NORSKE ABSTRAKTER PÅ ESC 2021

Effect of exercise training on vascular function and endothelial repair in heart failure with preserved ejection fraction: results from the OptimEx trial

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Background - Exercise training improves peak oxygen uptake (VO2) in heart failure with preserved ejection fraction (HFpEF), but the underlying mechanisms are unknown. In other cardiovascular diseases, exercise training improves vascular function and increases levels of circulating endothelium-repairing cells. We aimed to investigate the effects of moderate continuous training (MCT) and high intensity interval training (HIIT) on vascular function and cellular endothelial repair in HFpEF.

Methods - This was a prespecified subanalysis of the Optimizing Exercise Training in Prevention and Treatment of Diastolic Heart Failure randomized trial. HFpEF patients (n=180) were randomized to HIIT, MCT or attention control. At baseline and after 12 weeks, we measured peak VO2, fingertip arterial tonometry (n=109), brachial artery flow-mediated dilation (n=59), aortic pulse wave velocity (n=94), and flow cytometry (n=136) for endothelial progenitor cells (CD45dimCD34+VEGFR2+) and angiogenic T cells (CD3+CD31+CD184+). Changes in these parameters were compared between groups using linear mixed models. Parameters were correlated using Spearman's rho.

Results - At 3 months, we did not observe significant differences between HIIT, MCT and control group regarding changes in vascular function throughout the vascular tree (fingertip arterial tonometry, brachial artery flow-mediated dilation and central arterial stiffness, Table 1) or levels of circulating endothelium-repairing cells (endothelial progenitor cells and angiogenic T cells, Table 1). Results were similar at 12 months and when restricting analysis to patients with at least 70% adherence to training sessions. Patients with higher peak VO2 at baseline had lower numbers of circulating endothelial progenitor cells (rho=-0.22, p=0.011).

Conclusions - In patients with HFpEF, exercise training did not change vascular function or levels of endothelium-repairing cells. Thus, improved vascular function likely does not contribute to the change in peak VO2 after training. These findings are in contrast with the benefits of exercise on vascular function in heart failure with reduced ejection fraction and coronary artery disease.

Change from baseline to 3 months, mean (SD)	*HIIT*	*MCT*	*Control*	*P value time:group interaction*
Peak VO_2 (mL/kg/min)	+1.1 (3.0)	+1.6 (2.5)	-0.6 (3.3)	.001
Fingertip arterial tonometry (reactive hyperemia index)	+0.07 (0.92)	+0.08 (0.75)	+0.05 (0.77)	.902
Brachial artery flow-mediated dilation (%)	+1.2 (4.5)	-1.1 (2.3)	+0.5 (4.2)	.142
Aortic pulse wave velocity (m/s)	-0.4 (1.0)	-0.9 (2.6)	-0.5 (1.2)	.910
Endothelial progenitor cells (per 10^6 mononuclear cells)	-2 (43)	+14 (50)	0 (44)	.197
Angiogenic T cells (per 10^6 mononuclear cells)	-90 (2301)	+389 (2277)	-47 (2499)	.915

Cost-minimisation analysis of acute myocardial infarction rule-out in low-risk patients: primary care emergency setting versus hospital setting

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Background: Hospital management of low-risk chest pain contributes to extensive use of healthcare resources and emergency department crowding. High efficacy rule-out, with subsequent reduction in costs and length of stay, has been demonstrated for the ESC 0/1-hour algorithm using high-sensitivity cardiac troponins (hs-cTn) in hospital cohorts.

Purpose: To estimate potential differences in healthcare costs by assessing patients with low risk for acute coronary syndromes (ACS) in a primary care emergency setting using the ESC 0/1-hour algorithm compared to routine management in a hospital setting.

Methods: This cost-minimisation analysis compared direct costs of applying the 0/1-hour algorithm in a low-risk primary care cohort to a low-risk chest pain cohort at a large general hospital in Norway. Data from the prospective OUT-ACS study (One-hoUr Troponin in a low-prevalence population of Acute Coronary Syndrome,[1] inclusion period 2016-2018) were used to calculate costs per patient at a primary care emergency clinic. For the hospital setting estimates, anonymous data were extracted for all low-risk chest pain patients treated at a large general hospital in 2018. Cost items include complete hospital costs per different diagnosis-related groups as defined in national assessments, as well as resource items required to use the algorithm in primary care, including personnel time and test- and treatment costs. Primary outcome was the difference in healthcare costs when assessing the low-risk cohort in a primary care setting compared to a hospital setting. The secondary outcome was the difference in length of stay.

Results: The costs of assessing the low-risk cohort at the primary care emergency clinic and the general hospital were estimated at €178 and €1480, respectively (Table 1). Thus, the estimated reduction in health care costs among patients assessable by the 0/1-hour algorithm outside of hospital was €1302 per patient, with a mean decrease in length of stay of 18.9 hours. Additional diagnostic procedures (e.g. stress ECG and echocardiogram) were performed in 31.9 % (n=181/567) of the low-risk hospital cohort, which was part of the cost-driving estimate.

Conclusion: Assessment of patients considered as low-risk for ACS with the ESC 0/1-hour algorithm in a primary care emergency setting seems to decrease healthcare costs significantly, in addition to a reduction in both length of stay and potentially unnecessary hospitalisations.

Table 1 Low-risk assessment in a hospital versus primary care emergency setting, costs per patient

	General hospital setting *Low-risk hospital cohort (n=567)*	Primary care emergency clinic *OUT-ACS study cohort (n=1485)*	Difference
Costs per patient	DRG tariffs:* €1480	Laboratory and additional tests: €41 Personnel costs: €137	
Total	**€1480**	**€178**	**€1302**
Length of stay	**Mean: 22.3 hours**	**Mean: 3.4 hours**	**Mean: 18.9 hours**

* DRG: Diagnosis-related groups, a patient classification system that standardises all charges associated with an inpatient stay from the time of admission to discharge

€: Euro; OUT-ACS: One-hoUr Troponin in a low-prevalence population of Acute Coronary Syndrome [1]

Oral anticoagulation in atrial fibrillation patients at intermediate risk of stroke: a nationwide registry-based cohort (Atrial Fibrillation in Norway - AFNOR)

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Background: The effect of oral anticoagulants (OAC) on prevention of stroke must be carefully balanced against the potential risk of bleeding in patients with atrial fibrillation (AF). The net benefit of OAC in AF patients at intermediate risk of stroke remains unclear.

Aim: We aimed to determine whether the rates of ischemic and haemorrhagic stroke differ between users and non-users of OAC in a nationwide cohort of AF patients at intermediate risk of stroke.

Method: We investigated the association between initiation of OAC treatment and rates of ischemic and haemorrhagic stroke in a cohort of Norwegian patients with non-valvular AF aged ≥18 years with one non-sex CHA2DS2-VASc risk factor registered from 2011 to 2018, linking data from the Norwegian Population Registry, Patient Registry, Prescription Database and Cause of Death Registry. Individuals using OAC at baseline were excluded. Each individual had at least a three years

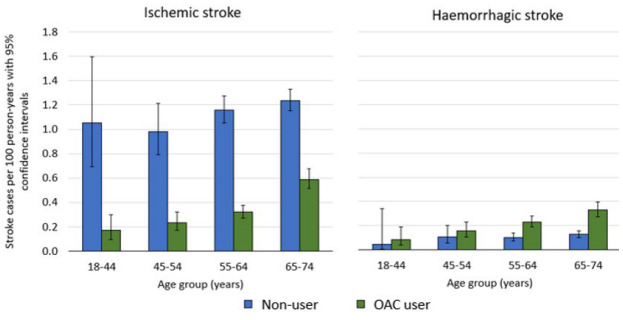
look-back period for identification of their first non-sex CHA2DS2-VASc risk factor, after which they entered the study cohort and were followed until occurrence of stroke, death, emigration, higher CHA2DS2-VASc score or end of follow-up on December 31, 2018. Individuals were defined as exposed to OAC from the first redeemed prescription of OAC with a reimbursement code for AF and throughout follow-up. Rates of ischemic and haemorrhagic stroke were calculated as the number of stroke cases per 100 person-years, with 95% confidence intervals (CI).

Results: During 2011-2018, a total of 61,631 individuals with AF and intermediate risk of stroke were included (mean age 63,8±7,6 years (SD); 37% women), of whom 75% initiated OAC treatment. In total, 1709 ischemic strokes (405 cases in OAC users and 1304 in non-users) were registered during 214,738 person-years, and 378 haemorrhagic strokes (251 cases in OAC users and 127 in non-users) during 213,487 person-years. The rate of ischemic stroke was 0.39 (95% CI, 0.35-0.43) and 1.19 (95% CI, 1.12-1.25) per 100 person-years in OAC users and non-users, respectively. The haemorrhagic stroke rate was 0.24 (95% CI, 0.21-0-27) and 0.12 (95% CI, 0.10-0.14) per 100 person-years in OAC users and non-users, respectively. Both ischemic and haemorrhagic stroke rates were highest among those over 65 years of age (Figure 1).

Conclusion: In a nationwide cohort of Norwegian AF patients at intermediate risk of stroke, three out of four initiated treatment with OAC. Use of OAC was associated with a considerably lower rate of ischemic stroke compared to non-OAC use. Although haemorrhagic stroke rates were increased in the OAC-users vs. non-users, the hemorrhagic stroke rates were generally low.

Figure 1. Rates of ischemic and haemorrhagic stroke per 100 person-years in AF-patients at intermediate risk of stroke (CHA2DS2-VASc score 1 in men, score 2 in women) by OAC use during 2011 to 2018. Age corresponds to age at attainment of the first non-sex CHA2DS2-VASc risk factor.

FIGUR



Integration of Scandinavian genetic data with UK biobank data implicates the RBM20 gene with atrial fibrillation pathogenesis

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Purpose: Atrial fibrillation (AF) is the most common sustained arrhythmia. It carries a large healthcare burden and is associated with serious complications. The arrhythmia has a substantial genetic component and is associated with several structural genes, including the gene TTN. A recent large genome-wide association study on AF found an association to RBM20. The RBM20 gene is a splicing factor targeting TTN, RYR2 and CAMK2D among other cardiac genes. Using Next-Generation Sequencing and data derived from the UK Biobank, we aimed to reveal the role of RBM20 in AF.

Methods and Results: We examined the burden of rare (Minor allele frequency (MAF)<0.01%) RBM20 loss-of-function (LOF) variants in whole-exome sequencing data from the UK Biobank (n = 175,280). AF was defined by ICD9/10, while individuals without AF were used as controls. Association tests aggregating rare variants in RBM20 using the Efficient Variant-Set Mixed Model Association Test (SMMAT) were performed to assess the effect of LOF RBM20 variants, adjusted for age, sex and principal components. We identified 33 LOF variants in RBM20, which were significantly enriched in AF (P = 0.0087).

To examine the effect of rare missense RBM20 variants in the splicing of TTN, we screened an in-house cohort of 531 Scandinavian early-onset AF patients using targeted sequencing. We filtered for rare (MAF<0.1%) and deleterious (defined as combined annotation dependent depletion score >20) variants and identified nine missense variants and three novel LOF variants in RBM20. To evaluate the effect of these RBM20 variants, we constructed a series of human RBM20 single nucleotide base exchange mutants. The splicing activity of the variants was measured with RT-qPCR

on HEK293 cells transfected with a TTN241-3 splicing reporter. Four of these variants resulted in a significantly altered splicing activity in TTN, with the largest effect observed for LOF variants.

In order to examine the biological effect of RBM20 variants on structural changes in atrial tissue, we used a Norwegian Brown rat animal model with loss of RBM20. In this model, Transmission Electron Microscopy revealed altered sarcomere and mitochondrial structure in its atrial cardiomyocytes. Furthermore, nanopore RNA sequencing of atrial tissue from the aforementioned animal model indicated altered expression in several key cardiac genes, including TTN and PITX2.

Conclusion: Rare RBM20 LOF variants are significantly enriched in AF cases, seen in a large population of 175,000 individuals. We demonstrated that the effect of LOF RBM20 on alternative TTN splicing can be detected on an individual level in patients with AF. Studies using an animal model indicates that LOF in RBM20 may affect atrial function through altered expression of several genes in the atria, and may cause structural changes in the atrial cardiomyocytes. This suggests that RBM20 may be involved in AF pathogenesis mediated through an atrial cardiomyopathy.

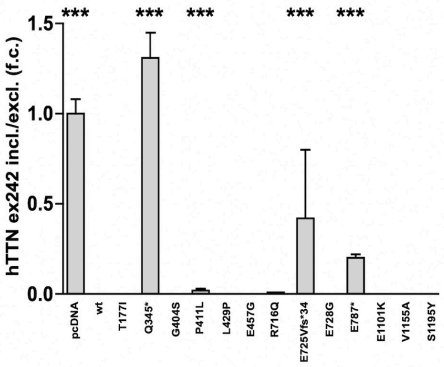

Figure 1. qRT-PCR analysis of HEK293 cells transfected with the TTN241-3 splicing reporter and the mutant *RBM20* expression constructs. The *RBM20*-P411L, *RBM20*-E725Vfs*34 and RBM20-E787* variants possessed significantly reduced splicing activity, while the *RBM20*-Q345* variant was completely inactive in splicing. *** indicates significantly altered splicing activity ($P < 0.001$)

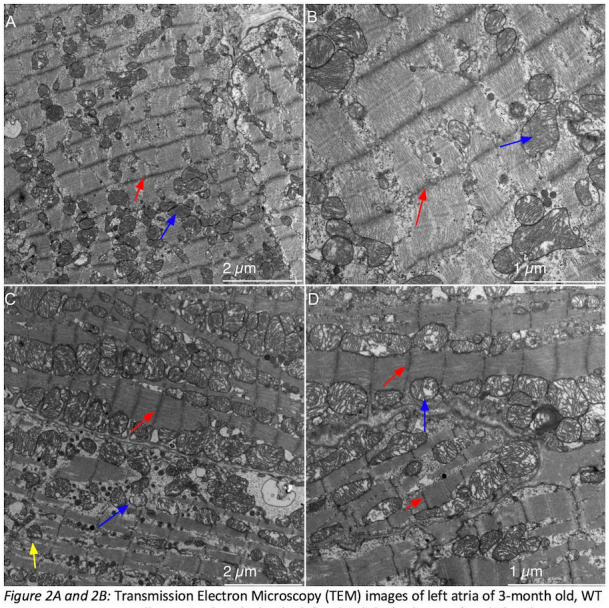

Figure 2A and 2B: Transmission Electron Microscopy (TEM) images of left atria of 3-month old, WT rat. Sarcomeres are well organized, with clearly defined Z-disks (red arrows) and I-bands.

Figure 2C and 2D: TEM images from left atria of 3-month old, haploinsufficient *RBM20* rat (*RBM20* +/-). In contrast to wildtype, Z-disks appear thin and fuzzy (red arrows), while I-bands and M-bands are blurry and poorly defined. Mitochondria are abundant and show compromised structure (blue arrows). Yellow arrows indicate myofibril degradation.

Prognostic value of fractional flow reserve using computed tomography for predicting major adverse cardiac events and mortality in kidney transplant candidates

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Background: Coronary artery disease (CAD) is highly prevalent in patients with severe chronic kidney disease (CKD), it is the leading cause of mortality and morbidity in the short and long term among kidney transplant candidates, and the prevalence of CAD is high even after kidney transplantation. Most institutions recommend non-invasive cardiac tests prior to transplantation. Previous studies have indicated that cardiac screening by coronary computed tomography angiography (CTA) in kidney transplant candidates before transplantation yields both diagnostic and prognostic information. Additional analysis by CT-derived fractional flow reserve (FFRct) may improve

diagnostic performance and have prognostic information.

Purpose: To establish the occurrence of major adverse cardiac events (MACE) and all-cause mortality in kidney transplantation candidates undergoing cardiac screening with coronary CTA with additional FFRct.

Methods: Coronary CTA scans from 340 consecutive kidney transplant candidates (CKD stage 4-5) undergoing cardiac evaluation with coronary CTA as part of the diagnostic work-up, between February 2011 and September 2019, were evaluated with subsequent FFRct analysis, the FFRct results were not clinically available.

Patients were categorized into three groups based on distal FFRct; normal FFRct > 0.80, moderate FFRct 0.80 to > 0.75, low FFRct ≤ 0.75. Secondary analysis was performed using lesion specific (≥ 50% stenosis on coronary CTA) FFRct values, with normal FFRct > 0.80 and abnormal ≤ 0.80.

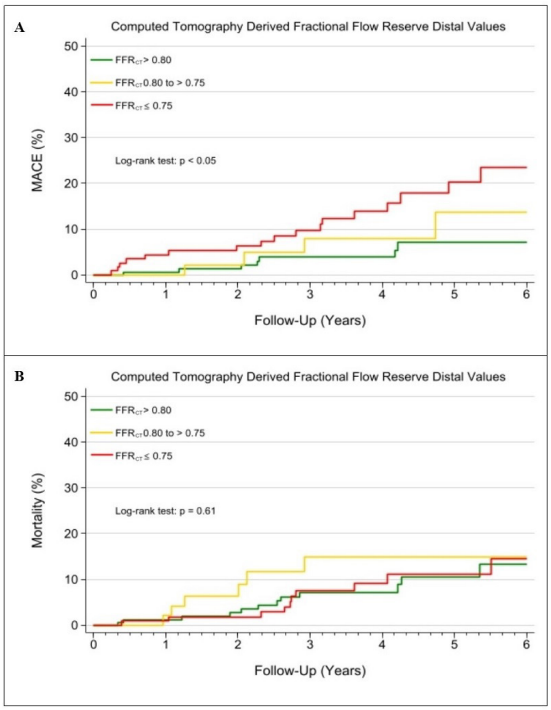
The primary end-point was MACE (cardiac death, cardiac arrest, myocardial infarction or revascularization unrelated to baseline work-up). The secondary end-point was all-cause mortality. End-point and baseline data were identified through patient files and registry data.

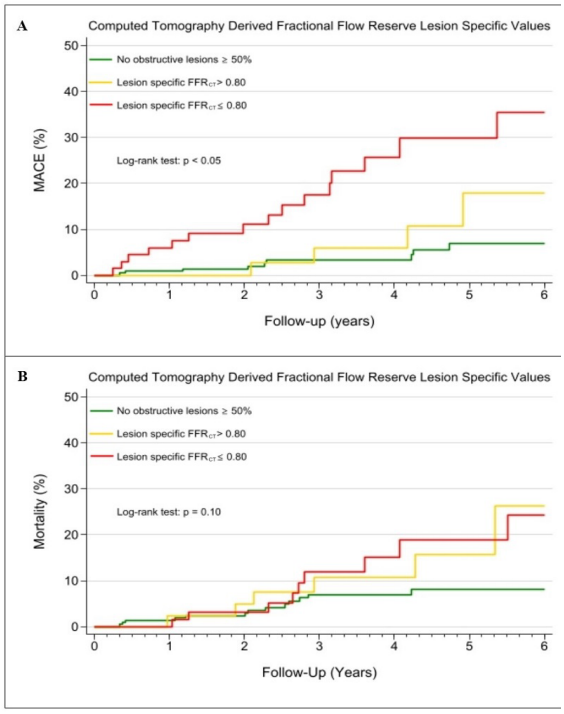
Results: Patients had a median age of 53 [45-63], 63% were men, 31% were on dialysis, the median follow-up time was 3.3 years [2.0-5.1]. During follow-up, MACE occurred in 28 patients (8.2%) and 28 patients (8.2%) died.

When adjusting for risk factors and kidney transplantation during follow-up, the primary analysis identified increased risk of MACE in patients with lower distal FFRct compared to patients with FFRct > 0.80; FFRct 0.80 to > 0.75; Hazard ratio (HR): 1.63 (95% CI: 0.48-5.58; p = 0.44), and FFRct with FFRct ≤ 0.75; HR: 3.27 (95% CI: 1.34-7.96; p <0.01). In the secondary analysis based on lesion-specific FFRct values, a FFRct ≤ 0.80 was associated with a higher risk of MACE compared to FFRct > 0.80; HR 3.21 (95% CI 1.01-10.20, p < 0.05).

There were no significant differences in mortality between groups.

Conclusions: In kidney transplant candidates, a low FFRct ≤ 0.75 was predictive of MACE but not mortality. A lesion-specific approach found similar results with increased risk of MACE in patients with lesion-specific FFRct ≤ 0.80. Thus, FFRct adds prognostic information to the cardiac evaluation of these patients with severe CKD.





Perceptions of efficacy and safety of generic medicines in patients after percutaneous coronary intervention

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Background: Generic medicines are bioequivalents to brand-name medicines, and compelling evidence for the safety and efficacy of generic medicines exists. However, negative perceptions about generic medicines can potentially reduce adherence to prescribed therapy and thereby efficacy of the treatment.

Purpose: To describe patients' perceptions of generic medicines after percutaneous coronary intervention (PCI), and to investigate the association between perceptions and sociodemographic and clinical factors. Furthermore, we sought to investigate if these perceptions change over time.

Methods: CONCARDPCI is a large-scale prospective multicentre cohort study on 3251 patients after PCI. The study was conducted between June 2017 and May 2020 at seven large referral PCI centres in Norway and Denmark. Clinical data, including invasive procedures and patient characteristics, were collected from the patients' medical records. Sociodemographic characteristics were obtained by self-report during index hospitalization after PCI. Postal or electronic questionnaires comprising questions regarding perceptions of generic medicines were distributed two (T1) and six (T2) months after discharge from hospital to included patients. The time intervals ensured that a sufficient amount of time had passed so that refill of prescriptions was necessary. To investigate perceptions of generic medicines and the associations with sociodemographic and clinical characteristics, logistic regression analysis was performed.

Results: Most patients were men (78%), married or living with a partner (75%), elderly (mean age 66 years, SD11, range 20-96 years), and 28% were admitted to hospital due to non-ST-segment elevation myocardial infarction. At T1, 70% perceived generic medicines to be as effective, safe (68%), produce the same side effects (64%), and contain the same active ingredients as brand-name medicines (64%). Perceptions of generic medicines were similar at T2. No significant associations were found with age, marital status, living alone, taking ≥5 medications, or participation in cardiac rehabilitation. However, Danish patients ($p<0.001$), those with a higher education level (college/university≥4 years) ($p=0.01$), total household income > 83.000 Euro ($p=0.007$), female gender ($p<0.001$), and history of coronary artery disease ($p=0.048$) had more positive perceptions of generic medicines.

Conclusion: Approximately one third of the patients had negative perceptions of generic medicines after PCI, and these negative perceptions do not seem to change substantially during the first six months after PCI. As negative perceptions of generic medicines have been found to be a barrier to medication adherence, improving patients' knowledge and confidence in generic medicines after PCI may be pivotal to reach treatment goals set forth by the 2018 ESC/EACTS Guidelines on myocardial revascularization.

