segment model (figure 1).



Example segmental CS analysis

Results: Segmental CS significantly recovered from baseline to 4 months follow-up (p<0.001). There was no significant treatment effect of CTO-PCI on strain recovery. Baseline segmental CS independently predicted recovery of SWT, incremental to baseline SWT and transmural extent of infarction (TEI) (p<0.001) in the dysfunctional segments, especially in the CTO territory (table 1).

Conclusions: Our study showed that segmental strain significantly improved over time in STEMI patients with a CTO with no treatment effect of CTO-PCI on strain recovery. Furthermore, segmental CS was a strong and independent predictor for segmental recovery, incremental to infarct. This finding needs further examination as, different from TEI, segmental CS can be measured without the use of a contrast agent, making it a possible alternative in patients with contrast allergy or renal failure

Prediction of segmental recovery

	Coefficient	SE	t	p-value*
Dysfunctional segments (s=1202)				
Segmental CS	-0.33	0.08	-4.07	<0.001
SWT	-0.54	0.05	-11.90	<0.001
TEI >50%	-2.92	2.75	-1.06	0.29
MVO present	-7.61	2.00	-3.81	<0.001
CTO PCI	4.87	2.45	1.99	0.049
Dysfunctional segments in CTO territory (s=498)				
Segmental CS	-0.47	0.14	-3.34	0.001
SWT	-0.43	0.08	-5.24	<0.001
TEI >50%	-6.04	6.06	-1.00	0.32
CTO PCI	7.82	3.04	2.57	0.01

**Outcomes were analyzed using multilevel analysis (linear regression).*

The effect of age on quality of life in patients with cardiac implantable electronic devices. The results of an EHRA Scientific Initiatives Committee multinational survey in Italian patients

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Background: Cardiac implantable electronic devices (CIEDs) are important therapeutic options to oppose the effects of bradyarrhythmias or to improve prognosis of patients with heart failure (HF). Aim of this study was to evaluate age-related attitudes, worries, psychological effects, and met or unmet needs in an Italian population after a CIEDs implantation.

Methods: Patients with CIEDs attending their periodical medical evaluation at the Electrophysiology Laboratories received a questionnaire specifically conceived by the EHRA Scientific Initiatives Committee as a part of a multicentre, multinational snapshot survey. Seven countries participated to the study, and a total of 1644 replies were collected. Of these, 437 (26%) were from Italy, which was the second country for number of participants. Present results refer to the Italian population only. CIEDs were stratified into devices to treat bradycardia (pacemaker - PM) or HF (cardiac resynchronization therapy - CRT; implantable cardiac defibrillators - ICD; CRT with defibrillator - CRT-D).

Results: The use of CIEDs was more common at advanced age (≤50: 3.2%; 51–75: 37.8%; >75 years: 59.0%). Men were implanted more frequently than women (62.5 vs. 37.5%), especially with defibrillators (men – PM: 57.9%; CRT: 57.1%; ICD: 75.3%; CRT-D: 75.0%; p=0.023). Older patients needed less information about CIEDs than younger ones (≤50: 35.7%; 51–75: 40.6%; >75 years: 50.0%; p=0.048), who would prefer to have more psychological support (p=0.043) and to be better informed about CIEDs-related consequences on physical (p=0.016) and sexual (p=0.027) activities, and on driving limitations (p=0.016). When compared to older subjects, younger individuals with CIEDs experienced more difficulties, especially in their professional activity and private life (≤50: 50.0%; 51–75: 29.7%; >75 years: 22.1%; p=0.011), and more worries, especially fear of abnormal functioning or a shock (≤50: 78.6%; 51–75: 29.7%; >75 years: 26.7%; p=0.009). Younger patients more often felt that their normal daily life was limited by the device (≤50: 7.1%; 51–75: 11.6%; >75 years: 1.6%; p=0.001); on the contrary, health related quality of life (HRQL) more often improved in elderly subjects (≤50: 42.9%; 51–75: 53.7%; >75 years: 68.6%; p<0.001). The degree of information about what to do with CIEDs when the end of life is approaching is scant, with no age-related differences (≤50: 75.0%; 51–75: 66.7%; >75 years: 73.6%; p=0.294). Only 8.6% of subjects aged 51–75 years (no one in the other groups) affirmed they would prefer their ICD was inactive at the end of life.