Inflammasome activation in epicardial, pericardial and subcutaneous adipose tissue in patients with coronary heart disease

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Background: The adipose tissue (AT) compartments surrounding the heart have been claimed to exert different pro-inflammatory properties with different associations with cardiovascular disease states. The epicardial AT (EAT), located close to the coronary arteries between the myocardium and the pericardial layer, seems to be associated with atherosclerosis and metabolic syndrome, whereas the pericardial AT (PAT), separated from the heart by the pericardium, is discussed to have less pro-inflammatory properties.

Purpose: The aim of the present study was to explore any differences in genetic regulation of pro-inflammatory markers included in the inflammasome related pathway in EAT, PAT and in subcutaneous AT (SAT). In addition, any relationship to the corresponding inflammatory markers in the circulation was explored.

Materials and methods: Biopsies from EAT, PAT and SAT, and arterial blood samples were collected from 52 patients with coronary heart disease

(CHD) undergoing coronary by-pass surgery (aged 48-82 years, 70% male, median body mass index (BMI) 27.3 kg/m2). RNA was extracted by use of RNeasy Lipid Tissue Mini Kits. Gene expression of Interleukin (IL) -1β, IL-18, NLRP3, Caspase-1, toll-like receptor 4 (TLR4), IL-6, IL-6 receptor and gp130 in the different adipose tissue compartments were analyzed using RT-PCR. Circulating levels where possible, were measured in serum with ELISAs.

Results: We demonstrated that IL-18 and IL-6 were about 4-fold higher expressed in EAT compared to PAT ($p< 0.01$, both) and SAT ($p<0.001$, both), whereas Caspase-1, IL-6R and gp130 were higher expressed in SAT compared to the other compartments (all p 0.06 - <0.001). TLR4 was significantly higher expressed in PAT compared to EAT ($p=0.01$) and SAT ($p<0.001$). No differences in the expression of IL-1β and NLRP3 were found. We could further demonstrate significant correlations between SAT and PAT expression of all the measured genes ($r= 0.358$-0.579, all $p\leq0.01$), except TLR4. No significant correlations between circulating levels and the genetic expression in either AT compartments were observed, and also limited correlations to BMI.

Conclusions: The results shows that only IL-18 and IL-6 were higher expressed in EAT, compared to the two other AT compartments in our non-obese CHD population. The results further show that the inflammasome related genes in pericardial AT associated strongly with subcutaneous AT, suggesting SAT to be more pro-inflammatory than previously expected.

Cardiac function is normal in most patients recovered from COVID-19

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Background: There are conflicting results regarding impaired cardiac function in patients that have recovered from COVID-19. Cardiovascular magnetic resonance (CMR) studies have revealed a very high frequency of cardiac involvement (78%) and ongoing myocardial inflammation (60%) in patients recently recovered from COVID-19. Findings are advocating further investigation of the long-term myocardial consequences of COVID-19 disease.

Purpose: We aimed to investigate left ventricular (LV) and right ventricular (RV) function by a comprehensive echocardiographic study in patients recovered from COVID-19 infection 3 months after admission to hospital.

Methods: All patients (n=92) had been hospitalized for COVID-19 and were examined with echocardiography three months after hospitalization. They were 59 ± 13 years, and 43 % were women. LV function was assessed by ejection fraction (EF) and global longitudinal strain (GLS) and RV function was measured by fractional area change (FAC), tricuspid annular plane systolic excursion (TAPSE) and RV GLS free wall. Tricuspid regurgitation pressure gradient was measured to estimate pulmonary artery pressure.

Results: LV EF was 63 ± 6% and LV GLS was -18.6 ± 2.2%. All patients had normal EF > 53%, but 10 showed signs of subtle impaired LV function by LV GLS (≥ -16%). Only two of these did not have hypertension, LV hypertrophy, diabetes or other preexisting diagnosis of heart disease explaining subtle LV dysfunction. All had normal RV FAC (48 ± 7%) and TAPSE (2.3 ± 0.3 cm). We found modestly impaired RV longitudinal function (RV GLS free wall > -25%) in 30% patients, but none had RV GLS worse than -20%. One-third of all patients with reduced RV GLS had signs of elevated pulmonary arterial pressures, which might impact the assessment of RV function.

Conclusions: Traditional echocardiographic parameters showed normal function in all hospitalized COVID-19 patients three months after hospital admittance. Approximately one-third had subtle ventricular dysfunction detected by sensitive echocardiographic methods, but these findings could mostly be explained by systemic or pulmonary hypertension. We cannot, however, exclude that a slight reduction in cardiac function in a minority of our patients was caused by the COVID-19 infection.

Cardiac arrhythmias 3 months after hospitalization for COVID-19

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Background: The long-term frequencies of cardiac arrhythmias in hospitalized coronavirus

disease 2019 (COVID-19) patients have not been thoroughly investigated.

Purpose: To describe the prevalence of cardiac arrhythmias, 3–4 months after hospitalization for COVID-19.

Methods and results: Participants with COVID-19 discharged from five large Norwegian hospitals were invited to participate in a prospective cohort study. We examined 201 participants (44% females, mean age 58.5 years) with 24-hour electrocardiogram 3–4 months after discharge. Body mass index (BMI) was 28.3 ± 4.5 kg/m2 (mean ± SD), and obesity (BMI > 30) was found in 70 participants (34%). Clinically significant arrhythmias were defined as; ventricular tachycardia (non-sustained or sustained), premature ventricular contractions (PVC) exceeding 200/24 h, or coupled PVC, atrial fibrillation/flutter, second-degree atrioventricular block (AV-block) type 2, complete AV-block, sinoatrial (SA) block exceeding 3 s, premature AV-nodal beats in bigeminy, supraventricular tachycardia (SVT) exceeding 30 s, and sinus bradycardia with less than 30 beats/min. High-sensitive cardiac troponin T (hs-cTnT) was measured at the 3-month follow-up.

Results: Cardiac arrhythmias were found in 27% (n=54) of the participants. Ventricular premature contractions and non-sustained ventricular tachycardia were the most common arrhythmias, found in 22% (n=44) of the participants. Premature ventricular contractions were the most frequent cardiac arrhythmia. More than 200 PVCs per day were observed in 37 participants (18%) with a mean of 1300 PVC/day, and in 35 (95%) of these participants, the PVCs were polymorphic.

Among 10 patients experiencing NSVT, 5 participants had previous CVD, including coronary heart disease (n=1), 1 atrial fibrillation, 2 venous thromboembolism, 4 heart failure. Atrial fibrillation was found in seven patients (3%), none of them of new-onset.

SA block > 3 seconds was only observed in one patient, and no incidence of high degree AV block was discovered. Pre-existing cardiovascular disease or hypertension (CVDH) were reported in 40% (n=81) of the participants. The CVDH group had an increased amount of arrhythmia compared to the group free of CVDH (p = 0.04). High PVCs showed a fair correlation with hs-cTnT levels at 3 months (ρ = 0.21 p = 0.048).

Conclusions: Three months following hospital discharge with COVID-19, cardiac arrhythmia was found in every fourth participant and was associated with a higher concentration of hs-cTnT at 3 months. The clinical implications of persistent ventricular arrhythmia following COVID-19 is not clear, but ventricular ectopy has been linked to increased risk of cardiac disease, including cardiomyopathy and sudden cardiac death.

Table 1. Cardiac arrhythmia after COVID-19 (n=201)

	Number	%
Non-sustained ventricular tachycardia	10	5.0
Premature ventricular contractions >200/24 hour	37	18.4
Atrial fibrillation/flutter*	7	3.5
Second degree- or complete AV-block	0	0
Sinus bradycardia (<30 bpm)	0	0
Sinoatrial block > 3 seconds	1	0
Premature AV-nodal beats in bigeminy	0	0
Supraventricular tachycardia > 30 seconds	3	1.5

*Paroxysmal. persisting or chronic
AV, atrial-ventricular; bpm, beats per minute

Sex-specific difference in cardiac function in patients with systemic sclerosis: association with cardiovascular outcomes

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Background: Cardiac involvement is an important cause of hospitalization and mortality in patients with systemic sclerosis (SSc) and advanced echocardiographic measures such as left ventricular (LV) global longitudinal strain (GLS) have already demonstrated to improve risk-stratification. However, possible sex differences in echocardiographic parameters including LV GLS have not been explored so far. Purpose: To compare standard and advanced echocardiographic parameters between men and women with SSc and evaluate their association with cardiovascular outcomes.

Methods: A total of 746 SSc patients from four different centers were included of which 628 (84%, 54±13 years) women and 118 (16%, 55±15 years) men. Baseline transthoracic echocardiographic (TTE) data with standard and advanced (LV GLS) measurements as well as clinical characteristics were analysed. The study endpoint was the composite of all-cause mortality and cardiovascular hospitalisations.

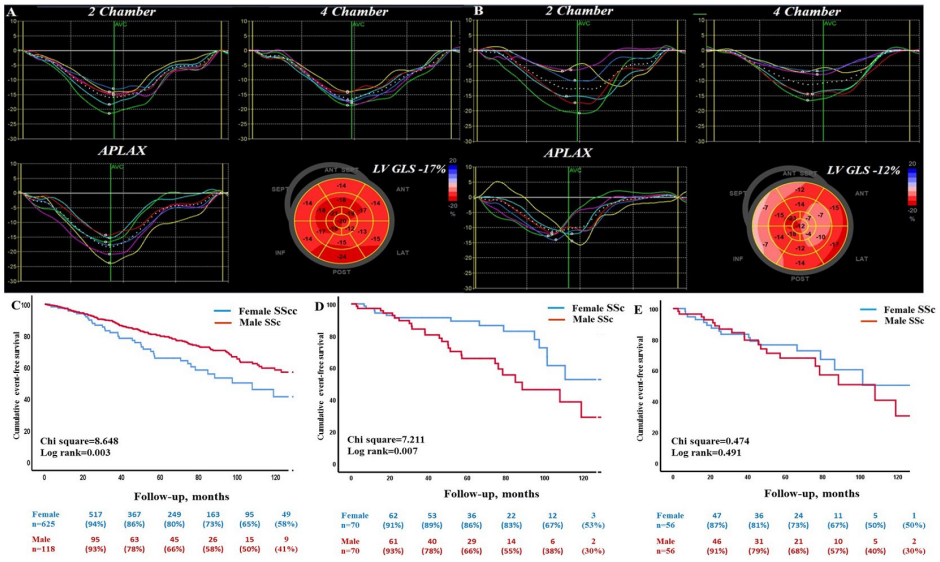

Figure: *LV GLS in woman (A) and man (B) SSc patients, Kaplan Meier survival curve for women and men SSc (C) patients, also adjusted for clinical variables: Age, diffuse SSc, DLCO-SB, lung fibrosis, disease duration, NT-pro BNP (D) and clinical variables +LV GLS (E).*

Results: Men and women showed several differences in terms of disease characteristics: greater modified Rodnan skin score, higher prevalence of diffuse cutaneous SSc, lung fibrosis and myositis, more impaired pulmonary function (DLCO) and higher creatine phosphokinase were observed in men, while women were characterized by longer disease duration, higher NT-proBNP and lower glomerular filtration rate. By TTE, men showed larger LV indexed volumes, lower LV ejection fraction and more impaired LV GLS (-19% (IQR -20%-[-17%]) vs. -21% (IQR:-22%-[-19%] p<0.001). Considering the significant differences in clinical characteristics between men and women, a propensity matching score was applied to explore whether sex-differences in TTE parameters were maintained. The matching was performed according to age, disease duration, presence of diffuse SSc, lung fibrosis, DLCO and NT-proBNP (n=140); after matching, LV GLS still showed significant difference between men and women (-19% IQR -20- [-18] vs. -20% (IQR:-22%-[-18], p=0.03) while LV volumes and ejection fraction did not. After a median follow-up of 48 months (IQR: 26-80), the combined endpoint occurred in 182 patients and Kaplan-Meier survival analysis (Figure) showed that men experienced higher cumulative event rates as compared to women (Chi-square 8.648; Log rank 0.003) even after matching for clinical characteristics (Chi-square 7.211; Log rank 0.007); however, sex difference in outcomes was neutralized after matching groups according to LV GLS. Furthermore, LV GLS showed a significant association with prognosis in the overall group ([HR]: 1.173; 95% [CI]; 1.106-1.244, p<0.001) without significant interaction with sex (p=0.373), indicating a consistent prognostic value of LVGLS for both men and women.

Conclusions: Among patients with SSc, LV GLS is more impaired in men as compared to women even after matching for clinical characteristics, and its impairment is associated with higher prevalence of death and cardiovascular hospitalization.

Changes in EPA and DHA during supplementation with Omega-3 fatty acids and incident cardiovascular events: secondary analysis from the OMEMI trial

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Background: In the OMEMI trial, elderly post-MI patients did not achieve reduction in cardiovascular events from supplementation of 1.8g n-3 polyunsaturated fatty acids (PUFA). In two recent trials of hypertriglyceridaemic patients the REDUCE-IT trial demonstrated an association between high levels of serum eicosapentaenoic acid (EPA) and reduced risk of CV events with 4 g/day icosapent ethyl supplements while in the STRENGTH trial no such association was present

in patients treated with 4 g/day of EPA+ docosahexaenoic acid (DHA).

Purpose: To assess associations between changes in concentrations of EPA and DHA during two years supplementation with n-3 PUFA and incident cardiovascular events in the OMEMI trial.

Methods: In the randomized controlled OMEMI trial, 1014 elderly patients with a recent acute myocardial infarction (AMI) were treated with 1.8g/day of EPA and docosahexaenoic acid (DHA) or placebo for two years, and followed for the primary outcome of MACE (AMI, coronary revascularization, stroke or heart failure hospitalization) and secondary outcome of new-onset atrial fibrillation (AF). Serum concentrations of EPA and DHA were measured at inclusion and at study completion by gas chromatography, and reported as % weight of total FA (%wt) in serum phospholipids.

Results: Serial EPA and DHA measurements at study inclusion and completion were available in 881 patients (92% of survivors). At baseline EPA and DHA concentrations were (mean±SD) 2.84±1.41 and 5.71±1.35 %wt, respectively. Higher baseline EPA and DHA concentrations were associated with previous n-3 PUFA supplementation, lower prevalence of current smoking and diabetes, lower levels of triglycerides and higher levels of HDL-cholesterol (all p<0.05). In patients randomized to n-3 PUFA, EPA and DHA increased with 2.32±1.92 and 0.91±1.19 %wt, respectively, whereas in the placebo group EPA and DHA decreased with -0.39±1.37 and -0.43±1.13 %wt, respectively. Greater increases in EPA and DHA during follow-up were associated with a lowering of triglyceride concentrations, increasing HDL concentrations, and lower baseline concentrations of EPA and DHA (all p<0.001). Among patients treated with n-3 PUFA (n=438), a greater increase in EPA was associated with a lower risk of incident MACE (HR 0.89 [95%CI 0.78-1.00] per %wt, p=0.059) and higher risk of new-onset AF in patients free of AF at inclusion (n=339): HR 1.31 [1.06-1.62] per %wt, p=0.012 (Figure). There were no such associations for changes in DHA: HR 0.86 (95%CI 0.70-1.05), p=0.13 for MACE and HR 1.29 (0.91-1.83), p=0.16 for new-onset AF.

Conclusion: Patients treated with 1.8 g/day n-3 PUFA for two years experienced a doubling of serum EPA concentrations. Greater increases in EPA were associated with a lower risk of MACE, but also a higher risk of new-onset AF. Changes in DHA concentrations were not associated with outcomes, suggesting that EPA may be the more important n-3 PUFA with respect to risk of cardiovascular events.

Associations of maternal hypertensive disorders during pregnancy with offspring risks of ischemic heart disease and stroke: a Nordic cohort study

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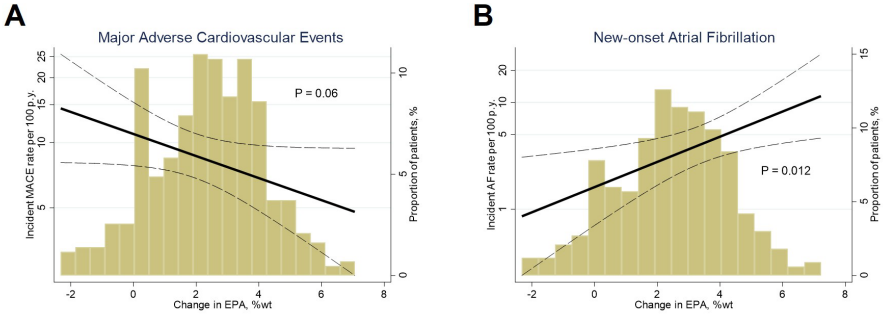
Background: A substantial body of evidence suggests that children exposed to maternal hypertensive disorders during pregnancy (HDP) have increased risks of preterm birth, fetal growth restriction and several cardiovascular risk factors (e.g., hypertension, obesity, diabetes) later in life. However, the direct evidence on the link between maternal HDP and the risk of severe cardiovascular diseases such as ischemic heart disease (IHD) and stroke in the offspring is very limited.

Objective: To investigate the associations between maternal HDP and the risk of IHD and stroke in the offspring.

Methods: We conducted a population-based cohort study by linking several national registers in Sweden and Finland. Live singleton births from the Swedish Medical Birth Register (1973-2014)



and the Finnish Medical Birth Register (1987-2014) were followed for IHD and stroke until 2014 by the national patient and cause of death registers. We performed Cox regression models to examine the association between maternal HDP and its subtypes, i.e., pre-existing chronic hypertension, gestational hypertension, and preeclampsia, and the risk of IHD, and stroke in the offspring while adjusting for relevant maternal and pregnancy-related confounders. We conducted sibling analyses to control for unmeasured shared familial (genetic and/or environmental) risk factors.

Results: Among the 5,807,122 singletons included in the study, 218,322 (3.76 %) children were born to mothers with HDP. During the up to 41 years of follow-up, 2,340 (0.04%) offspring were diagnosed with IHD and 5,360 (0.09%) were diagnosed with stroke. Offspring exposed to maternal HDP had an increased risk of IHD (adjusted hazard ratio (aHR), 1.29; 95% confidence interval (CI), 1.01-1.63), and stroke (aHR,1.33; 95% CI, 1.14-1.56). Significantly increased rates of stroke were also observed in children exposed to the subtypes of maternal HDP: pre-existing chronic hypertension (aHR, 1.64; 95% CI, 1.03-2.60), gestational hypertension (HR, 1.38; 95% CI, 1.08-1.77), and preeclampsia (HR, 1.26; 95% CI, 1.02-1.55). The associations between maternal HDP and offspring's IHD and stroke were independent of preterm birth and small for gestational age at birth. Maternal HDP remained associated with stroke in the offspring (aHR, 1.94; 95% CI, 1.16-3.22), but not with IHD (aHR, 0.89; 95% CI, 0.47-1.67) in the sibling analyses.

Conclusion: Children to mothers with HDP have increased rates of IHD and stroke from childhood to young adulthood. While the link between maternal HDP and IHD in the offspring seemed to be attributed to confounding by familial factors, the relation between maternal HDP and stroke persisted even when considering such confounding. Persons born to mothers with HDP may benefit from early screening and prevention efforts to reduce the risk of IHD and stroke later in life.

A nationwide registry study on heart failure in Norway from 2008-2018: variations in lookback period affect incidence estimates

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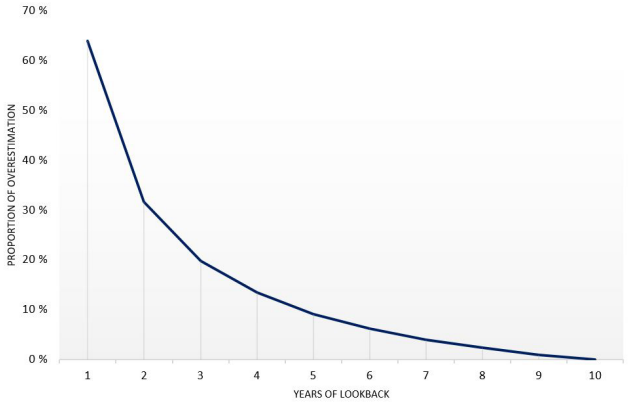
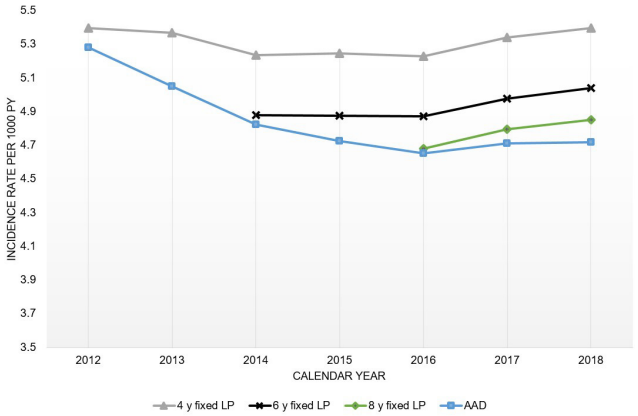
Background/introduction: Incidence estimations of heart failure from registry-based studies may vary because they depend on a retrospective search in the database to exclude previous events (prevalent cases), termed the lookback period.

Purpose: The aim of this study was to assess to what extent different lookback periods affect temporal trends in heart failure incidence utilizing national registry data.

Methods: We identified all heart failure hospital contacts (ICD-10 codes I11.0, I13.0, I13.2, I42.x and I50.x) in adult Norwegian individuals in the





Norwegian Patient Registry (NPR) during 2008-2018. To calculate the influence of varying lookback period on incident cases, we defined 2018 with 10 years of lookback as a reference and calculated the relative difference by using one through nine years of lookback. Temporal trends in age-adjusted incidence rates were estimated with sensitivity analyses using fixed and varying lookback periods (including all available data).

Results: Using a lookback period of 10 years, we identified 14 862 incident patients in 2018 (6 842 women, 8 020 men) with a diagnosis of heart failure. Compared to a 10-year lookback period, application of four, six, and eight years resulted in an overestimation of incident cases by 13.5%, 6.2% and 2.3%, respectively. This corresponds to incidence rates of 5.40, 5.04 and 4.85 per 1000 person-years, respectively. Figure 1 shows that the overestimation of incident cases declined with increasing number of years included in the lookback period. The overestimation was largest in the beginning of the observational period. When assessing temporal trends in incidence rate using a fixed lookback period, the incidence rates were lower with additional years in the lookback period. However, incidence rates increased regardless of whether four, six or eight years were applied. In contrast, incidence rates were lower and declined during the period when including all available data and thereby increasing the lookback period with time. Fig. 2 shows that a relatively shorter lookback period provided higher incidence rate estimates and that the direction of the curves were similar when using a fixed lookback period. Moreover, it shows that including all available data instead of using a fixed lookback period resulted in the misleading conclusion of declining incidence rates.

Conclusions: The length of the lookback period affects incidence estimates when calculating incidence rates from longitudinal health registry data. Our results suggest that one to five years of lookback is too short since incident cases are overestimated by 64% - 9%. A fixed lookback period of six year or more seems beneficial with less overestimation (≤ 6 %).

A randomized clinical study evaluating effects of high-intensity interval training on myocardial microvascular dysfunction

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Background: Myocardial microvascular function assessed with the Index of Microcirculatory Resistance (IMR) after heart transplantation (HTx) predicts the development of cardiac allograft vasculopathy (CAV) and adverse long-term outcome. This study aimed to evaluate the otherwise beneficial effects of high-intensity interval training (HIT) on microvascular dysfunction development.

Methods: Eighty-one de novo HTx patients were randomized to nine consecutive months of HIT or standard care rehabilitation. Coronary physiology assessment with a pressure wire was performed in the left anterior descending coronary artery. IMR was calculated by multiplying the mean distal coronary pressure by the mean hyperemic transit time. Results obtained at three and twelve months after HTx were compared to assess the treatment effect of HIT.

Results: Results were available for 60 patients. 71% were men, and the mean age was 48±13. IMR in the HIT group (n = 26) decreased from 14.8±9.5 to 13.8±8.0, change = 1.2, 95% CI [-2.6 to 4.9] and increased in the standard care group (n = 34) from 13.8±5.8 to 16.8±12.0, change = -3.5, 95% CI [-7.1 to 0.1]. The mean difference between groups was 4.7, 95% CI [-9.7 to 0.4], p = 0.07.

Conclusion: These results suggest that early initiation of HIT improves microvascular function.

Assessment of left ventricular mechanics in right ventricular overload using in silico rat models

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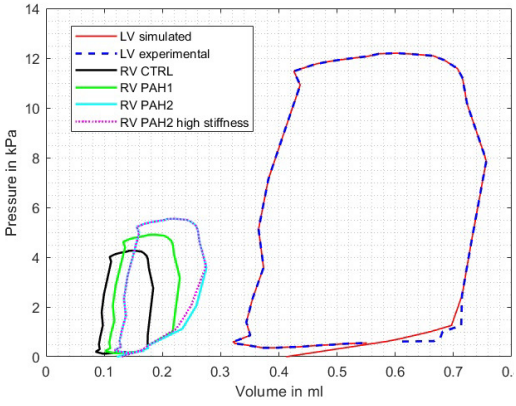
Background: To preserve cardiac function in overload conditions, the RV adapts by developing muscular hypertrophy through progressive tissue remodelling. This process may lead to a vicious cycle with detrimental effects on RV diastolic and systolic function, as seen in pulmonary arterial hypertension (PAH) patients [1]. However, how RV overload affects LV function and remodelling remains an open question [2]. Computational models of cardiac physiology offer an opportunity for investigating mechanisms difficult or impossible to analyse otherwise due to the existence of overlapping factors and technical limitations.

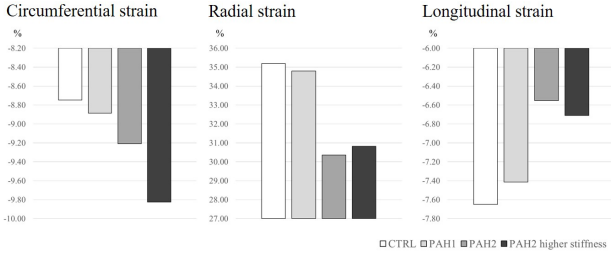
Aim: This study aims to assess the acute effects of RV overload and increased myocardial passive stiffness on the LV mechanical properties in an anatomically-based computational model of healthy rat heart.

Methods: A computational simulation pipeline of cardiac mechanics based on the Holzapfel-Ogden model has been implemented using MR images from a healthy rat. Whereas LV function was modelled realistically using catheter

measurements conducted on the same subject than the MR imaging, RV function was based on representative literature values for healthy and PAH rats with RV overload. The following cases were defined (Fig.1): CTRL, with normal RV function; PAH1, with 30% increase in RV ESV (end-systolic volume) and 15% increase in RV ESP (end-systolic pressure) in comparison to CTRL; and PAH2, with 60% increase in RV ESV and 30% increase in RV ESP compared to CTRL. The cardiac cycle was simulated for all cases whilst fitting the experimentally measured LV pressure and volume values from a healthy rat, which allowed quantifying the effects of RV overload on LV function.

Results: The increase of average circumferential strain in the LV correlated with the degree of RV overload simulated (CTRL: -8.7%, PAH1: -8.9%, PAH2: -9.2%), whilst average radial (CTRL: 35.2%, PAH1: 34.8%, PAH2: 30.3%) and longitudinal strains decreased (CTRL: -7.7%, PAH1: -7.4%, PAH2: -6.6%), as seen in Fig.2. However, regional differences in strain were significant: under RV overload conditions, circumferential strain increased in the septum (-3.5% difference in PAH2 vs. CTRL) but lower values were observed in the lateral wall (+1.7% difference in PAH2 vs. CTRL). Cardiac function of case PAH2 was simulated also with increased myocardial passive stiffness (2.67 kPa instead of 1.34 kPa) which presented a mild strain increase in the mid LV ventricle in comparison to PAH2 with normal stiffness (circumferential strain: -0.8%, radial strain: +0.5%, longitudinal strain: -0.2%).





CONCLUSION: Our study provides mechanistic evidence on how RV overload and increased passive myocardial stiffness causes a redistribution of strain and fibre stress in the LV, which may play a significant role in LV remodelling and function.

Association of glycated haemoglobin A1c levels with cardiovascular outcomes in the general population: results from the BiomarCaRE consortium

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Background: Glycated haemoglobin A1c (HbA1c) is used to monitor the quality of diabetes treatment; however, its role in predicting cardiovascular outcomes in the general population remains uncertain.

Purpose: The additional use of glycated haemoglobin A1c (HbA1c) as a biomarker might highlight subjects of the general population with an increased risk for cardiovascular outcomes with cardiovascular disease, cardiovascular mortality or overall-mortality.

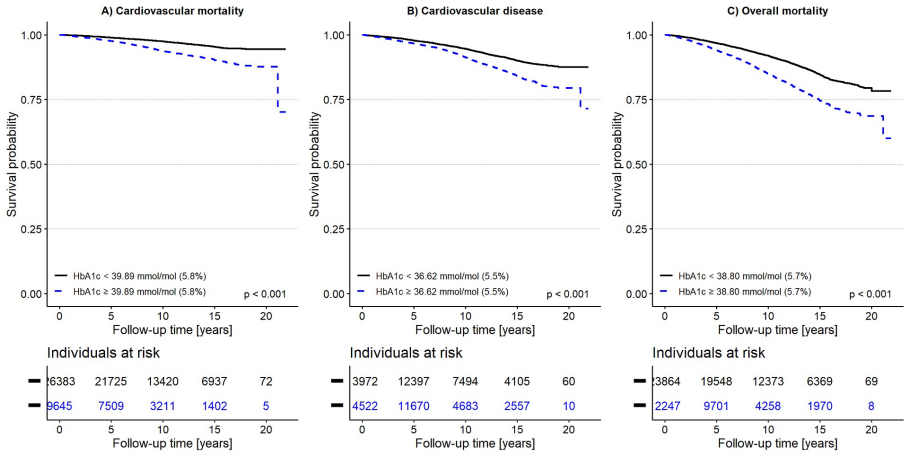
Methods: Data from six prospective population-based cohort studies across Europe comprising 36,180 participants were analysed. HbA1c was evaluated in conjunction with classical cardiovascular risk factors

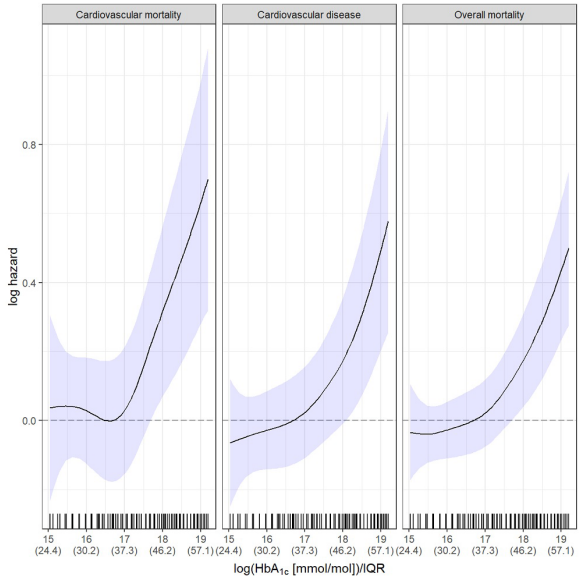
(CVRFs) for association with cardiovascular mortality, cardiovascular diseases (CVD), and overall mortality in the study population, in non-diabetic (N=32,477), and diabetic participants (N=3,703).

Results: Kaplan-Meier curves showed higher event rates with increasing continuous log-transformed HbA1c levels. Cox regression analysis revealed significant associations between HbA1c (in mmol/mol) log-transformed divided by interquartile range and the examined outcomes, with a hazard ratio (HR) of 1.12 (95% confidence interval (CI):1.04–1.20,p=0.0019) for cardiovascular mortality, 1.10 (95% CI:1.04–1.16,p<0.001) for CVD, and 1.09 (95% CI:1.05–1.14,p<0.001) for overall mortality per one unit increase.

An increased risk of CVD was observed in subjects without diabetes with increased HbA1c levels (HR 1.09; 95% CI:1.01-1.16,p=0.021). An HbA1c cut-off value of 39.89 mmol/mol (5.8%), 36.62 mmol/mol (5.5%), and 38.80 mmol/mol (5.7%) for cardiovascular mortality, CVD, and overall mortality, respectively, was determined for selecting individuals at an increased risk.

Conclusion: HbA1c was demonstrated to be an independent prognostic biomarker for all investigated outcomes in the general European population. An approximately linear relationship was observed between an increase of HbA1c levels and the outcomes. Elevated HbA1c levels were also associated with the outcomes in participants without diabetes (i.e. HbA1c levels < 6.5% (<48mmol/mol) which underlines the importance of HbA1c levels in the overall population.





Association of markers of vascular inflammation with blood pressure in midlife: the Hordaland Health Study

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Background: Hypertension is a pro-inflammatory condition. A steeper rise in blood pressure (BP) has been observed in middle-aged women than men. However, sex-specific associations of vascular inflammation with midlife BP has not been much explored.

Purpose: To test the association of markers of vascular inflammation, including neopterin, kynurenin:tryptophan ratio (KTR) and high sensitive C-reactive protein (CRP) with BP.

Methods: Circulating levels of neopterin, KTR and CRP were measured in 2042 women and 1646 men aged 47-49 years from the community-based Hordaland Health study. The associations with systolic and diastolic BP were tested in sex-specific linear regression analyses and adjusted for body mass index, serum total- and high-density lipoprotein cholesterol, triglycerides, creatinine, physical activity, daily smoking and diabetes.

Results: Compared to men, women had lower average BP (124/72 vs. 131/78 mmHg, p<0.001), higher plasma neopterin (7.5 vs 7.0 nmol/l, p<0.001) and comparable plasma KTR and serum CRP (both p>0.05). In multivariable analyses 1) higher neopterin was associated with higher diastolic BP in women, but not in men; 2) higher CRP was associated with higher systolic and diastolic BP in women, but not in men; 3) no association of higher KTR with BP was found in either sex (Table 1). A significant sex-interaction between neopterin and diastolic BP was found.

Table 1. Association between inflammatory markers and systolic and diastolic blood pressure in 47-49 years old women and men: The Hordaland Health study

		Women		Men		Sex interaction
		Multivariable		Multivariable		
Variable		β	*p*	β	*p*	*p*
log Neopterin						
	Systolic BP	0.001	0.967	-0.038	0.128	0.238
	Diastolic BP	**0.086**	**<0.001**	0.007	0.779	**0.017**
log KTR						
	Systolic BP	-0.019	0.415	-0.029	0.245	0.773
	Diastolic BP	0.029	0.209	0.012	0.645	0.627
log CRP						
	Systolic BP	**0.064**	**0.009**	0.021	0.427	0.326
	Diastolic BP	**0.077**	**0.002**	0.019	0.491	0.182

BP, blood pressure; KTR, kynurenin:tryptophan ratio; CRP, high sensitive C-reactive protein
Multivariable models are adjusted for body mass index, serum total- and high-density lipoprotein cholesterol, triglycerides, creatinine, physical activity, daily smoking and diabetes.

Conclusion: Among participants in the Hordaland Health study, higher circulating levels of neopterin and CRP with higher BP was found among women only, suggesting that vascular inflammation contributes to BP elevation in middle-aged women.

Associations of circulating polyunsaturated fatty acids with coronary artery calcium score in hospitalized patients with suspected coronary artery disease

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Background: Inadequate intake of polyunsaturated fatty acids (PUFAs) is recognized as a modifiable risk factor for atherosclerotic cardiovascular disease (CVD) (1,2). The n-6 PUFA linoleic acid (LA) constitutes the predominant portion of total dietary PUFAs (3). However, whereas cardiometabolic effects of PUFAs belonging to the n-3 series have been studied for decades, less attention has been payed to potential health effects from n-6 PUFAs (4). Further, there has been concern regarding possible proinflammatory properties of several n-6 PUFA related metabolites.

Purpose: We explored correlations of serum total PUFAs, LA and the n-3 PUFA docosahexaenoic acid (DHA) with the inflammation marker GlycA. Further, we evaluated associations of total PUFAs, LA and DHA with the extension of atherosclerosis, as determined by the Agatston coronary artery calcium (CAC) score(5).

Methods: The study includes 250 patients who were hospitalized due to acute chest pain and referred to coronary CT angiography (CCTA) during in hospital stay. Exclusion criteria included diagnosis of acute myocardial infarction and/or revascularization within 24 hours after admittance. Serum levels of total PUFAs, LA, DHA and GlycA were analyzed by NMR technology in samples that had been frozen and stored at -80 °C. After logarithmic transformation, relations of total PUFA, LA, and DHA with GlycA were evaluated by Pearson correlation analyses. The associations with CAC score were visualized in generalized additive regression plots and further evaluated in linear regression models including age, gender, body mass index, diabetes, hypertension and smoking status as independent covariables.

Results: Mean (SD) age was 57.6 (12.0) years, and 91 (36.4%) of the patients were women. Median (25th-75th percentiles) serum levels (in mmol/L) were for total PUFA 6.36 (5.76-7.06), LA 5.00 (4.51-5.55), DHA 0.36 (0.31-0.43) and GlycA 1.04 (0.94-1.13). Interestingly, GlycA was strongly, positively correlated with total PUFA (r = 0.54). LA (r = 0.53) and DHA (r = 0.27), all P<0.001. In contrast, total PUFA and LA were inversely associated with CAC score both providing standardized betas of -0.17, P=0.03 after multivariable adjustments. No significant associations were found between CAC score and DHA or GlycA (P ≥0.22). Further, the addition of GlycA to the multivariable model did not materially affect the relationship between CAC score and total PUFA or LA, which remained statistically significant (P=0.04).

Conclusion: In patients undergoing CCTA due to acute chest pain, serum levels of total PUFA and LA were strongly positively correlated with the pro-inflammatory marker GlycA. Still, total PUFA and LA were both inversely associated with the CAC score and the associations remained statistically significant after adjustments for CVD risk factors and GlycA levels. Future studies should further address the diverse effects of n-6 PUFAs on inflammatory pathways, atherogenesis and coronary calcification.

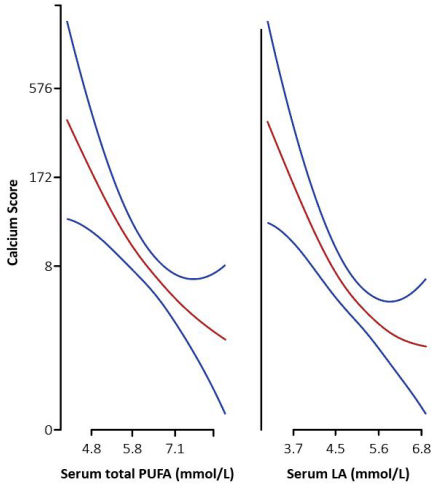

Figure 1 - The associations between coronary artery calcium score and serum total PUFA and LA obtained by generalized additive regression.

Cardiovascular risk associated with long-term anabolic-androgenic steroid abuse: an observational study from Norway

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Background: The use of anabolic-androgenic steroids (AAS) has become highly prevalent among recreational weightlifters. Numerous case reports have suggested an association between AAS use and a vast range of different cardiovascular diseases, including sudden cardiac death (SCD) and coronary artery disease (CAD). Few clinical studies have evaluated the risk of SCD and the prevalence of CAD in individuals with long-term AAS use.

Purpose: To evaluate the risk of ventricular arrhythmias and the prevalence of CAD among men with long-term AAS use.

Methods: Strength-trained men with at least three years of cumulative AAS use were recruited from recreational gyms. The control group consisted of strength-trained competing athletes who self-reported never using any performance enhancing drugs (non-users). AAS use was verified by sophisticated blood and urine analyses. Study participants went through a comprehensive cardiovascular evaluation including exercise ECG, 24 h ECG, heart rate variability (HRV) measures, signal averaged ECG (SAECG) and QT dispersion (QTd). Coronary computed tomography angiography (CCTA) was performed in AAS users. Not all participants had all tests.

Results: We included 51 AAS users and 21 non-users. Median age (25th-75th percentile) was 33 (29-37) years in the user group and 33 (29-42) years in the non-user group. Forty-eight (94%) of the users had been using AAS for five years or more. Characteristics are presented in the table. AAS users had significantly lower HDL values compared to non-users (p<0.001). No signs of ischemia or arrhythmias were detected during exercise ECG, however maximal exercise capacity was lower than in the control group and also compared to age-standardized values. A considerable, but statistically non-significant reduction was seen in overall HRV estimated as the standard deviation of the RR intervals for normal sinus beats (SDNN) (p=0.05). No difference was seen regarding left ventricular late potentials or QTd (table). Eight (19%) of the forty-two AAS users undergoing CCTA had at least a mild degree of CAD, and four of them three-vessel disease.

	AAS users (n=51)	Non-users (n=21)	P value
Clinical characteristics			
Age (years)	33 (29-37)	33 (29-42)	0.664
Systolic blood pressure (mmHg)	129 (117-136)	123 (116-130)[a]	0.383
Diastolic blood pressure (mmHg)	78 (72-87)	70 (68-79)[a]	0.018
BMI (kg/m^2)	31.5 (29.4-33.7)	29.3 (26.6-35.3)	0.218
Laboratory analyses			
Hemoglobin (g/dL)	16.8 (15.9-17.3)	15.0 (14.4-15.6)	<0.001
HDL (mmol/L)	0.73 (0.39-1.18)	1.25 (1.13-1.40)	<0.001
FSH (U/L)	<1.0 (<1.0-<1.0)	3.4 (2.6-3.9)	<0.001
LH (U/L)	<0.6 (<0.6-<0.6)	3.1 (2.8-3.8)	<0.001
Free androgen index (FAI)	306 (66-786)	56 (38-64)	<0.001
Maximal exercise capacity	*n=43*	*n=12*	
Watt	270 (230-290)	280 (260-350)	0.033
Metabolic equivalents (METs)	9.6 (8.6-10.8)	11.2 (8.6-13.6)	0.131
Heart rate variability	*n=29*	*n=9*	
SDNN (ms)	124 (110-136)	160 (140-176)	0.053
Late potentials	*n=31*	*n=20*	
Late potentials* (n, %)	2 (6)	2 (10)	0.640
fQRS > 114 ms (n, %)	6 (19)	3 (15)	1.000
RMS voltage < 20 µV (n, %)	1 (3)	2 (10)	0.553
LAS duration > 38 ms (n, %)	2 (6)	1 (5)	1.000
QT dispersion	*n=29*	*n=10*	
Maximal difference (ms)	58 (42-66)	59 (44-72)	0.640

Data are presented as median (25th-75th-percentile) unless otherwise specified. P values were obtained from a Wilcoxon Rank sum test or Fisher's exact test. [a]) n=19. BMI, body mass index.
*) Characteristics of late potentials include ≥ 2 of the following: 1) fQRS>114 ms; 2) RMS voltage<20 µV; 3) LAS>38 ms.

Conclusion: No ECG-findings indicated an increased risk of ventricular arrhythmias among the long-term AAS users. However, their maximal exercise capacity was lower than in controls, and one fifth of the long-term AAS users had verified CAD on CT coronary angiography.

Chest pain characteristics and their ability to predict NSTEMI according to gender and age in patients presenting with suspected ACS

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Background: The epidemiologic panorama of acute myocardial infarction (AMI) has changed during the past decades with a lower rate of ST elevation myocardial infarction (STEMI) and higher rate of non-ST elevation myocardial infarction (NSTEMI). Most studies on presenting symptoms in patients with AMI include high rates of STEMI patients and were performed during a time when high-sensitivity cardiac troponin assays (hs-Tn) were not available. Hence, our knowledge on typical symptoms and their ability to predict AMI may not apply to the majority of today´s patients in the emergency departments (ERs).

Purpose: Report chest pain characteristics and additional symptoms in patients presenting with suspected acute coronary syndrome (ACS) without ST elevations in a contemporary cohort diagnosed with hs-Tn. Assess the risk of having an NSTEMI based on symptom characteristics for women, men and patients ≥ and < 70 years of age and evaluate the strength of associations between symptom and gender or age category.

Methods: A total of 1506 patients >18 years admitted with suspected ACS without ST elevation were included in the WESTCOR study from Sept. 2015 to May 2019. Diagnoses were adjudicated by two independent cardiologists. Information about symptoms was retrospectively collected from electronic medical records. Odds ratios (OR) for NSTEMI were calculated for all symptoms, and logistic regression was used to assess the interaction between genders and age groups ≥ and < 70 years of age.

Results: 66.8% of all patients presented with both typical location and character. More women than men presented with atypical location (9.4 vs 6.8%, p<0.001) while more men presented with atypical character (21.1 vs 17.9%, p=0.004). Women significantly more often than men reported radiating pain and typical additional symptoms (figure). Differences between age groups were most often non-significant.

Both genders and age groups had significantly increased odds of NSTEMI if pain radiated to both arms, was triggered by physical activity or happened in the course of chest pain prodromes, see table. Men had significantly lower OR for AMI compared to women if pain was dependent of position, respiration or palpation (OR 0.17 vs 0.53, p-value for interaction 0.047). Younger patients had significantly lower OR for NSTEMI compared to older patients if pain radiated to the left arm (OR 0.73 vs 1.67, p-value for interaction 0.045) and higher OR if exertional chest pain had been present during the last week prior to admission (OR 4.08 vs 1.81, p-value for interaction 0.025). We did not find that women had higher risk of NSTEMI if they presented with atypical pain compared to men (OR 0.50 vs 0.72, not significant).