Conclusions: HRQL after CIEDs implantation improves more frequently in older patients, who are the majority of those receiving a device. The psychological burden of CIEDs is more frequently perceived at younger ages. End of life issues are seldom discussed.

Factors associated with troponin elevation and risk of cardiac events in patients with heart failure and preserved ejection fraction

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On behalf: TOPCAT study group

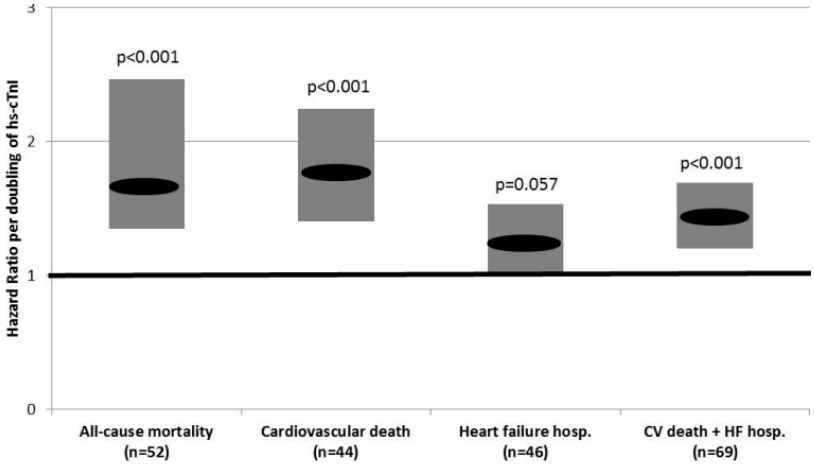
Background/Introduction: Cardiac troponins (cTn) are frequently elevated in patients with chronic heart failure and reduced ejection fraction (HFrEF) and correlate with the risk for death and HF hospitalization. However, identification of factors associated with elevation of cTn concentrations and our understanding of the association of cTn levels with cardiovascular (CV) events in patients with HF and preserved ejection fraction (HFpEF) are limited.

Purpose: To determine the clinical correlates of cTn elevation and the relationship of cTn levels with the risk of specific CV events in patients with HFpEF.

Methods: Of 1767 subjects in the TOPCAT trial with symptomatic HFpEF randomized in the Americas, 236 had baseline measurements of high sensitivity troponin I (hs-cTnI) by the Abbott ARCHITECT STAT assay. We identified clinical correlates of hs-cTnI elevation at baseline in multivariable linear regression models and correlated baseline hs-cTnI levels with adjudicated CV outcomes over mean follow-up time of 2.6±1.5 years using multivariable Cox models. Model discrimination was assessed using the Harrell C statistics.

Results: The median concentration of hs-cTnI at baseline was 6.2 ng/L (interquartile range 3.4–12.9) and levels were detectable in 99.8% of the patients. In multivariable models, higher hs-cTnI concentrations were associated with male gender, black race, lower estimated glomerular filtration rate (eGFR) and higher N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels (R2=0.26). After adjustment for these predictors, baseline hs-cTnI level was associated with elevated risk for all-cause mortality, cardiovascular death and composite CV death or HF hospitalization (Figure). In this adjusted model, C statistics for hs-cTnI in discriminating time to CV death or HF hospitalization was 0.76 (95% CI 0.70–0.81). Patients in the highest quartile of hs-cTnI demonstrated a 4-fold risk of the composite CV death or HF hospitalization compared to the 1st quartile (HR 3.64 (95% CI 1.53–8.68), p=0.004) in the adjusted model.

Conclusion: In ambulatory patients with HFpEF, elevations in hs-cTnI are associated with male gender, black race, lower eGFR, and higher NT-proBNP. Levels of hs-cTnI are independent predictors of all-cause mortality and CV mortality or HF hospitalization in this patient population.



Hazard ratios (black oval) are presented with 95% CI (gray box) per doubling of hs-cTnI adjusted for race, sex, eGFR and NT-proBNP