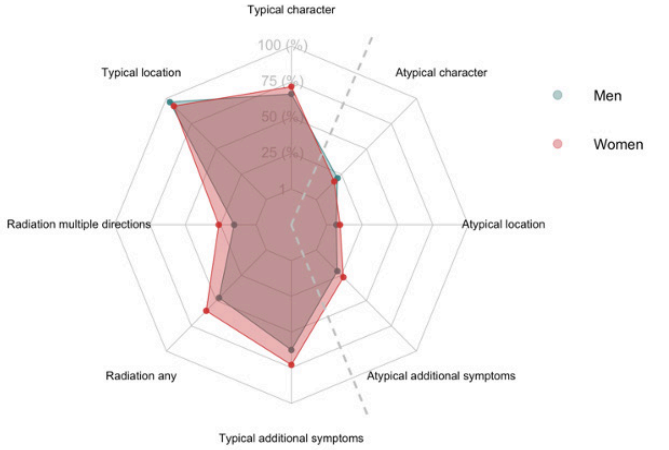
Conclusion: Radiation to both arms has the strongest predictive value for NSTEMI. We do not find that women or older patients have higher odds ratio for NSTEMI if they present with atypical symptoms.

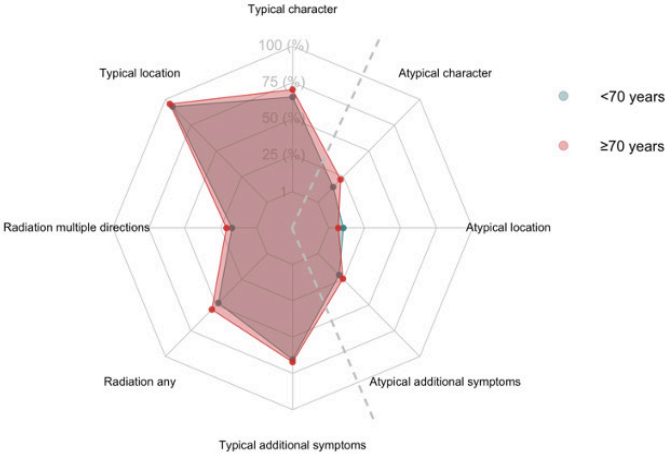
Incidence of symptoms and positive OR for AMI grouped by gender and age

	Incidence (%)	Positive OR (95% CI)				
		All (n=1506)	Men (n=909)	Women (n=597)	<70 years (n=1039)	≥70 years (n=467)
Chest pain as presenting sympt.	1467 (97.4)	1.55 (0.47-5.09)	2.05 (0.48-8.75)	0.97 (0.12-7.76)	1.98 (1.28-3.04)	2.67 (1.60-4.44)
Location*						
Retrosternal	660 (45.0)	2.09 (1.51-2.89)	2.24 (1.51-3.34)	1.75 (0.98-3.10)	1.98 (1.28-3.04)	2.67 (1.60-4.44)
Precordial	316 (21.5)	0.27 (0.15-0.48)	0.24 (0.12-0.46)	0.30 (0.09-0.98)	0.33 (0.16-0.66)	0.20 (0.07-0.56)
Thorax, other parts	396 (27.0)	0.95 (0.67-1.37)	1.05 (0.68-1.64)	0.85 (0.45-1.60)	1.05 (0.65-1.70)	0.75 (0.43-1.32)
Shoulders or arms	34 (2.3)	0.72 (0.22-2.40)	0.74 (0.17-3.26)	0.73 (0.09-5.65)	1.00 (1.00-4.37)	0.41 (0.05-3.18)
Jaw or neck	25 (1.7)	1.45 (0.49-4.26)	3.88 (0.91-16.4)	0.64 (0.08-4.89)	0.79 (0.10-6.15)	1.68 (0.44-6.36)
Sum typical location	1390 (94.8)	1.35 (0.61-2.98)	1.60 (0.48-5.32)	0.97 (0.33-2.83)	2.32 (0.55-9.73)	1.09 (0.41-2.94)
Epigastrial or abdominal	81 (5.5)	1.07 (0.54-2.11)	0.81 (0.31-2.09)	1.67 (0.62-4.49)	0.21 (0.03-1.53)	1.74 (0.78-3.87)
Other location†	34 (2.3)	0.22 (0.03-1.65)	-	0.56 (0.07-4.30)	0.43 (0.06-3.20)	-
Sum atypical location	77 (5.2)	0.79 (0.42-1.51)	0.57 (0.22-1.45)	1.29 (0.53-3.18)	0.27 (0.07-1.13)	1.24 (0.57-2.68)
Character						
Tight/crushing	960 (63.7)	1.33 (0.82-2.14)	1.44 (0.80-2.59)	1.18 (0.51-2.75)	1.06 (0.67-1.65)	0.92 (0.55-1.52)
Dull/heavy	81 (5.4)	1.16 (0.59-2.32)	0.73 (0.28-1.89)	2.37 (0.85-6.58)	0.39 (0.09-1.64)	1.90 (0.81-4.45)
Sum typical character	1033 (68.6)	1.48 (0.83-2.64)	1.18 (0.62-2.26)	3.37 (0.80-14.3)	1.36 (0.68-2.71)	1.76 (0.76-4.06)
Burning	89 (5.9)	2.21 (1.27-3.83)	3.14 (1.61-6.10)	1.14 (0.39-3.38)	2.01 (0.98-4.10)	2.00 (0.85-4.69)
Stinging	218 (14.5)	0.42 (0.23-0.77)	0.34 (0.16-0.73)	0.57 (0.20-1.64)	0.41 (0.19-0.86)	0.48 (0.17-1.39)
Other atypical‡	2 (0.1)	-	-	-	1.04 (0.99-1.10)	1.02 (0.96-1.09)
Sum atypical character	299 (19.9)	0.83 (0.54-1.28)	0.82 (0.49-1.37)	0.78 (0.35-1.74)	0.76 (0.43-1.34)	1.11 (0.55-2.24)
Typical pain §	981 (66.8)	1.52 (0.94-2.48)	1.39 (0.78-2.50)	1.99 (0.76-5.19)	1.41 (0.75-2.68)	1.83 (0.86-3.90)
Atypical pain ¶	224 (15.3)	0.66 (0.40-1.07)	0.72 (0.40-1.29)	0.50 (0.19-1.31)	0.71 (0.37-1.34)	0.55 (0.26-1.16)
Radiation						
Multiple directions	298 (19.8)	1.63 (1.13-2.34)	1.62 (1.00-2.61)	2.06 (1.14-3.73)	1.84 (1.17-2.89)	1.36 (0.74-2.52)
Both arms	66 (4.4)	9.40 (5.62-15.7)	8.28 (4.44-15.4)	11.7 (4.68-29.1)	12.50 (6.58-23.75)	5.35 (2.26-12.62)
Left arm	296 (19.7)	1.05 (0.71-1.56)	1.05 (0.65-1.69)	1.08 (0.54-2.17)	**0.73 (0.42-1.28) ††**	**1.67 (0.93-3.00) ††**
Right arm	20 (1.7)	0.86 (0.20-3.74)	1.65 (0.35-7.87)	-	0.73 (0.09-5.62)	1.03 (0.12-8.94)
Both shoulders	25 (1.7)	1.97 (0.73-5.31)	0.64 (0.08-5.01)	4.49 (1.36-14.9)	0.73 (0.09-5.62)	3.05 (0.87-10.68)
Left or right shoulder	92 (6.1)	0.16 (0.04-0.67)	0.14 (0.02-1.04)	0.21 (0.03-1.58)	0.14 (0.02-0.98)	0.20 (0.03-1.53)
Jaw	321 (21.3)	1.41 (0.98-2.03)	1.70 (1.06-2.70)	1.34 (0.74-2.46)	1.53 (0.97-2.41)	1.29 (0.70-2.38)
Epigastrium or abdomen	38 (2.5)	1.18 (0.46-3.07)	0.36 (0.05-2.71)	2.96 (0.95-9.29)	0.74 (0.17-3.16)	2.30 (0.58-9.09)
Back	189 (12.5)	1.42 (0.92-2.20)	1.71 (0.95-3.07)	1.41 (0.71-2.80)	1.31 (0.73-2.34)	2.59 (0.23-28.97)
Numbness upper extremities	128 (8.5)	1.12 (0.65-1.94)	1.07 (0.55-2.08)	1.21 (0.46-3.22)	1.15 (0.59-2.24)	1.31 (0.48-3.60)
Any radiation	789 (52.4)	1.69 (1.21-2.35)	1.82 (1.22-2.70)	1.77 (0.93-3.34)	1.47 (0.95-2.27)	2.25 (1.33-3.79)
Additional symptoms#						
Shortness of breath	628 (41.7)	1.06 (0.77-1.45)	1.11 (0.75-1.64)	1.05 (0.60-1.85)	1.03 (0.68-1.57)	1.14 (0.69-1.88)
Nausea	318 (21.1)	0.93 (0.63-1.37)	1.01 (0.61-1.68)	0.95 (0.50-1.80)	0.75 (0.43-1.29)	1.23 (0.68-2.20)
Vomiting	43 (2.9)	2.38 (1.15-4.93)	2.33 (0.97-5.64)	2.45 (0.68-8.89)	1.68 (0.57-4.96)	3.27 (1.15-9.27)
Diaphoresis or clamminess	287 (19.1)	1.79 (1.25-2.56)	2.01 (1.32-3.06)	1.19 (0.58-2.45)	1.90 (1.21-2.99)	1.86 (1.02-3.38)
Palpitations	174 (11.6)	0.69 (0.40-1.20)	0.90 (0.47-1.75)	0.47 (0.16-1.33)	0.61 (0.28-1.35)	0.72 (0.33-1.58)
Dizziness	226 (15.0)	0.38 (0.21-0.70)	0.43 (0.21-0.91)	0.35 (0.12-0.98)	0.39 (0.18-0.86)	0.38 (0.15-0.98)
Sum typical add. symptoms	1005 (66.7)	0.98 (0.70-1.37)	1.11 (0.75-1.66)	0.84 (0.45-1.56)	0.97 (0.63-1.51)	1.01 (0.60-1.70)
Dependent of position	124 (8.2)	0.43 (0.20-0.94)	**0.17 (0.04-0.71) ††**	**1.10 (0.42-2.90) ††**	0.41 (0.15-1.15)	0.50 (0.15-1.66)
Dependent of respiration	149 (9.9)	0.19 (0.07-0.52)	0.13 (0.03-0.55)	0.33 (0.08-1.39)	0.23 (0.07-0.73)	0.15 (0.02-1.11)
Pain upon palpation	177 (11.8)	0.38 (0.19-0.75)	0.21 (0.07-0.69)	0.69 (0.29-1.66)	0.44 (0.19-1.03)	0.29 (0.09-0.97)
Sum atypical add. symptoms	351 (23.3)	0.28 (0.16-0.48)	**0.17 (0.07-0.39) ††**	**0.53 (0.25-1.11) ††**	0.28 (0.14-0.57)	0.28 (0.12-0.67)
Effect of NG	268 (17.8)	1.78 (1.24-2.57)	1.49 (0.71-3.13)	1.57 (0.57-4.31)	1.23 (0.56-2.71)	2.18 (0.87-5.50)
Debut of symptoms						
During physical activity	285 (18.9)	2.91 (2.06-4.10)	2.63 (1.74-3.96)	3.29 (1.75-6.19)	3.32 (2.14-5.16)	2.42 (1.39-4.22)
After physical activity	72 (4.8)	1.27 (0.64-2.52)	1.02 (0.42-2.47)	1.86 (0.62-5.60)	1.47 (0.64-3.34)	1.06 (0.30-3.76)
Acute/chronic stress	115 (7.6)	0.26 (0.10-0.72)	0.10 (0.01-0.71)	0.62 (0.19-2.07)	0.19 (0.05-0.77)	0.60 (0.14-2.63)
During rest	1027 (68.2)	0.50 (0.36-0.69)	0.56 (0.38-0.83)	0.41 (0.23-0.73)	0.45 (0.30-0.69)	0.52 (0.31-0.87)
Unknown	18 (1.2)	2.98 (1.05-8.45)	5.30 (1.40-20.0)	1.29 (0.16-10.5)	2.40 (0.50-11.47)	3.17 (0.74-13.57)
Last 24 hours						
Exert. chest pain >once	48 (3.2)	1.80 (0.86-3.77)	1.12 (0.42-2.94)	4.36 (1.32-14.4)	2.33 (0.86-6.31)	1.15 (0.38-3.50)
Last week						
Exertional chest pain	268 (17.8)	3.00 (2.13-4.26)	2.77 (1.84-4.18)	3.25 (1.73-6.10)	**4.08 (2.63-6.34) ††**	**1.81 (1.03-3.15) ††**
Shortness of breath	60 (4.0)	1.36 (0.66-2.82)	1.20 (0.45-3.19)	1.77 (0.59-5.30)	1.16 (0.40-3.34)	1.46 (0.53-4.06)
Pain similar to previous AMI	57 (3.8)	0.72 (0.29-1.84)	0.45 (0.14-1.47)	2.09 (0.45-9.82)	0.55 (0.13-2.32)	0.85 (0.25-2.97)

* In patients having chest pain at presentation. † Back and other locations. ‡ Tearing, ripping and other characters. § Typical pain is defined as typical location and character ¶ Atypical pain is defined as either atypical location or character, or both. # If not stated considered negative. **4 groups; no pain; VAS 1-3.5; VAS 3.5-6.5; VAS >6.5.

†† P-value <0.05 for difference





Circulating trimethyllysine predicts total and cardiovascular mortality in patients with and without coronary heart disease

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Background: The carnitine precursor trimethyllysine (TML) is associated with the microbiota-derived metabolite trimethylamine N-oxide (TMAO) and predicts future cardiovascular events in patients with established coronary heart disease (CHD).

Purpose: To examine circulating TML as a predictor of total and cardiovascular mortality in two independent cohorts of subjects with or without CHD.

Methods: By Cox regression modelling, risk associations were examined in 6393 subjects in the community-based Hordaland Health Study (HUSK). A replication study was performed among 4117 patients undergoing coronary angiography for suspected stable angina pectoris in the Western Norway Coronary Angiography Cohort (WECAC).

Results: During a median follow-up of 10.9 years in the HUSK-cohort, 884 (13.8%) subjects died, of whom 287 from cardiovascular causes. After adjustments for traditional cardiovascular risk factors, the hazard ratio (HR) (95% CI) for total mortality comparing the 4th vs. 1st TML-quartile was 1.66 (1.31-2.10, p<0.001). Particularly strong associations were observed with cardiovascular mortality (HR [95% CI] 2.04 [1.32-3.15, p=0.001]). Corresponding risk estimates in the WECAC-cohort (median follow-up of 10.3 years) were 1.35 (1.10-1.66, p=0.004) for total and 1.45 (1.06-1.98, p=0.02) for cardiovascular mortality. Additional adjustments for plasma TMAO did not materially influence the risk estimates in either cohort, and no effect modification by TMAO was observed.

Conclusions: Circulating TML is associated with increased risk of total and cardiovascular mortality in both subjects with and without CHD.

Complement activation is associated with neutrophil extracellular traps and all-cause mortality in ST-elevation myocardial infarction

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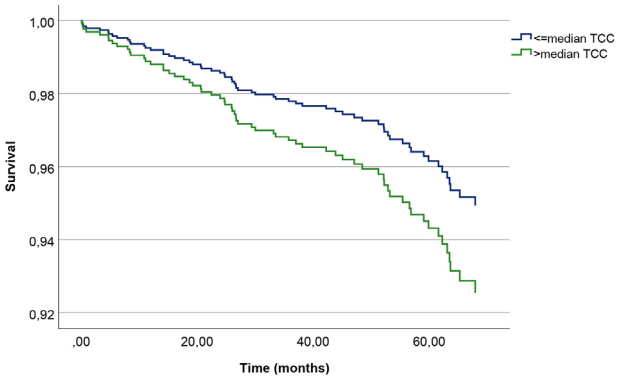
Background: The complement system and neutrophil extracellular traps (NETs) are both parts of the innate immune system, and have been implicated in the ischemia-reperfusion injury in patients with ST-elevation myocardial infarction (STEMI). There is experimental evidence of reciprocal activation between the complement system and NETs. Any such link in patients with STEMI has not been investigated.

Purpose: To investigate a potential association between complement activation and clinical outcomes after STEMI, and assess any interplay between complement activation and NETs in this situation.

Methods: Patients with ST-elevation myocardial infarction were included at a median of 18 hours after percutaneous coronary intervention (n=864). The terminal complement complex (TCC) was measured by ELISA as a marker of complement activation. As markers of NETs were myeloperoxidase-deoxynucleic acid (MPO-DNA) and citrullinated histone 3 (CitH3) measured by ELISAs, while double stranded DNA (dsDNA) was measured by a nucleic acid stain. Patients were followed for a median of 4.6 years. The primary endpoint was a composite of new myocardial infarction, unscheduled revascularization, stroke, hospitalization for heart failure and death, whichever occurred first. All-cause mortality was also recorded.

Results: The composite endpoint occurred in 184 (21.3%) patients, while 70 (8.1%) died during follow-up. When dichotomizing at median TCC, the group with above-median TCC levels did not have an increased risk of reaching the composite endpoint (hazard ratio (HR): 1.069, 95% CI: [0.801, 1.428], p=0.651). However, this group exhibited an increased risk of all-cause mortality (HR: 1.650, 95% CI: [1.020, 2.671], p=0.041). This risk persisted when adjusting for age, sex, hypertension and LDL-cholesterol (HR: 1.673, 95% CI: [1.014, 2.761], p=0.044), but the significance was lost when adjusting for NT-proBNP (HR: 1.492, 95% CI: [0.885, 2.515], p=0.133). TCC was correlated to dsDNA (r=0.127, p<0.001) and CitH3 (r=0.102, p=0.003), but not MPO-DNA. The group with both TCC and dsDNA in the highest quartile exhibited a significantly higher incidence of all-cause mortality than the remaining population (17.6% vs, 7.2%, p=0.002). When examining the predictive value of TCC and dsDNA on all-cause mortality in ROC curve analysis, the area under the curve (AUC) for TCC was 0.549 (95% CI: [0.472, 0.625]), while the AUC for dsDNA was 0.653 (95% CI: [0.584, 0.722]). When combining TCC and dsDNA the predictive value was marginally higher than for TCC alone (AUC: 0.649, 95% CI: [0.579, 0.720])

Conclusion: In this STEMI population, complement activation measured by TCC was not associated with the primary composite endpoint, but was associated with increased risk of death. TCC was weakly correlated with markers of NETs. Despite a high mortality rate in patients with high levels of TCC and dsDNA, combining these variables did not increase the prognostic value compared to TCC alone.



Death of a child and the risk of heart failure: a population-based cohort study from Denmark and Sweden

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Background: Increasing evidence suggests that the death of a child is associated with increased risks of ischemic heart diseases and atrial fibrillation and the association is in

part attributable to stress-related mechanisms. However, knowledge regarding the risk of heart failure (HF) after the death of a child is very limited.

Purpose: To study the association between the death of a child and the parents' risk of HF.

Methods: We conducted a population-based cohort study involving parents of live-born children recorded in the Danish and Swedish Medical Birth Registers during 1973-2016 and 1973-2014, respectively (n=6,717,531). We retrieved information on child death, HF diagnosis and parents' sociodemographic characteristics from several nationwide registries. We performed Poisson regression models to estimate incidence rate ratio (IRR) and 95% confidence intervals (CI) for HF.

Results: A total of 129,829 (1.9%) parents lost at least one child during the follow-up. Bereaved parents had a 35% higher risk of HF than non-bereaved parents [IRR (95% CI): 1.35 (1.29-1.41)]. The association was present not only if the child died due to cardiovascular or other natural causes [IRR (95% CI): 1.48 (1.25-1.75) and 1.35 (1.27-1.44), respectively], but also in case of unnatural deaths [IRR (95% CI): 1.32 (1.24-1.42)]. There was a trend toward a U-shaped association according to the deceased child's age at loss and the risk of HF. Bereaved parents who lost their only child or had three or more remaining live children at the time of loss had higher HF risk than those with one or two live children at the time of loss. We found no clear evidence for a difference in the association of interest over time.

Conclusions: The death of a child was associated with an increased risk of HF. The finding that not only cardiovascular and other natural deaths, but also unnatural deaths were associated with HF suggests that stress-related mechanisms may contribute to the development of HF.

Deep learning for automated left ventricular outflow tract diameter measurements in 2D echocardiography

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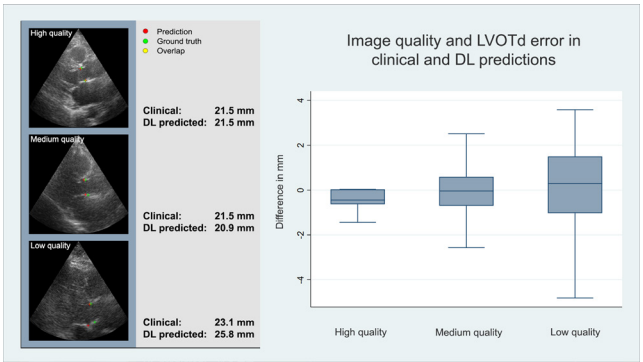
Background: Left ventricular outflow tract diameter (LVOTd) is routinely measured to calculate stroke volume and estimate aortic valve area by the continuity equation. Despite LVOTd being regularly measured clinically, significant inter- and intraobserver variability is evident. This variability is highly impactful on both aortic stenosis evaluation and cardiac output calculation due to the squaring of the LVOT radius.

Purpose: We aimed to investigate if LVOTd measurements from clinical echocardiographic examinations could be used in a deep learning (DL) model to automatically perform LVOTd measurements with equivalent accuracy and improved consistency compared to current practice.

Methods: Data was collected from clinical echocardiographic examinations performed on 656 consecutive patients admitted to the cardiac catheterization laboratory at a university hospital in January – December 2018. Parasternal views with cardiologist annotated LVOTd coordinates were assessed for 1314 echocardiographic still images. The quality of the still image and annotated LVOT ground truth were individually graded as high, medium and low by experienced cardiologists to establish a rigorous training basis. Spatial geometry data was preserved for each still image in order to distinguish between different degrees of image zoom. Data was randomly split into training, validation and testing sets (68%, 17%, 15%). A fully convolutional network based on the Resnet50 architecture was used with a custom loss function with heatmap regression. Image augmentations were added to extend the dataset.

Results: When including echocardiographic images of any quality (n=1314) in the model training and inference, the median absolute difference between cardiologist LVOTd and DL LVOTd was 0.97 mm (95% Confidence interval (CI) 0.79-1.14). Using only high and medium quality still images and ground truth (n=869) in the training and inference, median absolute difference decreased to 0.81 mm (95% CI 0.60-0.96). Adding image augmentations to this dataset further improved the model, resulting in a median LVOTd absolute difference of 0.66 mm (95% CI 0.51-0.78). The LVOTd error in inference increased with decreasing image quality, as



shown in Figure 1, with two predictions (0.9%) failing completely.

Conclusion: Deep learning models are capable of measuring LVOTd with comparable accuracy to cardiologists when trained on clinical data. Data quality affects both training and inference. Even with a slightly lower accuracy when used on lower quality echocardiographic images, DL-assisted LVOT measurement has a clear potential to increase repeatability and consistency of LVOTd measurements.

Echocardiographic parameters of myocardial work in relation to prolonged strenuous physical exercise

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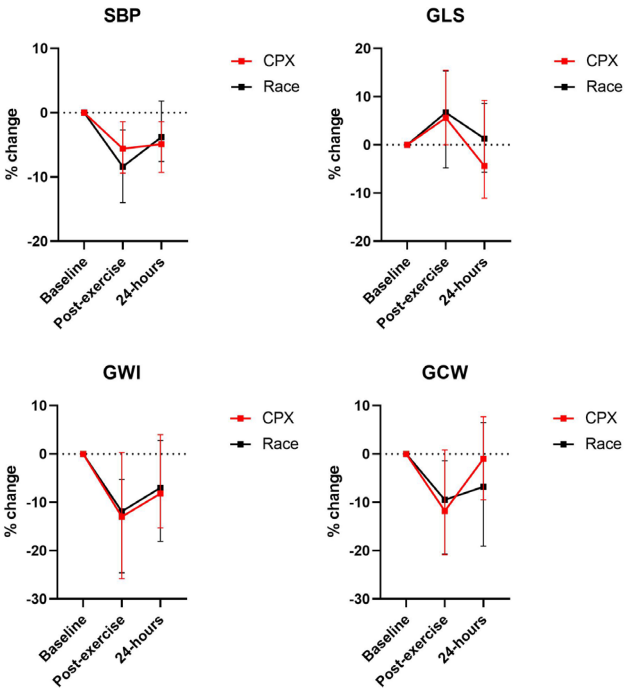
Background: Myocardial work (MW) assessed by echocardiography is a novel measure of left ventricular (LV) function. This measure is load-independent, and therefore a more accurate method for assessing LV function when there are changes in loading conditions. The purpose of this study was to examine alterations in MW parameters, blood pressure (BP) and LV global longitudinal strain (LV GLS) in relation to strenuous exercise, and to compare the response between two different physical stress situations.

Methods: 59 healthy recreational athletes were assessed by echocardiography before-, immediately- and 24 hours after two episodes of high-intensity endurance exercise. The first exercise was a cardiopulmonary exercise (CPX) test, which included both a stepwise lactate threshold- and a maximal oxygen uptake test. The second exercise was a 91-km mountain bike leisure sport cycling competition. Global work index (GWI), global constructive work (GCW), global wasted work (GWW) and global work efficiency (GWE) were estimated from LV pressure-strain loops, constructed from a combination of LV GLS and non-invasive BP, using commercially available software package (Echopac V.202, GE).

Results: Subjects were 52 (43-59) years old (73 % men). The duration of the CPX-test was 43 (40-45) minutes, and the race was 230 (210-245) minutes. The average heart rate during the CPX-test and the race was 144 (140-153) and 154 (148-161) beats per minute (bpm), respectively. The relative changes (percent) in systolic blood pressure (SBP) and LV GLS compared with pre-exercise values are demonstrated in Figure 1a, and GWI and GCW compared with pre-exercise values in Figure 1b. GWI at baseline was 2156 (1899-2400) mmHg% and GCW 2383 (2152-2668) mmHg%. There was a significant reduction in LV GLS (p=0.015), SBP, GWI and GCW following the CPX-test and the race (p <0.001), while there was an increase in heart rate and cardiac output (p<0.001). After the race, there was a significant (p=0.001) increase in GWW, and a reduction (p=0.006) in GWE.

Conclusion: There was a significant reduction in GWI and GCW after both the CPX-test and the race, suggesting that these markers reflect increased myocardial exhaustion following strenuous physical exercise.



Effect of revascularization on exercise-induced changes in cardiac and pro-thrombotic biomarkers in patients with coronary artery disease

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Introduction: Exercise-induced increase in cardiac and pro-thrombotic biomarkers have previously been shown in patients with coronary artery disease (CAD) before revascularization, which may be due to myocardial ischemia.

Purpose: We aimed to examine whether resting levels and exercise-induced changes of high sensitive cardiac Troponin T (cTnT), NT-proBNP, pro-thrombin fragment (F) 1+2, D-dimer, tissue factor pathway inhibitor (TFPI) and endogenous thrombin potential (ETP) were affected by revascularization in patients with CAD. We hypothesized that resting and exercise-induced levels of the biomarkers would be reduced after revascularization.

Methods: Patients presenting with symptoms of CAD were included. A maximal exercise ECG stress test (EST) (EST1) was performed, and venous blood samples were drawn at rest and within five min after termination. All patients underwent coronary angiography. Patients (n=20) with confirmed CAD, fully revascularized with percutaneous coronary intervention (PCI) and without symptoms of angina, were invited to perform a second EST (EST2), at the same workload (median 145W), at a median of 66 days after revascularization. Mean exercise duration at both time points were 11:30 min:sec. Of the total population 15 patients were treated with PCI on stenosis located on LAD and 5 patients with stenosis on RCA.

Results: Significant increase in cTnT and NT-proBNP from resting to post exercise levels at EST1 was found as expected ($p<0.001$, both). Also at EST2, increased levels were observed ($p<0.01$, both), however, not significantly different from the changes at EST1. Resting levels of cTnT at EST2 compared to EST1 were significantly higher (median 8.1 vs 7.1 ng/L, $p=0.02$). At both visits significant increase in D-dimer ($p=0.008$ and <0.001), F1+2 ($p=0.009$ and 0.001) and TFPI ($p<0.001$ and 0.001) during exercise were demonstrated, with no difference in these changes. There were no significant changes in ETP during exercise at any visit, but resting levels were reduced at EST2 vs EST1 ($p<0.01$). Also resting levels of TFPI were reduced at EST2 ($p<0.01$).

Conclusion: After revascularization there was still significant increase in exercise-induced release of cardiac and pro-thrombotic biomarkers, thus revascularization does not affect the ability to release these biomarkers. Also, the higher resting levels of cTnT after revascularization indicate that revascularization per se does not affect secretion of cardiac biomarkers, probably due to the disease state. The lower resting levels of ETP and TFPI after revascularization may, however, be indicative of reduced thrombin generation potential and endothelial activation.

Employment status three years after percutaneous coronary intervention- a nationwide prospective cohort study

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Background: Return to work plays an important part in social readjustment after an acute coronary event, and has important implications for both the individual and the society. Updated knowledge is lacking regarding long-term employment after percutaneous coronary intervention (PCI).

Aims: The aims of this study were to determine employment status three years after PCI and to assess predictors for return to work stratified by gender.

Methods: We included first-time PCI patients from the NorStent Trial, who were of working age (<60 years; n=2488) at a three-year follow-up. Employment status were assessed using self-report.

Results: Fifty-seven percent of females and 73% of males who were <60 years of age at the index event were employed at follow-up ($p<0.001$). Living with a partner, higher levels of education, and living in the western part of Norway were associated with a higher chance of being employed in males, while higher levels of education were associated with a higher chance of being employed in females. Prior cardiovascular morbidity and former smoking were associated with lower chance of being employed in males, while being older was associated with lower chance of being employed in females.

Conclusion: A significant number of working-age coronary heart disease patients are unemployed three years after coronary revascularization. Our

findings indicate a need for revised and gender specific initiatives to promote vocational support.

Exercise training inhibits left ventricular collagen upregulation in mice with hypertrophic cardiomyopathy

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Background: Hypertrophic cardiomyopathy (HCM) is estimated to affect 1:500, and is characterised by otherwise unexplained left ventricular (LV) hypertrophy, cardiomyocyte disarray, fibrosis, diastolic dysfunction, and ventricular arrhythmias. Historically, patients with HCM have been discouraged from participation in high intensity sports and exercise. However, the 2020 Sports Cardiology Guidelines recommend that patients with HCM should receive advice about exercise training (ET) based on individual risk assessment. To learn more about the effects of ET in HCM, we exposed mice carrying an HCM-causative sarcomere mutation (Myh6R403Q/+ (R403Q) mice) to high intensity interval training.

Purpose: To investigate the effect of exercise training on hypertrophic cardiomyopathy in mice.

Methods: R403Q mice were stratified to treadmill exercise (n=11) or sedentary behaviour (n=11). After 3 weeks, we induced HCM by giving CsA in the feed for 3 weeks, while the ET or sedentary behaviour continued for a total of 6 weeks. Each bout of treadmill running consisted of a 10-minute warm up, followed by 5 intervals of 8 minutes at high intensity (90 % of VO2 max speed at week 0) and 2 minutes at medium intensity (60 % of VO2 max speed at week 0). Every third day of the ET protocol we increased the high and medium intensity running speeds by 0.6 and 0.4 m/min, respectively. We performed echocardiography after 0, 3, and 6 weeks of the 6-week protocol. After completion of the protocol, we recorded lung and whole heart weight, and harvested LVs for molecular analyses.

Results: Confirming the expected HCM phenotype, R403Q mice that received CsA (R403Q SED+CsA) had a 1.3-fold increase in whole heart weight ($p<0.0001$), 1.5-fold increase in lung weight ($p<0.001$), and 2.4-fold increase in maximal left ventricular posterior wall (LVPW) thickness measured by echocardiography ($p<0.0001$) compared to sedentary wild type littermates given CsA (WT SED+CsA). Heart weight, lung weight, and maximum LVPW thickness were also increased 1.5- ($p<0.0001$), 1.6- ($p<0.0001$), and 2.0-($p<0.0001$) fold, respectively, compared to R403Q not given CsA (R403Q SED-CsA). R403Q ET+CsA mice increased their running distance before exhaustion 2.0-fold compared to baseline ($p=0.010$), and ran 1.6-fold longer than R403Q SED+CsA ($p=0.020$). In R403Q ET+CsA mice, LV mRNA expression of Col1a2 was 51 % ($p=0.021$), and Col3a1 49 % ($p=0.013$) of R403Q SED+CsA expression levels. Compared to R403Q SED+CsA mice, exercise training did not affect heart weight, maximum LV posterior wall thickness or lung weight in R403Q ET+CsA mice.

Conclusion: Treadmill ET inhibited upregulation of LV collagen expression in mice with HCM, but did not affect hypertrophy. This could indicate that ET during early development of HCM attenuates development of fibrosis.

Gender differences in characteristics, treatment and outcomes in ST elevation myocardial infarction patients in four european countries

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Introduction: Women receive less evidence-based care than men and have higher mortality after myocardial infarctions than men. But it is not known how the gender difference in risk fac-

Table 1. In-hospital management and overall-mortality rates. Data on STEMI patients 2014-2017.

	Estonia (n=4 584)		Hungary (n=23 685)		Norway* (n=12 414)		Sweden (n=23 342)	
	Men (n=2 816)	Women (n=1 768)	Men (n=14 580)	Women (n=9 105)	Men (n=8 786)	Women (n=3 628)	Men (n=16 161)	Women (n=7 181)
In-hospital management % (95% CI)								
Coronary angiography	86.2 (84.9-87.5)	71.1 (69.0-73.3)	91.4 (88.9-92.8)	85.0 (84.1-86.0)	89.9 (89.3-90.5)	71.7 (70.2-73.1)	95.2 (94.8-95.5)	88.3 (87.5-89.0)
PCI	78.7 (77.2-80.2)	63.2 (60.9-65.5)	90.2 (89.7 - 90.7)	86.1 (85.3 - 86.8)	83.8 (83.0-84.6)	63.4 (61.8-65.0)	91.8 (91.4-92.2)	83.1 (82.2-84.0)
Fibrinolysis	14.3 (13.1-15.7)	9.2 (7.9-10.7)	NA	NA	14.2 (13.5-15.0)	10.6 (9.6-11.6)	1.6 (1.4-1.8)	1.1 (0.9-1.4)
CABG	4.3 (3.4-5.1)	2.15 (1.5-2.9)	NA	NA	1.6 (1.4-1.9)	1.0 (0.7-1.4)	2.3 (2.1-2.6)	1.3 (1.0-1.6)
Mortality rates % (95% CI)								
30-days	10.2 (9.1-11.4)	18.3 (16.6-20.2)	10.9 (10.4 - 11.4)	17,1 (16,4 - 17,9)	9.7 (9.1-10.3)	18.9 (17.7-20.2)	8.2 (7.8-8.6)	13.0 (12.2-13.8)
1-year	16.7 (15.3-18.1)	28.1 (26.0-30.2)	17.2 (16.6 - 17.8)	26.2 (25.3 - 27.1)	12.5 (11.8-13.2)	24.6 (23.2-26.0)	12.4 (11.8-13.0)	20.3 (19.3-21.4)

*data for 2013-2016. CABG=coronary artery bypass grafting, CI = confidence interval, PCI = percutaneous coronary intervention, NA= not answered.

tors, treatments and outcomes differs between European countries.

Purpose: In order to investigate the gender differences in European countries with different economic predispositions we aimed to describe and compare baseline characteristics, in-hospital management, medications at discharge and death outcomes of man and woman ST-elevation infarction (STEMI) patients following routine clinical practice in Sweden, Norway, Hungary and Estonia.

Methods: The study population is patients over the age of 18 with STEMI who were treated in hospital 2014–2017 (for Norway between 2013–2016) and registered in one of the national myocardial infarction registers. Patients with non-ST elevation infarction and unstable angina were excluded. Risk factors, hospital treatment, and prescription medications were obtained from the national myocardial infarction registries from each country. Mortality in-hospital, after 30 days and after 1 year, was obtained from national death registers.

Results: Women were on average older, had more comorbidities and higher mortality in hospital, after 30 days and one year after hospitalization. Women received coronary angiography, percutaneous coronary intervention, left ventricular ejection fraction assessment and evidence-based drugs to a lesser extent than men.

Conclusions: The study illustrates that there are differences in characteristics, management, treatments and outcomes between men and women in all of the studied countries no matter economic predispositions. Generally, women are treated with guideline recommended therapy to a lesser extent than men in the studied countries.

Growth differentiation factor 15 - a strong prognostic marker in patients presenting with acute chest pain without acute myocardial infarction

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Background: Patients who present with acute chest pain who are not diagnosed with acute myocardial infarction (AMI) may still carry an increased cardiovascular risk. Growth differentiation factor-15 (GDF-15) has earlier been shown to be a strong prognostic marker in the general population and after AMI. However, the prognostic value in the chest pain population without AMI is unknown.

Purpose: The objective of this study was to investigate the prognostic power of GDF-15 in patients presenting with acute chest pain without myocardial infarction.

Methods: A total of 984 patients admitted with suspected NSTE-ACS were included. After excluding patients with AMI the remaining 849 patients were followed for median 722 days (range 1 to 1112 days). The primary endpoint was all-cause mortality. The secondary endpoint was all-cause

mortality or AMI. GDF-15 was measured in biobanked admission samples, and patients were divided into two groups based on GDF-15 levels (1: ≤1800 pg/ml, 2: >1800 pg/ml). Kaplan-Meier survival curves according to GDF-15 concentrations ≤1800 pg/ml or >1800 pg/ml were generated. Cox proportional hazards regression analysis was used to estimate unadjusted and adjusted hazard ratios, the latter using age, sex, hypercholesterolemia, current smoking, diabetes, hypertension, BMI, previous myocardial infarction and eGFR < 60ml/min/1.73m2 as covariates. The incremental prognostic value of adding GDF-15 to cardiac troponin T was estimated.

Results: GDF-15 concentrations were strongly associated with outcome. GDF-15 concentration were higher in non-survivors than survivors (median 2572 pg/ml vs. 910 pg/ml, p <0,001). In the category with GDF-15 >1800 pg/ml, 28 (17.9%) died, and 49 (31.4%) patients met the secondary endpoint, whereas in the category with GDF-15 levels <1800 pg/ml, only 12/693 (1.7%) died and 25 (3.6%) reached the secondary endpoint, respectively. GDF-15 >1800 pg/ml was associated with an increased risk of death with an unadjusted hazard ratio (HR) of 10.9 (95% CI: 5.6 – 21.5, p: 0.001) and an adjusted HR of 5.2 (95% CI: 1.4 – 19.4, p: 0.014). The risk of death or AMI in patients with GDF-15 >1800 pg/ml was also increased with an unadjusted HR of 9.5 (95% CI 5.9 – 17.7 p: 0.001) and an adjusted hazard ratio of 4.6 (95% CI: 1.7 -12.27, p: 0.002).

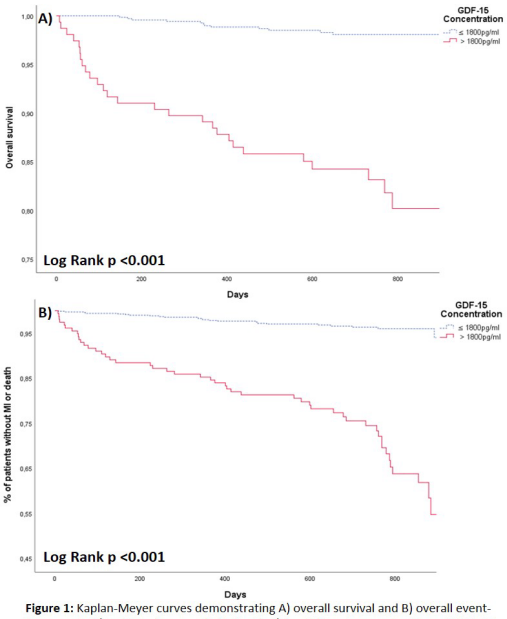

Figure 1: Kaplan-Meyer curves demonstrating A) overall survival and B) overall event-free survival (death and myocardial infarction) for different concentrations of GDF-15 (Blue dotted line: ≤ 1800 pg/ml, red line: >1800 pg/ml) in 849 patients presenting with acute chest pain without myocardial infarction.

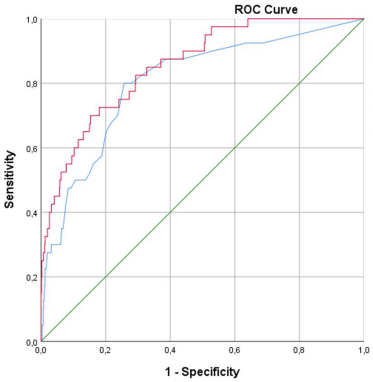

Figure 2: ROC curves comparing the ability to predict all-cause mortality for troponin T (blue curve) with Troponin T and GDF-15 combined (red curve).

Adding GDF-15 to troponin T led to an increase in C-statistic from: 0.80 (95% CI: 0.73- 0.88) to 0.86 (95% CI 0.79 – 0.91) in predicting all-cause mortality. The optimal cut-off value for predicting the primary endpoint was estimated to be 1818 pg/ml, resulting in a Youden Index of 0.55 with a specificity of 85% and sensitivity of 70%.

Conclusion: GDF-15 is a strong prognostic marker in patients presenting with acute chest pain without AMI and may aid identifying those patients with high cardiovascular risk who require further diagnostics and treatment.

Gut leakage markers in response to strenuous exercise in patients with suspected coronary artery disease

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Introduction: Although regular physical activity is associated with reduced risk of cardiovascular disease (CVD), acute vigorous exercise seems to transiently increase the risk of acute coronary events in patients with underlying CVD. Some studies have reported regular physical activity to associate with microbial diversity, whereas elevated levels of gut leakage markers have been shown after strenuous exercise in healthy individuals. Any predictive value of a temporary increase in gut leakage markers on the risk of coronary events in susceptible individuals is unknown.

Purpose: We aimed to explore gut leakage markers in response to a bout of strenuous exercise in patients with symptoms of chronic coronary syndrome (CCS). We hypothesized that gut leakage markers would increase after

acute strenuous exercise, and that the increase would be higher in patients with angiographically verified CAD.

Methods: Patients referred to exercise stress testing or coronary angiography due to symptoms suggestive of CCS were included (n=327). A maximal exercise ECG stress test was performed using a bicycle ergometer. Venous blood samples were drawn at rest prior to the test and within 5 min after the test ended, for analysis of soluble cluster of differentiation 14 (sCD14), lipopolysaccharide-binding protein (LBP) and intestinal fatty-acid binding protein (I-FABP) by ELISAs. Quantification of lipopolysaccharide (LPS) and relative quantification of gene expression of the toll-like receptor 4 (TLR4) in circulating leukocytes was performed in a subset of patients (n=101). Patients then underwent coronary angiography, and were grouped according to the degree of CAD.

Results: Of the 287 patients who completed the exercise stress test and coronary angiography, 69 (24%) had no CAD, 88 (31%) had non-significant CAD and 130 (45%) had significant CAD. Mean exercise duration was 10:05 ± 4:46 min and the duration did not differ between the groups. There were no significant differences in resting levels of gut leakage markers between the groups. In the total population, sCD14, LBP and LPS increased significantly after exercise ($p<0.0001$, all), whereas I-FABP did not. The gene expression of TLR4 decreased significantly after exercise ($p<0.0001$). There were no differences in exercise-induced changes in any of the measured markers between groups with no CAD, non-significant CAD and significant CAD.

Conclusion: In patients with symptoms suggestive of CCS, LPS, LBP and sCD14 increased significantly after strenuous exercise, suggesting that even short bouts of vigorous exercise are associated with gut leakage. The decrease in gene expression of TLR4 may be discussed to be compensatory to the increase in LPS or possibly reflecting an increase in TLR4 translation in response to LPS. The presence of CAD or not did not seem to impact exercise-induced increase in gut leakage markers.

Had percutaneous coronary intervention, now what? searching the internet for health information

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Background/Introduction: Health information and secondary prevention strategies after percutaneous coronary intervention (PCI) are pivotal to reduce the risk of new cardiac events and achieve good quality of life. However, whether patients are digitally active and have sufficient electronic health literacy (eHL) skills to access, understand and use internet-based health information remain unclear.

Purpose: To determine the extent to which patients after PCI are digitally active, and determine associations of health related internet use and socio-demographic factors with eHealth literacy.

Methods: This study is a sub-study of the prospective, multicenter CONCARDPCI study including >3000 patients after PCI. A total of 1956 patients were included from three Norwegian university hospitals between June 2017 and May 2019. Clinical data were collected through Norwegian Registry of Invasive Cardiology and patient medical records. Sociodemographics were obtained by self-report during index hospitalization. The eHealth Literacy Scale (eHEALS) assessed patient's eHL at baseline, measured on an 8-40 scale. De novo created questions assessed patient's health-related internet use, and use of the national health portal for information was measured at baseline and 2- and 6-month follow-up. Linear regression analysis determined the association between eHEALS, use of the internet, and sociodemographic factors.

Results: Most participants were men (78%), mean age 66 years (range; 20-96 years, SD 10.9). A total of 94% of the participants reported to have access to the internet, 67% had used the internet to find health information, and 54% had used the national health portal. After 6 months, patients increased their use of the national health portal (54% to 66%). Use of health applications on mobile phones or tablets increased from 10% to 40% from 2- to 6- month follow-up ($P<0.001$). At baseline 45% found the internet useful or very useful to make health decisions, and 57% found access to health resources on the internet to be important or very important. However, 50% were uncertain about how to use the information to make decisions about their own health. The eHEALS mean score was low; 25,66 (SD 6,24). Adjusted for sociodemographic factors there was an significant association between eHEALS and use of the internet to find health information at baseline (coefficient 11.41, 95%CI 8.05-14.57, P=0.001). At 2-month follow-up there was an significant association between eHEALS and use of the internet to find information about health, prevention, illness or treatment (coefficient 9.027, 95%CI 6.78-11.06, P=0.001), and the use of health appli-

cations (coefficient 3.197, 95%CI 0.24-6.30, P=0.046).

Conclusions: This study provided evidence that higher eHL predicts use of the internet to find health information and indicates that eHL and sociodemographic factors have an impact on how patients use, and can make use of, eHealth technology.

Impact of chronic mitral regurgitation on 3D atrial size and mechanics. Insights from the prospective 3D-PRIME study

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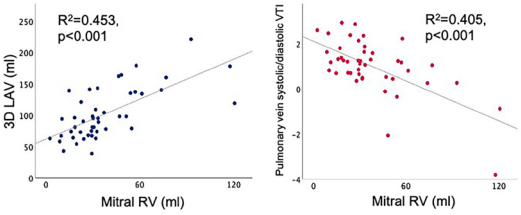
Background: Chronic mitral regurgitation (MR) leads to progressive left atrial (LA) dilation. Its relative contribution to 3-dimensional (3D) LA structural and functional remodelling and the impact of concomitant clinical and hemodynamic factors, has been less explored.

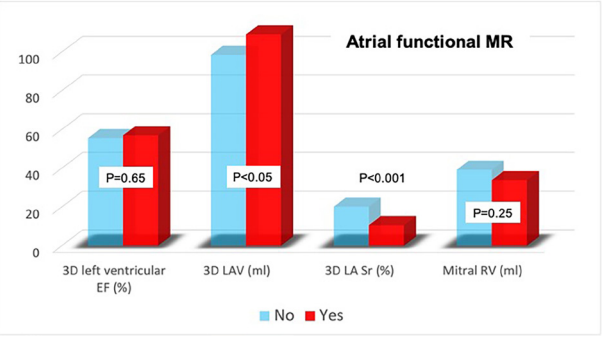
Aims: To assess 3D LA size and mechanics, as well as mean LA pressure estimated from the pulmonary vein flow, in relation to chronic MR severity.

Methods: In the prospective 3D-PRIME (3D Echocardiography and Cardiovascular Prognosis in Mitral Regurgitation) study, 46 patients with chronic MR (69±13years, body mass index (BMI) 26.2±4.3kg/m2, 50% women, 26% with atrial fibrillation, 30% with severe MR) recruited at one heart valve center were investigated with 2D and 3D transthoracic and transesophageal echocardiography. MR severity was quantified by the regurgitant volume (RV) and MR classified as organic, atrial functional or ventricular functional, as by current recommendations. LA size was measured by 3D maximum volume (LAV) indexed for body surface area (LAVI), LA mechanics by 3D peak relative increase in longitudinal volume in the reservoir phase (Sr), and mitral size by 3D annulus area and total leaflet area. Pulmonary vein Doppler flow profile was recorded in both right and left upper veins, and mean LA pressure was estimated from the average pulmonary vein systolic/diastolic velocity time integral ratio.

Results: Average mitral RV was 38±26ml, LAVI 53ml/m2, and Sr 17±11%. Increased mitral RV correlated with higher LAV and mean LA pressure (Figure 1), larger mitral annulus area (r=0.42) and total leaflet area (r=0.38) (all p<0.01), but not with Sr. In backward stepwise multivariate linear regression analyses, increased LAVI was independently predicted by larger mitral RV, higher age and atrial fibrillation (R2=0.62), higher mean LAP by larger mitral RV, body mass index and atrial fibrillation (R2=0.55), while lower Sr was associated with higher age and atrial fibrillation (R2=0.62) (all p<0.001). Patients with atrial functional MR (30% of the total group) had the largest LAVs and lowest Sr despite slightly lower mitral RV (Figure 2).

Conclusion: Chronic MR is associated with progressive increase in LA volume, mean LA pressure, and mitral annulus and total leaflet area. While MR is accompanied by low 3D LA longitudinal deformation, impaired LA mechanics is multifactorial and related closely to age and history of atrial arrythmias.





Impact of epicardial adipose tissue accumulation on left ventricular mass and hypertrophy in non-obstructive coronary artery disease

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Increased left ventricular mass index (LVMi) and left ventricular hypertrophy (LVH) by echocardiography are common in obesity and important cardiovascular risk predictors associated with myocardial ischemia in non-obstructive coronary artery disease (CAD). Accumulation of epicardial

adipose tissue (EAT) suggest a possible direct impact on LVMi and LVH.

Purpose: To explore the association between EAT volume, LVMi and LVH in patients with chest pain and non-obstructive CAD.

Methods: We included 129 patients with chest pain and non-obstructive CAD (<50% stenosis) by coronary computed tomography (CT) angiography. EAT volume was quantified using a semiautomatic analysis software on non-contrast cardiac CT images. Patients were grouped according to EAT volume, where high EAT volume was adjudicated when EAT volume was in the highest tertile (≥125 ml). Left ventricular mass was assessed by echocardiography, calculated by the Devereux formula and indexed for height in the allometric power of 2.7 (LVMi). LVH was defined as LVMi >46.7 g/m2.7 in women and >49.2 g/m2.7 in men. Coronary artery plaque burden was assessed as calcium score and segment involvement score on coronary CT angiography.

Results: High EAT volume was more common in men with higher BMI, waist circumference, serum triglycerides and higher prevalence of hypertension and obesity (all p<0.05). Age, coronary calcium score and coronary artery segment involvement score did not differ between groups. Patients with high EAT volume had higher LVMi compared to those with low EAT volume (42.5 g/m2.7 vs. 36.1 g/m2.7, p=0.003), while there was no difference in EAT volume among patients with or without LVH. In univariable logistic regression analysis, high EAT volume was associated with higher LVMi (OR 1.05 [95% CI 1.01-1.10] per g/m2.7, p=0.015). After adjusting for hypertension and obesity in a multivariable model, higher LVMi remained significantly associated with high EAT volume (Model 1, Table), but the association was attenuated after adjusting for sex (Model 2, Table).

Conclusion: High EAT volume was associated with increased LVMi in patients with non-obstructive CAD, independent of hypertension and obesity, while there was no association with LVH. This suggest that direct infiltration of adipose tissue in the myocardium may contribute to the development of increased LVMi.

	Model 1			Model 2		
Variables	**OR**	**95% CI**	**p-value**	**OR**	**95% CI**	**p-value**
LVMi (g/m$^{2.7}$)	1.05	1.00-1.09	0.049	1.03	0.98-1.07	0.279
Hypertension	6.09	1.68-22.09	0.006	7.36	1.92-28.16	0.004
Obesity	3.75	1.46-9.59	0.006	4.63	1.66-1.,95	0.003
Male sex	-	-	-	4.85	1.93-12.14	0.001

Incomplete functional reverse remodelling of the left ventricle one year after bariatric surgery. Insights from the prospective FatWest study.

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Background: Patients with severe obesity are predisposed to development of left ventricular (LV) hypertrophy with subsequent increased myocardial oxygen demand and impaired myocardial function. Bariatric surgery leads to rapid weight loss and improves cardiovascular risk profile.

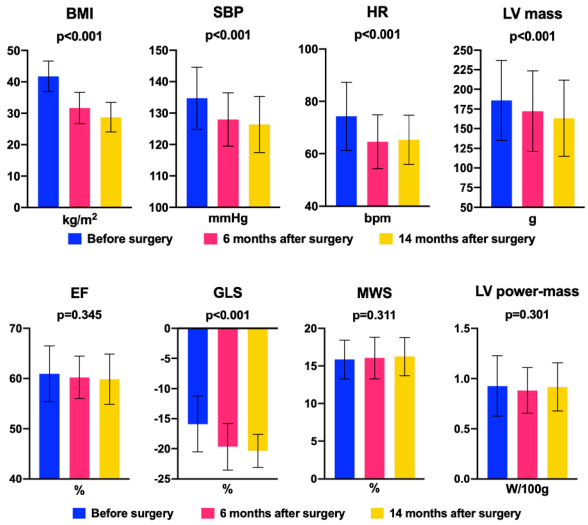
Purpose: To assess whether LV systolic function, wall mechanics, and cardiac power improve 1 year after bariatric surgery.

Methods: 91 severely obese patients (43±10 years, 70% women, body mass index [BMI] 41.7±4.9 kg/m^2, 55% with hypertension, 17% with diabetes mellitus) underwent echocardiography before, 6 and 14 months after Roux-en-Y gastric bypass surgery in the prospective FatWest (Bariatric Surgery on the West Coast of Norway) study. We assessed LV systolic function by biplane ejection fraction (EF), LV wall mechanics by midwall shortening (MWS) and global longitudinal strain (GLS), and cardiac power normalized for LV mass by 0.222 x cardiac output x mean blood pressure (BP)/LV mass.

Results: Surgery induced a significant reduction in BMI, heart rate, systolic BP, and LV mass (Figure 1). Prevalence of LV hypertrophy fell from 34 to 20% 14 months after surgery (p<0.001), while that of concentric geometry remained stable: 8 vs 10% (p=0.36). GLS improved by 28%, however LV EF and MWS did not change (Figure 2). LV power at rest decreased postoperatively, reflecting the lower BP and heart rate, but was unaltered when normalized for LV mass (Figure 2). In backward stepwise multivariate regression analyses, 1 year improvement in GLS was predicted by the systolic BP reduction (p<0.05) (R^2 0.73, p<0.001), while low 1-year MWS was independently associated with female gender, concentric geometry and higher myocardial oxygen demand (all p<0.01) (Nagelkerke R^2 0.44, p<0.001), and lower 1-year LV power-mass with female gender and LV hypertrophy (p<0.01) (R^2 0.24, p<0.001).

Conclusion: In severely obese patients, LV longitudinal function normalizes 1 year after bariatric

surgery, mainly due to the BP reduction. LV midwall mechanics and power do not improve, especially in women and patients with persistent LV geometric abnormalities.



Increased VO2 peak after a structured exercise-training program is associated with reduced levels of cardiac myosin binding protein C in patients with symptomatic chronic heart failure.

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Background: Cardiac myosin-binding protein C (cMyC), a cardiac contractile protein, is a novel biomarker of myocardial injury, rising earlier and disappearing faster than cardiac troponins. It is a promising biomarker for use in triage of patients with chest pain presenting in the emergency department. It also has prognostic significance in patients with heart failure. However, the effects of systematic exercise training on plasma levels of cMyC has previously not been evaluated.

Purpose: The aim of this study was to assess the effect of a 12-week exercise training program on changes in plasma levels of cMyC in patients with chronic symptomatic heart failure with reduced ejection fraction (HFrEF). The changes in plasma levels of cMyC in an intervention group, performing structured exercise programs, were compared to those in a control group, instructed to perform regular recommended exercise (RRE) according to current guidelines.

Methods: This was a post hoc analysis of the SMARTEX-HF trial in 215 patients with symptomatic HF with Left Ventricular Ejection Fraction (LVEF) <35% and NYHA II-III. The patients were randomly assigned to High Intensity Interval Training (HIIT, n=77), Moderate Continuous Training (MCT, n=65) or RRE, (n=73) for 12 weeks. HIIT and MCT groups constituted the intervention group (IG). Measurements and clinical data were acquired before and after the 12-week intervention.

Statistical analysis: We divided the patients in two groups with Δ VO2Peak above and below the median of the sample. The absolute changes of cMyC were then compared between the two groups.

Mann-Whitney U test was used to compare continuous variables between the groups. Chi-squared test and Fisher exact test were used to compare categorical variables, as appropriate. A two-tailed $p < 0.05$ was considered significant.

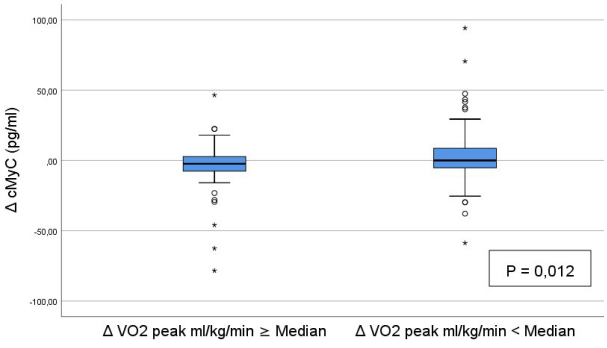
Results: There were no differences in changes of cMyC plasma levels, measured at baseline and after the intervention, between patients in the IG and RRE-group (p= 0.580).

When dividing the entire study population according to Δ VO2Peak higher or lower than median

value 0.48 ml/kg/min, we found a statistically significant greater reduction of cMyC values after 12 weeks of exercise training for those with higher than median Delta VO2Peak values compared to those with lower values (p =0.012). This finding was even stronger for the percentage change in cMyC levels (p=0.004 between groups).

Conclusion: In patients with symptomatic chronic HFrEF performing a structured 12-week exercise training program, a greater increase in Δ VO2Peak is significantly associated with a reduction in cMyC, suggesting cMyC may provide a dynamic measure of cardiorespiratory state.

Baseline characteristics	High ΔVO_{2Peak} (108)	Low ΔVO_{2Peak} (107)	p-value
Age, years (SD)	59 (12)	64 (11)	0,002
Sex female, n (%)	26 (24)	14 (13)	0,038
Heart failure <12 mo, n (%)	17 (16)	18 (17)	0,853
NYHA class 2, n (%)	83 (77)	67 (63)	0,023
NYHA class 3, n (%)	25 (23)	40(37)	0,023
Etiology, ischemic, n (%)	58 (54)	68 (64)	0,143
Previous myocardial infarction, n (%)	57 (53)	55 (41)	0,502
Previous CABG, n (%)	22 (20)	29 (27)	0,383
Previous PCI, n (%)	37 (34)	51 (48)	0,086
Atrial fibrillation chronic, n (%)	9 (8)	19 (18)	0,049
Atrial fibrillation paroxysmal, n (%)	12 (11)	17 (16)	0,049
History of hypertension, n (%)	41 (38)	41 (38)	1
History of diabetes mellitus, n (%)	20 (18)	31 (29)	0,069
History of COPD, n (%)	8 (7)	8 (8)	0,985
Current smoking, n (%)	16 (15)	22 (21)	0,127
ACE inhibitor n (%)	65 (60)	78 (73)	0,048
ARB, n (%)	38 (35)	26 (24)	0,081
ß-Blocker, n (%)	102 (94)	103 (96)	0,527
Aldosterone antagonist	54 (50)	68 (64)	0,045
Diuretic, n (%)	78 (72)	80 (75)	0,673
Digoxin or digitoxin, n (%)	17 (16)	14 (13)	0,579
Statin, n (%)	63 (58)	79 (74)	0,016
Body Mass Index, kg/m2 (SD)	31 (9)	30 (7)	0,398
Systolic blood pressure, mm Hg (SD)	120 (18)	120 (17)	0,801
NT-proBNP, ng/L (IQR)	804 (1176)	1111 (1674)	0,002
CRP, (SD)	3,0 (4,2)	4,1 (6)	0,255
LVEF, % (SD)	29 (7)	28 (6)	0,309
LVEDV, mL, (SD)	246 (73)	257 (81)	0,327
LVEDD, mm, (SD)	68 (8)	69 (8)	0,784



Increased risk of COVID-19-associated death in people under 70 with cardiovascular disease compared to the general population- A nationwide, registry-based study from Norway

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Introduction Reports from early in the pandemic suggested that older people with comorbidities were at increased risk of severe disease and death from COVID-19, including in Norway, where by September 2020 a majority of the COVID-19-associated deaths were in people with cardiovascular disease (CVD). However, it is uncertain if the increased risk seen in people with CVD could rather be explained by age and sex, both strong risk factors.

Purpose To compare the incidence and mortality of COVID-19 in people with CVD to the general Norwegian population, controlling for age and sex, to better identify the risk of death in those with CVD.

Methods We used data from the Norwegian Surveillance System for Communicable Diseases and Norwegian Cardiovascular Disease Registry to identify all test-positive cases and COVID-19-associated deaths in Norway up to June 30, 2020, as well as information on previously diagnosed CVD. CVD was defined as a composite of hypertension, myocardial infarction, stroke, heart failure and atrial fibrillation between 2012 to 2019. Standardized incidence and mortality ratios (SIR and SMR) were used to provide a measure of risk in people with CVD compared to the general population, stratified by age and sex.

Results There were 8809 test-positive cases and 260 COVID-19-associated deaths, with 1015 cases in people with CVD and 137 deaths. In people with CVD there was decreased incidence (SIR 0.58, 95% CI 0.55-0.62), except for people over 90, who had increased risk (SIR 2.53 (1.66-3.66) for men and SIR 2.95 (2.20-3.85) for women)

Table 1. Standardized incidence and mortality of COVID-19 in people with pre-existing CVD

Incidence		Cases with CVD (n)	SIR (95% CI)	Mortality		Deaths with CVD (n)	SMR (95% CI)
Total		**1015**	**0.58 (0.55 to 0.62)**	**Total**		**137**	**1.20 (1.01 to 1.42)**
Male	<60 years	188	0.66 (0.57 to 0.76)	Male	20-69 years	14	11.90 (6.70 to 19.26)
	60-69 years	110	0.35 (0.29 to 0.42)		70-79 years	15	0.88 (0.51 to 1.41)
	70-79 years	133	0.65 (0.55 to 0.77)		80-89 years	30	1.38 (0.95 to 1.94)
	80-89 years	88	0.70 (0.56 to 0.85)		90+ years	15	1.08 (0.62 to 1.72)
	90+ years	25	2.53 (1.66 to 3.66)	Female	20-69 years	1	3.66 (0.21 to 16.10)
Female	<60 years	131	0.45 (0.38 to 0.53)		70-79 years	11	1.88 (0.98 to 3.22)
	60-69 years	69	0.39 (0.30 to 0.49)		80-89 years	23	0.90 (0.58 to 1.31)
	70-79 years	111	0.80 (0.66 to 0.96)		90+ years	28	0.99 (0.68 to 1.41)
	80-89 years	111	0.60 (0.50 to 0.72)				
	90+ years	49	2.95 (2.20 to 3.85)				

CI = confidence interval. CVD = cardiovascular disease, SIR = standardized incidence ratio, SMR = standardized mortality ratio

(Table 1). Despite the lower incidence, mortality was marginally increased (SMR 1.20 (1.01-1.42)) which was attributable to men 20-69 years (SMR 11.90 (6.70-19.26)). People aged 70 and above had the same risk of death from COVID-19 as the comparable general population without CVD.

Conclusion This nationwide analysis from the first wave of the COVID-19 pandemic provides evidence that in people under 70 years with COVID-19, CVD was associated with an increased risk of death, despite lower incidence. We hypothesise the decreased incidence to be a result of social distancing and other measures adhered to in the beginning of the pandemic. However, those over 90 were not protected from this as they were more likely in a care setting where social distancing is more difficult, or a sign of increased testing in this group, which could introduce bias. Our analysis benefits from reliable, high-quality Norwegian registry data as well as being one of few nationwide studies not dependent on highly selected hospital reporting. The study is limited by relatively small numbers of deaths, especially in younger age groups, leading to possible residual confounding by age and sex as groups had to be pooled. Also, we did not control for other comorbidities. This analysis serves to support risk mitigation strategies in people with CVD and a basis to identify different risk patterns in later waves of the pandemic.

Increasing use of amiodarone in Norway

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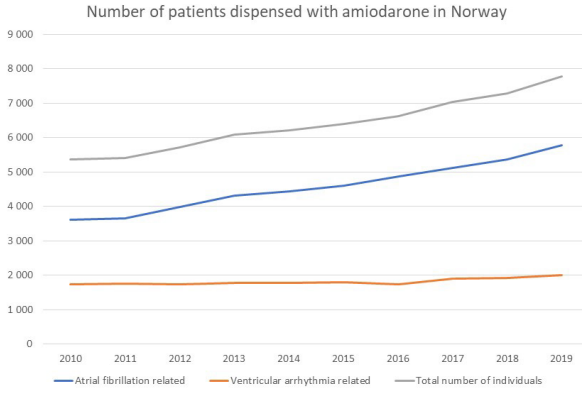
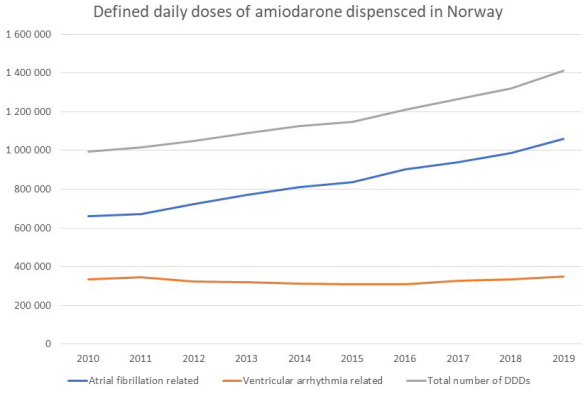
Background: Amiodarone may be used against ventricular arrhythmias to reduce ICD-shocks, and for rhythm control in patients with atrial fibrillation. The 2020 ESC atrial fibrillation guidelines upgraded the recommendation for amiodarone in rhythm control to class I, level of evidence A, although still with a caution to consider other antiarrhythmic drugs first. Amiodarone is the most potent antiarrhythmic drug in clinical use, but it has frequent and potentially severe side effects affecting several organ systems. We have seen an increasing number of patients with amiodarone-induced thyrotoxicosis.

Purpose: We wanted to study the prescription rate of amiodarone in Norway, which indications were most prevalent, and whether there had been any changes over time.

Methods: From the Norwegian Prescription Registry, we have collected data on how many patients had received amiodarone, and the number of defined daily doses delivered (DDDs), related to various reimbursement categories.

Results: From 2010 to 2019, the number of individuals receiving amiodarone from a pharmacy in Norway increased from 5359 to 7789 (45 % increase), and the number of DDDs delivered from 994905 to 1412796 (42 % increase)





(Figure). With an atrial fibrillation-related reimbursement code, we found during the same period an increase of individuals from 3616 to 5776 (60 % increase) and number of DDDs from 661531 to 1061601 (60 % increase). The dispenses for ventricular arrhythmia-related reimbursement codes were close to unchanged during the same period of years (Figure). The fraction of amiodarone use related to atrial fibrillation increased from 66 % in 2009 to 75 % in 2019.

Conclusion: We observed a 42-45 % increase in the total use of amiodarone over 10 years, and almost the whole increase was related to atrial fibrillation. In 2019, atrial fibrillation-related diagnoses accounted for 75 % of the total amount of amiodarone dispensed in Norway. Due to the several side effects of amiodarone, we are concerned if the threshold for use of amiodarone diminishes.

Leadless pacemaker implant in patients requiring CIED extraction: outcomes based upon timing of extraction

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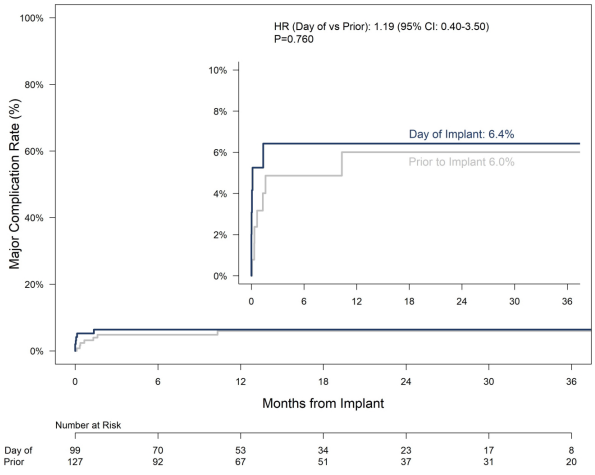
Background: Previous results from global Micra Transcatheter Pacemaker clinical trials have demonstrated leadless pacing as a safe and attractive option for patients with prior cardiac implantable electronic device (CIED) infection and extraction. Whether outcomes differ based upon the timing of prior device extraction has not been studied.

Purpose: To describe characteristics and outcomes of patients undergoing CIED extraction during or prior to Micra implantation.

Methods: Patients who underwent CIED explant and Micra implantation were identified from the Micra Post-Approval Registry and Micra Acute Performance studies. Baseline characteristics were summarized. A Fine-Gray competing risk model was used to compare risk for major complication through 24 months.

Results: Of the 2739 patients included in the studies, 99 (3.6%) patients had CIED extraction the day of Micra implantation (same day) and 127 (4.6%) patients had CIED extraction within 30 days prior to Micra implantation (prior). Although infection was the primary reason for CIED extraction in both groups, a larger proportion of prior patients underwent extraction for this reason (87.4% vs. 42.4%). In contrast, more same day patients underwent CIED extraction for physician/elective reasons (16.2% vs. 3.1%). Same day patients prior device history included pacemaker (42 dual chamber and 30 single chamber), ICD (1 single chamber and 4 dual chamber), CRT (7 CRT-ICD and 13 CRT-P) while prior patients device history included pacemaker (29 single chamber, 80 dual chamber), ICD (3 dual chamber), CRT (5 CRT-ICD and 7 CRT-P). Overall, patients with extraction were aged 72.8 ± 14.3 years, predominantly male (65.9%), and medical history was similar between groups, with the exception to CHF, which was higher for the same day group (18.2% vs 6.3%, P=0.021). The implant success rate was 98.0% for same day patients and 100% for prior patients. Median procedure duration was not significantly different between the groups (26.0 minutes and 25.0 minutes for same day and prior, respectively). Average follow-up duration was 16.5 ± 13.8



months (range 0-53.4) for same day patients and 18.2 ± 15.2 months (range 0-58.3) for subsequent patients. The rate of acute major complications (<30 days) was 5.1% for same day and 3.2% for prior. Through 24 months, the rate of major complications was 6.4% for same day and 6.0% for prior (HR: 1.19, 95% CI: 0.40 – 3.50, P=0.76, Figure). The rate of major complications related to infection was low and did not differ by group (1.01% vs. 1.57%, P=1.00)

Conclusion: The Micra leadless pacemaker was implanted with a high success rate following CIED extraction. Outcomes following CIED extraction appear similar, whether the extraction is performed during or prior to Micra implant.

Left atrial appendage function by strain predicts subclinical atrial fibrillation in patients with cryptogenic stroke/TIA

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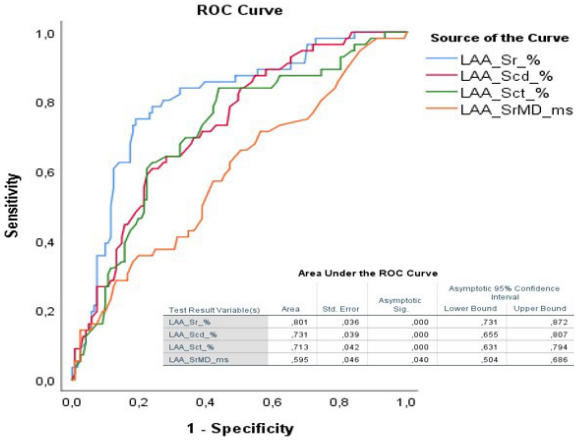
Background: Left atrial (LA) function by strain has shown to be promising to predict clinical atrial fibrillation (AF) in patients with cryptogenic stroke/TIA. However, there is little knowledge, if this novel method may prospectively predict subclinical AF (SCAF) and moreover, if left atrial appendage (LAA) function by strain and mechanical dispersion may be more sensitive to improve prediction of SCAF.

Purpose: The aim of the present study was to investigate if LA and LAA function by strain could improve the prediction of SCAF in patients at risk.

Methods: In this prospective study (mean follow-up 859±226 days), 185 patients with cryptogenic stroke/TIA, mean age 68±13years, 33% female and no history of clinical AF or SCAF, were included. All participants underwent 2D and 3D transesophageal and transthoracic echocardiography in sinus rhythm after index cryptogenic stroke/TIA (mean 5±3days). LAA and LA functions by phasic strain, including reservoir strain (Sr), conduit strain (Scd) and contraction strain (Sct) and mechanical dispersion of Sr were assessed. SCAF episodes were detected by cardiac monitoring during follow up (mean 257±273 days).

Results: LAA function by strain was decreased in those with SCAF (60/32% of all patients) compared to those without: Sr: 19.2±4.5% vs. 25.6±6.5% (p<0.001), Scd: -11.0±3.1% vs. -14.4±4.5% (p< 0.001), Sct: -7.9±4.0% vs. -11.2±4% (p< 0.001), respectively, while mechanical dispersion by Sr strain was increased, 34±24ms vs. 26±20ms (p=0.02). However, LA function by strain and mechanical dispersion did not differ in patients with SCAF compared to patients without. By ROC analyses, LAA strain and mechanical dispersion were highly significant in prediction of SCAF. LAA reservoir strain showed the best AUC of 0.80 (95% CI 0.73 - 0.87) with a cut-off value of 22.2%, sensitivity of 80%, and specificity of 73%, p<0.001. (Figure)

Conclusions: For the first time, we showed, that left atrial appendage function by strain and mechanical dispersion predicts SCAF, as opposed to left atrial function. Left atrial appendage function by strain may be useful in risk prediction in patients at considerable AF risk.



Left bundle branch block causes left atrial dyssynchrony: a result of atrio-ventricular mechanical interaction

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Introduction: Left bundle brach block (LBBB) leads to left ventricular (LV) mechanical dyssynchrony with septal flash and delayed lateral wall contractions. Since atrium and ventricle are anatomically connected, dyssynchronous LV con-

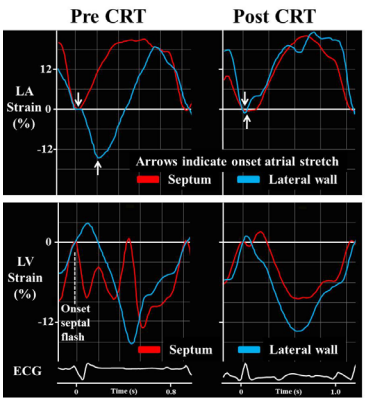
tractions may be transmitted to the left atrium, thereby disturbing left (LA) function.

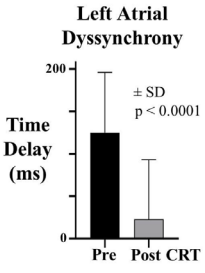
Purpose: To test the hypothesis that patients with LBBB have LA dyssynchrony induced by tethering to the dyssynchronous left ventricle.

Methods:Myocardial strain was measured by speckle-tracking echocardiography in 20 non-ischaemic heart failure patients with LBBB, before and 6 months after cardiac resynchronization therapy (CRT), and in 20 healthy controls. For the LA, dyssynchrony was measured as time delay between onset of the interatrial septum and the lateral wall, and for the LV, between onset septal flash and onset lateral wall contraction. White arrows in Figure indicate onset LA stretch.

Results: As shown in the Figure, patients with LBBB and HF had marked LA reservoir phase dyssynchrony. Before CRT time delay from onset LA septal stretch to onset lateral wall stretch was 125±71 ms (mean±SD), and decreased to 23±70 (p<0.0001) with CRT. In controls there was a small delay of 34±56 ms. The LA dyssynchrony correlated with LV dyssynchrony (r=0.50, p=0.033), supporting the hypothesis that LA dyssynchrony in LBBB represents mechanical interaction due to tethering between the respective walls.

Conclusions: Patients with LBBB had marked LA reservoir phase dyssynchrony, which was abolished with CRT. The LA dyssynchrony was attributed to direct LV-LA mechanical interaction. The observed LA resynchronization by CRT represent an additional benefit of CRT in patients with heart failure.





Long-term survival after a pharmacoinvasive strategy in patients with ST-elevation myocardial infarction and long distances to primary percutaneous coronary intervention - a prospective cohort study

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Background: In patients with ST-elevation myocardial infarction (STEMI), a pharmacoinvasive (PI) strategy is the recommended reperfusion method if primary percutaneous coronary intervention (pPCI) cannot be performed within 120 minutes from diagnosis. Long-term prognosis for STEMI patients with long transfer distances to pPCI is sparsely documented.

Purpose: To compare short- and long-term survival, and cardiovascular (CV) death in STEMI patients treated with PI or pPCI strategy.

Methods: Consecutive STEMI patients admitted to our cardiac invasive centre were registered prospectively during 2005-2011 in a local quality registry. Follow-up data throughout 2013 were provided by the Norwegian Cause of death registry. Effects of treatment strategy were determined using a propensity score weighted analysis, adjusting for treatment-outcome confounding. Outcomes were 30-day mortality, overall survival and CV death during follow-up.

Results: Of 4762 STEMI patients, 543 (11.4%) were treated with thrombolysis before admission for rescue- or early coronary angiography (PI strategy), and 4044 (84.9%) were admitted for a pPCI strategy (3,7% excluded due to unspecified treatment strategy). Median age was 60 and 63 years in the PI and pPCI groups (19.5% and 24.1% women, respectively). Median time to reperfusion was 110 minutes (25-75th percentile: 75-163; symptom-to-thrombolysis) versus 230 minutes (149-435; symptom-to-balloon). Crude 30-day mortality was 3.9% and 6.6% in the PI- and pPCI groups. Median follow-up was 4.5 years (max 8.3 years). The overall 8-year survival was 84.6% (95% CI 79.4-88.4) in the PI group and 72.6% (95% CI 70.1-74.9) in the pPCI group (crude hazard ratio [HR] 0.56 (95% CI 0.43-0.72, p<0.0001). After propensity score weighting (based on age, gender, smoking, previous hypertension, stroke, diabetes, myocardial infarction, angina pectoris and peripheral artery disease, kidney function and pre-hospital resuscitation), patients had estimated 25% lower risk of

long-term mortality with a PI strategy (weighted HR 0.75; 95% CI 0.53-1.07, p=0.113, Figure 1A). Cumulative incidence rate of CV death was 12.8 (PI strategy) and 27.8 (pPCI strategy) pr 1000 person-years (crude incidence rate ratio 0.46; 95% CI 0.32-0.68, p<0.0001), and was significantly lower in the PI group after weighting on the propensity score (p=0.048, Figure 1B).

Conclusions: There was a non-significant 25% lower risk of mortality up to 8 years with a PI versus pPCI strategy in STEMI patients with long transfer distances to PCI, after adjustment for treatment-outcome confounding. Importantly, long-term incidence of CV death was significantly lower in the PI group. These findings from real life practice support the use of a PI strategy in STEMI patients without contraindications to thrombolysis, when pPCI within 120 minutes from diagnosis is not possible.

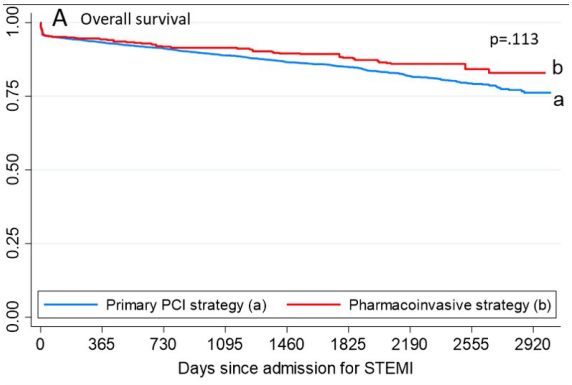

Figure 1A. Pharmacoinvasive (b) versus primary PCI (a) strategy for STEMI patients. Cumulative survival; propensity score weighted, Kaplan-Meier estimator

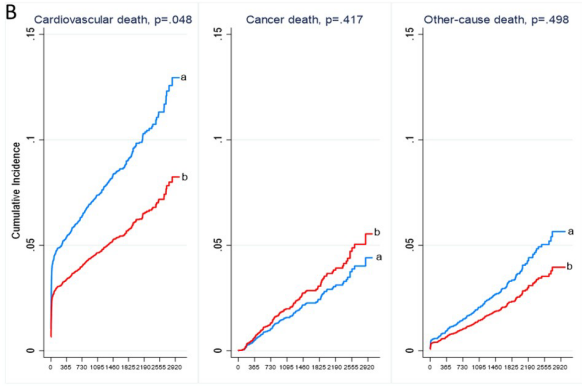

Figure 1B. Pharmacoinvasive (b) versus primary PCI (a) strategy for STEMI patients. Causes of death; propensity score weighted cumulative incidence functions, accounting for competing risks.

Low levels of dihomo-gamma-linolenic acid are associated with all-cause death in elderly patients with a recent myocardial infarction.

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Background: In a previous study*, low levels of the omega-6 fatty acid (FA) dihomo-gamma (γ)-linolenic acid (DGLA; C20:3w6), were independently associated with poor 7-year outcome in elderly patients after acute coronary syndrome.

Aim: In order to further evaluate DGLA as a predictor of outcome, we measured n-6 FAs including DGLA in serum samples from elderly subjects with a recent acute myocardial infarction (AMI).

Methods: Baseline samples from the OMEMI (Omega-3 Fatty acids in Elderly with Myocardial Infarction) trial* in which a total of 1027 patients, aged 70 to 82 years, were included 2-8 weeks after an MI, were used. The pre-specified primary outcome during 2 years follow-up was major adverse cardiac events (MACE), which consisted of nonfatal MI, unscheduled coronary revascularization, stroke, all-cause death, or hospitalization for heart failure. Cox regression analysis was used to relate serum n-6 FA levels, measured by gas chromatography and reported as % weight of total FA (%wt) to the risk of incident cardiovascular events. Three models were employed in the multivariable analysis, adjusting for: 1) age, sex and body mass index; 2) + baseline omega-3 FA supplementation; 3) + prevalent hypertension.

Results: Median DGLA levels at baseline (n= 1.002) were 2.89 (Q1-Q3 2.43 – 3.38) %wt. After 2 years follow-up, 152 patients experienced incident MACE, including n=55 all-cause death.

The univariate hazard ratio (HR) for MACE, employing continuous DGLA values was 0.89 (95% CI 0.72-1.08) per %wt increase in DGLA, p=0.24, and for all-cause death 0.72 (95% CI 0.48-1.07), p=0.11. In the multivariable Cox regression models for MACE, concentrations

of DGLA did not reach statistical significance; p=0.12, 0.09 and p=0.07 in Models 1, 2 and 3, respectively.

In univariate analysis, HR for total death in the three higher quartiles of DGLA as compared to the lowest quartile was 0.51 (95% CI 0.30–0.80), p=0.016. Results remained statistically significant in all the multivariable models. Model 1: HR 0.54 (0.31-0.95), p=0.03; Model 2: HR 0.50 (0.28-0.91) p=0.02; Model 3: HR 0.49 (0.27-0.88), p=0.017.

Conclusion: Low serum levels of DGLA were associated with increased risk of all-cause death after AMI in elderly patients, thus, suggesting DGLA to be protective.

Mitral and tricuspid annulus disjunction frequently coexist

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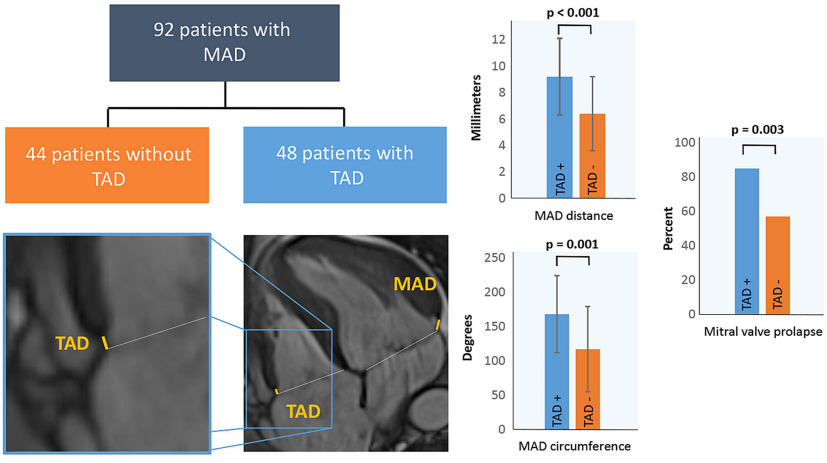
Background: Mitral annulus disjunction (MAD) is an abnormal atrial displacement of the mitral annulus, frequently found in patients with high-risk arrhythmogenic mitral valve prolapse syndrome. It is unknown whether the annulus disjunction extends to the right side of the heart as tricuspid annulus disjunction (TAD), and whether it is associated with right ventricular electrical instability.

Purpose: We aimed to explore the presence of TAD, and if extended annulus disjunction was associated with ventricular arrhythmias.

Methods: We included patients with previously described MAD assessed by cardiac magnetic resonance imaging (CMR) in an ambispective cohort study. MAD and TAD was defined as ≥1 mm separation between the respective atrial wall-valve leaflet junction and the top of the ventricular myocardium. TAD was assessed in the lateral and inferior right ventricular free wall by means of the 4-chamber and right ventricular 2-chamber views, respectively. MAD circumference was assessed by a CMR study protocol with six left ventricular long axis views separated by 30 degrees. Mitral valve prolapse was defined as ≥2 mm superior displacement of any part of the mitral leaflets beyond the mitral annulus. Ventricular arrhythmias were defined as aborted cardiac arrest or non-sustained/sustained ventricular tachycardias recorded by electrocardiogram (ECG), stress ECG or Holter monitoring.

Results: We included 92 patients with MAD (62% female, age 47±16 years, 71% mitral valve prolapse). TAD was found in 48 (52%) patients, both in the lateral (n=40, 83%) and inferior (n=30, 63%) right ventricular free wall. Patients with TAD were older (age 51±16 years vs. 43±14 years, p=0.01), had greater MAD circumference (168±56° vs. 117±62°, p=0.001) and greater MAD distance (9.2±2.9 mm vs. 6.4±2.8 mm, p<0.001). Additionally, patients with TAD had more frequently mitral valve prolapse (40 patients [85%] vs. 25 patients [57%], p=0.003), whereas similar frequency of bileaflet prolapse (17 patients [39%] vs. 10 patients [39%], p=0.99). Ventricular arrhythmias had occurred in 38 (41%) patients, who were younger (age 40±14 years vs. 52±15 years, p<0.001) and had less frequently TAD (14 patients [37%] vs. 34 patients [63%], p=0.01; univariate odds ratio 0.34 [0.15-0.81], p=0.02). However, TAD was not associated with ventricular arrhythmias when adjusted for age (multivariate odds ratio 0.46 [0.18-1.15], p=0.10).



Conclusions: TAD by CMR was highly prevalent in patients with MAD and was a marker of severe annulus disjunction and mitral valve prolapse. TAD was not associated with more ventricular arrhythmias. This novel marker warrants further research to explore the clinical implications of right-sided annulus disjunction.

Myocardial infarction after prostate cancer diagnosis in Norway: a population-wide registry-based study

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Background Survival after prostate cancer (PCa) is high for many patients, and it is now more likely they will die from cardiovascular disease than from PCa specific causes. However, patients with active malignancies have been excluded from trials to evaluate best treatments for myocardial infarction (MI). As people with PCa become a larger subpopulation of those experiencing a MI, clinicians need more comprehensive evidence regarding MI in people with PCa and if they are receiving optimal treatment.

Purpose To identify the Norwegian population diagnosed with PCa that have experienced a MI after their cancer diagnosis using routinely collected registry data, and describe relevant patient and treatment characteristics, as well as identify areas of missing data.

Methods We used data from Cancer Registry Norway to identify all people diagnosed with PCa between 2004 and 2019. Cancer data was linked with the Norwegian Myocardial Infarction Registry to identify PCa patients that were hospitalised for a MI as well as important features of the MI treatment period. Descriptive statistics were used to describe the number of people with PCa, important cancer specific features and variables related to the MI, as well as to explore missing data within collected variables.

Results We identified 70646 people diagnosed with PCa in Norway between 2004 and 2019, of which, 2929 (4.1%) experienced a MI (3465 MIs in total). Most had a single MI (2528, 86.3%), around 10.7% (314) had two MIs, and 3.0% (87) had three or more. Of all the MIs, 20.7% (718 in 700 patients) were classified as ST elevated MIs and 76.2% (2641 in 2218 patients) as non-ST elevated MIs (Table 1). Around 9% of patients were missing a baseline prostate specific antigen value and over 20% did not have an identified cancer stage. Thrombolysis and percutaneous intervention had a high number of records with unknown status of these treatments (58.5% and 36.6%, respectively).

Conclusions This population-wide registry-based study has demonstrated that linkage between Cancer Registry Norway and Norwegian Myocardial Infarction Registry provides a comprehensive dataset to further study the relationship between PCa and MI in the Norwegian population. This study benefits from data sourced from registries that have previously been found to be highly comprehensive and accurate. There was evidence of some variables with higher missing data, but we are confident that our planned further linkages with the Norwegian Cardiovascular Disease

Table 1: Prostate cancer and myocardial infarction characteristics based on ST elevation status

	Percent missing	STEMI (n = 718 in 700 patients)	NSTEMI (n = 2641 in 2218 patients)
Age at PCa diagnosis- mean years (SD)	0.0%	69.0 (8.2)	71.6 (8.3)
PSA at PCa diagnosis- median (IQR)	8.9%	10 (6.7-18)	11.7 (7.2-25)
Gleason score at PCa diagnosis	5.5%	6 or less: 246 (35.1%) 7a: 186 (26.6%) 7b: 88 (12.6%) 8: 90 (12.9%) 9: 47 (6.7%) 10: 6 (0.9%)	6 or less: 708 (31.9%) 7a: 508 (22.9%) 7b: 312 (14.1%) 8: 317 (14.3%) 9: 222 (10.0%) 10: 29 (1.3%)
PCa stage at PCa diagnosis	22.9%	Local: 378 (54.0%) Regional: 138 (19.7%) Distant metastatic: 31 (4.4%)	Local: 1111 (50.1%) Regional: 461 (20.8%) Distant metastatic: 129 (5.8%)
Current smoker at MI	10.2%	156 (22.3%)	344 (15.5%)
Diabetes mellitus at MI	0.7%	109 (15.6%	479 (21.6%)
Hypertension treatment at MI	1.0%	336 (48.0%)	1211 (54.6%)
Time from PCa diagnosis to first MI- mean years (SD)	0.0%	5.5 (3.6)	5.5 (3.6)
Type of MI	0.5%	Type 1: 689 (96.0%) Type 2: 17 (2.4%)	Type 1: 2138 (81.0%) Type 2: 444 (16.8%)
Thrombolysis	58.5%	Pre-hospital: 46 (6.4%) At hospital: 38 (5.3%)	Pre-hospital: 0 (0%) At hospital: 3 (0.1%)
PCI	36.6%	563 (78.4%)	1010 (38.2%)
In-hospital mortality	0.0%	87 (12.1%)	161 (6.1%)
1 year mortality	-	152 (21.7%)	486 (21.9%)

IQR = interquartile range; MI = myocardial infarction; NSTEMI = non-ST elevated myocardial infarction; PCa = prostate cancer; PCI = percutaneous intervention; SD = standard deviation; STEMI = ST elevated myocardial infarction

Registry and Norwegian Patient Registry, as well as using other clinical data, will help to overcome the current missing data issues. It is our plan to carry this research forward to provide a comprehensive, longitudinal analysis of how patients with PCa experience and are treated for an acute MI in Norway including PCa specific risk factors, comparison with current guidelines and if further guidelines should be created for people with PCa.

Myocardial work in overweight and obesity: impact of sex and central haemodynamics

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Background: Women with increased body mass index (BMI) have better left ventricular (LV) global longitudinal strain (GLS) than men. LV global myocardial work index (GWI) is a novel measure of myocardial function that adjusts for afterload and offers the opportunity to differentiate between early systolic dysfunction and elevated myocardial workload.

Purpose: To investigate sex differences in myocardial work in women and men with increased BMI.

Methods: Clinical and echocardiographic data from 467 participants (61% women, average age 47±9 years) with a BMI above 27 kg/m^2 and without cardiac disease was analysed. Central pulse wave analysis was assessed by applanation tonometry. GWI was calculated by GLS and post-echocardiography blood pressure (BP). Covariables of GWI were identified by linear regression analysis with collinearity tools.

Results: Women had higher BMI (31.4 vs. 31.0 kg/m^2) and higher aortic augmentation pressure (12±7 vs. 8±6 mmHg), but lower clinic systolic BP (127±17 vs. 134±14 mmHg) compared to men (all P < 0.05). Women also had higher LV GLS (20.0±2.8 vs. 18.8±2.8 %) and GWI (2126±385 vs. 2047±389 mmHg%)(both P < 0.05). In univariable regression analyses, higher GWI was significantly associated with higher age, clinic systolic BP, wall stress, ejection fraction, aortic augmentation pressure, left atrial size, and LV ejection time, and with lower waist circumference (all P < 0.05), but not with BMI. In multivariable linear regression analyses, adjusting for these correlates, female sex was independently associated with higher GWI (Table 1, model 1). After additional adjustment for aortic augmentation pressure, the association between GWI and sex became non-significant (Table 1, model 2).

Conclusions: Women with increased BMI have higher GWI compared to men, despite lower BP. Higher GWI in women is mainly explained by elevated workload due to higher central aortic stiffness.

TABLE 1. Covariables of global work index in multivariable linear regression analyses

Variables	Model 1 (R^2 = 0.281)		Model 2 (R^2 = 0.292)	
	Standardized β coefficient	P value	Standardized β coefficient	P value
Female sex	0.125	0.007	0.076	0.129
Age (years)	0.122	0.007	0.079	0.101
Waist circumference (cm)	-0.095	0.023	-0.097	0.021
Clinic systolic blood pressure (mmHg)	0.239	<0.001	0.196	<0.001
Clinic heart rate (beats/min)	-0.113	0.016	-0.082	0.085
Meridional wall stress (dyne/cm^2)	0.199	<0.001	0.190	<0.001
Ejection fraction (%)	0.238	<0.001	0.244	<0.001
Left atrial volume index (ml/m^2)	0.136	0.001	0.136	0.001
Systolic ejection time (ms)	0.117	0.013	0.113	0.016
Augmentation pressure (mmHg)			0.127	0.016

Myocardial work still reflect function while strain simply measure deformation when afterload increases

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Introduction: Global longitudinal strain is recommended by the European Society of Cardiology to detect subclinical left ventricular (LV) dysfunction, but is markedly load-dependent. Myocardial work was recently introduced as a clinical tool to study LV function by pressure-strain analysis. Since myocardial work incorporates afterload, it is assumed to be less afterload-dependent than strain, but the relationship with afterload is incompletely understood.

Hypothesis: Myocardial work is a better tool than strain, to measure myocardial function during elevated afterload.

Methods: In eleven anesthetized dogs, LV volume and longitudinal strain were measured by sonomicrometry, and pressure by micromanometry. Myocardial work was calculated by pressure-strain analysis. Additionally, stroke work was calculated as the area of the pressure-volume loop. Afterload was instantly increased by aortic constriction using a pneumatic cuff around the ascending aorta. Measurements were performed at baseline, during moderate- and marked afterload elevations.

Results: Table 1 summarizes the results. LV pressure (LVP) successively increased with moderate and marked afterload elevation, while

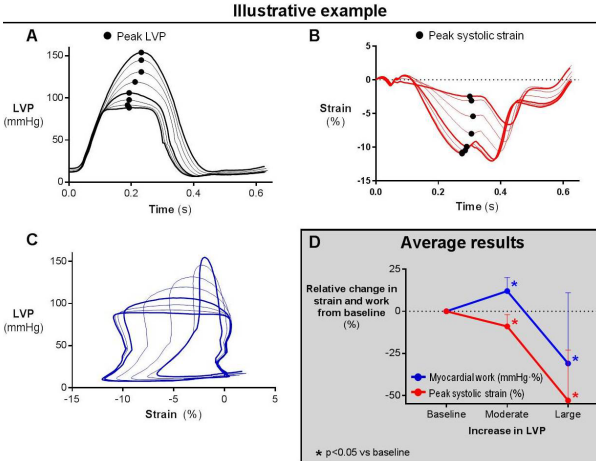

Table 1 (n=11)

	Baseline	Moderate afterload increase	Marked afterload increase	ANOVA
Peak LVP, mmHg	92±12	111±13*	138±19*†	p<0.001
Heart rate, bpm	109±10	109±10	109±10	NS
ED volume, ml	69±21	69±22	73±25*†	p=0.011
ES volume, ml	51±19	53±20*	62±24*†	p<0.001
Stroke volume, ml	17±3	16±3*	12±4*†	p<0.001
LV EF, %	26±6	24±5*	17±6*†	p<0.001
Longitudinal Strain, %	6.9±2.4	6.3±2.2*	3.1±2.0*†	p<0.001
Myocardial work, mmHg·%	551±175	614±183*	353±212†	p=0.018
Stroke work, mmHg·ml	1200±305	1326±315*	942±464†	p=0.012

Values are mean ± SD. One-way analysis of variance (ANOVA) was used to compare baseline, moderate- and marked afterload increase. Post hoc tests with Bonferroni adjustment were done when ANOVA showed significance. * p<0.05 vs. baseline. † p<0.05 vs. moderate afterload increase. LVP = left ventricular pressure; bpm = beats per minute; ED = end-diastolic; ES = end-systolic; LV = left ventricular; EF = ejection fraction.

longitudinal strain was successively reduced. Myocardial work and stroke work, on the other hand, increased with moderate afterload elevation, but was then reduced at marked afterload increase (Figure 1 and Table 1). Stroke volume and ejection fraction corresponded to strain and were reduced with afterload elevation.

Conclusions: Longitudinal strain and myocardial work have qualitatively different responses to increased afterload. While moderate changes in afterload cause reductions in strain that can be falsely interpreted as reductions in contractility, myocardial work increases as it incorporates the increased workload at moderately elevated afterload.

Normal values for indexed left atrial end-systolic volume by two- and three-dimensional echocardiography. A cross-sectional population study.

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Background: The left atrium volume and function gives important prognostic and diagnostic information. Normal values for left atrial end-systolic volume index (LASVI) is derived from 4-chamber and 2-chamber views or three-dimensional (3D) imaging. In current recommendations LASVI above 34 ml/m2 has been regarded dilated when assessing diastolic function and left ventricular filling pressures. It is not known if improved image quality by new scanners or more dedicated atrial focused views provide the same normal reference ranges.

Material and methods: We examined a large sub-population participating in a population based health study by high-end echocardiographic scanners. LA volume was assessed at end-systole in two-dimensional (2D) recordings focusing on the left atrium to avoid foreshortening. Additionally, 3D full volume recordings were acquired stitching 2-4 cardiac cycles when feasible using breath hold. All echocardiograms were analyzed offline using dedicated commercial software with manual tracing of the endocardial border and calculation of volume by the summation of discs method in 2D recordings.

Results: 2462 of 5763 invited persons was examined by echocardiography. 1048 persons were excluded due to known heart disease, atrial fibrillation, antihypertensive treatment, diabetes mellitus or findings of clear pathology on echocardiography leaving 1414 persons presumed free of cardiovascular disease or major risk factors for the analyses.

Mean ± SD age was 57.9 ± 12.4, and 55.8 % was females. Mean (SD) LASVI in females and males were 27.6 ± 9.7 ml/m2 and 30.7 ± 11.1 ml/m2 by 2D imaging, respectively. Similarly, mean ± SD LASVI in females and males were 29.1 ± 6.8 ml/m2 and 30.5 ± 7.9 ml/m2 by 3D. The distribution of LASVI by age is showed in figure 1. The mean ± SD difference between 2D and 3D intra-

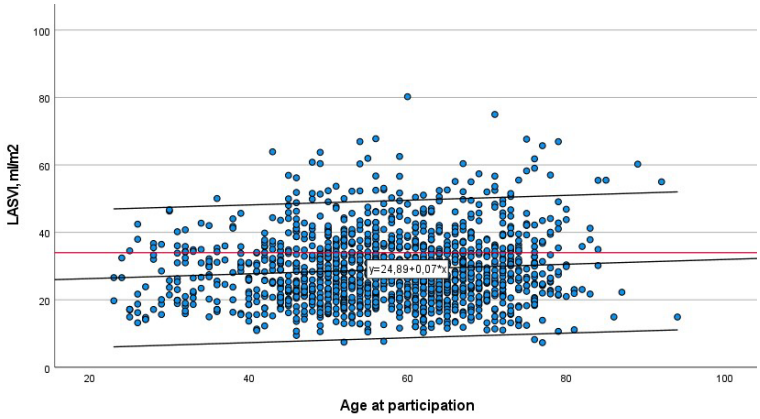

Figure 1. Indexed left atrial end-systolic volume, summation of discs method using adjusted left atrial view vs age. The red line denotes 34 ml/m2 used as the cut-off value in present guidelines.

individual measurements were 0.31 ± 9.0 ml/m2 corresponding to 1.1%. By 2D assessment 24.1% of this presumed healthy cohort had a LASVI over 34 ml/m2, with more males than females had enlarged left atria by this definition (32.7% vs 20.1%, p <0.001).

Conclusion: New reference ranges for left atrial size is provided for 2D and 3D recordings. By dedicated 2D recordings normal values are larger than previously recorded, and the difference between 2D and 3D recordings are less than previously reported.

Obesity prevalence and associations with socio-economic and behavioral factors in population-based studies in Russia and Norway, 2015-2017

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Background: Obesity is an epidemic of XXI century, as its prevalence doubled during the last forty years. As Russia and Norway are countries with different life expectancy there could be differences in obesity and its correlates.

Purpose: To investigate and compare prevalence and socio-economic and behavioral factors associated with obesity in Russia and Norway with data from population-based studies.

Methods: We used multivariable logistic regression to examine associations of obesity (body mass index>30 kg/m2) with socio-economic factors (age, education, marital status, and poor financial situation defined as difficulty to afford clothes) and behavioral characteristics (smoking, alcohol use) in participants aged 40-69 years from the Know Your Heart study (Russia, 2015-2017, N=4 106) and the seventh Study (Norway, 2015-16, N=17 604). All results for covariates are mutually adjusted. Between-study comparisons of the associations of obesity with the same covariates were performed through investigation of their interactions with the "study" variable.

Results: The age-standardized prevalence of obesity was higher in Russia among women (36.8 vs 22.0%, p<0.001) and did not differ among men (26.7 vs 25.7%, p=0.224). In Russian women, obesity was positively associated with age of 50-69 years relative to 40-49 years (OR=2.5, 95% CI 2.0-3.1), no university education (OR=1.5, 95% CI 1.2-1.8), and poor financial situation (OR=1.5, 95% CI 1.2-1.9). In Norwegian women, obesity was negatively associated with the age of 50-69 years (OR=0.8, 95% CI 0.8-1.0), current smoking (OR=0.8, 95% CI 0.7-1.0) and drinking alcohol ≥2 times per week (OR=0.6, 95% CI 0.5-0.6), and positively associated with no university education (OR=1.5, 95% CI 1.3-1.7), previous smoking (OR=1.3, 95% CI 1.1-1.4), and drinking ≥5 alcohol drinks per occasion (OR=1.7, 95% CI 1.3-2.2). In Russian men, obesity was positively associated with living with spouse/partner (OR=1.5, 95% CI 1.1-2.2), drinking alcohol ≥2 times per week (OR=1.4, 95% CI 1.1-1.8), and negatively associated with current smoking (OR=0.6, 95% CI 0.4-0.8). In Norwegian men, obesity was positively associated with no university education (OR=1.4, 95% CI 1.2-1.6), previous smoking (OR=1.3, 95% CI 1.2-1.5), and drinking ≥5 alcohol drinks per occasion (OR=1.7, 95% CI 1.5-1.9), and negatively associated with current smoking (OR=0.8, 95% CI 0.7-1.0) and drinking alcohol ≥2 times per week (OR=0.7, 95% CI 0.6-0.7). Interactions with the "study" variable in women were significant for age, financial situation, frequency of alcohol use; in men - for living with spouse/partner, frequency of alcohol use, number of alcohol drinks taken per occasion.

Conclusion: The prevalence of obesity was higher in Russian compared to Norwegian women, but there was no difference between Russian and Norwegian men. There were different between-country patterns of the associations of obesity with the socio-economic and behavioral characteristics.

One size does not fit all - a realist review of screening for asymptomatic atrial fibrillation in Indigenous communities in Australia, Canada, New Zealand and United States

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Background/Introduction: Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia and it is increasing in prevalence and incidence globally. True prevalence is underestimated because silent/asymptomatic AF is frequent and under-detected, but can cause stroke. Guidelines recommend opportunistic screening for AF in patients aged ≥65 years old. A growing body of evidence from hospital and community-based studies in Australia, New Zealand, Canada and United States indicates this age limit is lower for Indigenous people. Screening for AF meets the World Health Organisation (WHO) criteria for successful routine screening, yet little is known about successful implementation of AF screening in Indigenous communities in developed countries.

Purpose: The aim of this study is to use a realist approach to identify what works, how, for whom and under what circumstances for AF screening of Indigenous communities in Australia, Canada, New Zealand and United States.

Methods: In the realist review, eight databases were searched for studies targeted at AF screening in Indigenous communities. Realist analysis was used to identify context-mechanism-outcome configurations across 11 included records (reporting on 5 studies). Snowball referencing and grey literature were used to iteratively incorporate evidence to enhance the refined programme theory that was the product of the realist analysis.

Results: The realist review included studies using multiple screening strategies such as using tools to increase screening, using different screening environments and training screeners to provide culturally centred care. The realist analysis identified a number of mechanisms that can improve AF screening in Indigenous communities.
The contextual factors enabling AF screening programs in Indigenous communities include wider community engagement, opportunistic non-clinical settings, using portable and easy to use devices, increasing knowledge, motivation and confidence in screening amongst Indigenous healthcare workers as well as improving follow-up protocols for abnormal results tailored to screen setting. Barriers to effective AF screening include time-poor working environments, conflicting cultural issues, navigating communication of abnormal results and logistical issues with device use (Figure 1).

Conclusion(s): Since the life-course risk for AF in Indigenous population is different, a modified screening strategy needs to be put in place. This realist review provides lessons learned for successful implementation of AF screening programs

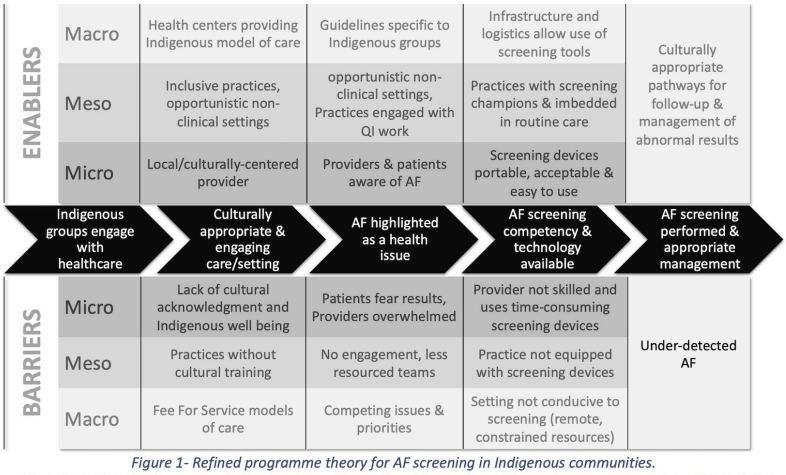

Figure 1- Refined programme theory for AF screening in Indigenous communities. Micro (Individual & Interpersonal factors), Meso (Institutional factors) and Macro (Infrastructural factors). AF= Atrial Fibrillation, QI= Quality Improvement.

for Indigenous communities. In order to tackle the gap in cardiovascular burden in Indigenous people, this study calls for action to develop AF screening guidelines for Indigenous populations and provides a guide for policy makers about timely and effective AF screening programs for Indigenous communities.

One-year impact of bariatric surgery on echocardiographic markers of vascular disease: results from the prospective FatWest study

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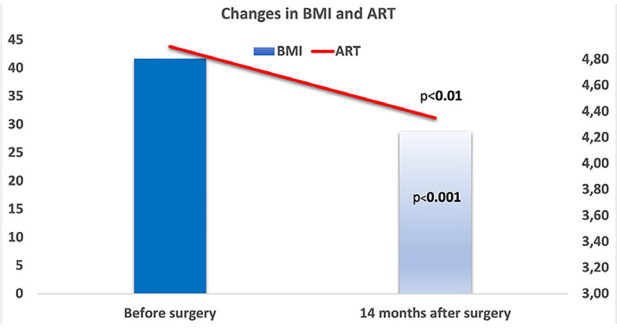
Background: Aortic root plaque and aortic valve sclerosis (AVS) are known echocardiographic markers of atherosclerosis. Obesity increases the atherothrombotic risk, while large surgical weight loss improves the cardiovascular risk profile. It is unclear whether the severity of vascular disease associated with severe obesity changes after bariatric surgery.

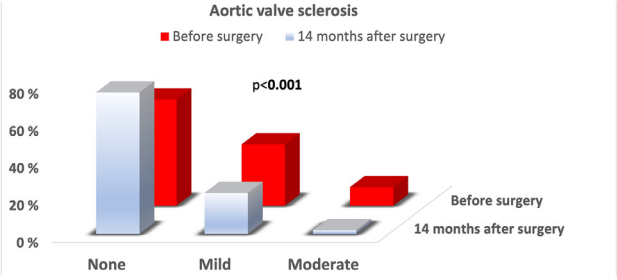
Purpose: To assess the 1-year impact of bariatric surgery on aortic root wall thickness (ART) and AVS.

Methods: 91 severely obese patients (43±10 years, preoperative body mass index [BMI] 41.7±4.9 kg/m2, 55% hypertensive, 17% diabetic) underwent echocardiography preoperatively and 14 months after Roux-en-Y bypass surgery in the prospective FatWest (Bariatric Surgery on the West Coast of Norway) study. We measured the end-diastolic maximum ART and categorized AVS as mild, moderate or severe based on combined aortic cusp thickness and hyperechoic valve lesions. Left ventricular (LV) structural remodelling was assessed by LV mass and geometry. In 52 patients with clinical signs of obstructive sleep apnea, preoperative polysomnography data including apnea-hypopnea index and mean nightly oxygen saturation were evaluated.

Results: Preoperatively, 39% had mild-moderate AVS, and an average ART of 4.9±1.7mm (Figures 1-2). Presence of AVS at baseline was associated with higher LV mass, while ART was higher in men, older patients and increased with lower nightly oxygen saturation (r=-0.29, p<0.05). During the first preoperative 14 months, patients experienced a 12.9±3.8kg/m2 BMI and 0.6±1.9mm ART reduction, and AVS prevalence lowered by 45% (Figures 1-2). In backward stepwise multivariate regression analyses with adjustment for changes in clinical variables, LV mass and geometry, less ART reduction at 14 months was independently predicted by higher age, higher postoperative BMI and presence of AVS (R2 0.53, all p<0.05). Persistent AVS was associated with higher age and preoperative diabetes (R2 0.24, p<0.05).

Conclusion: In patients undergoing bariatric surgery, a reduction in echocardiographic markers of vascular disease was observed 1 year postoperatively, particularly in younger, non-diabetic patients.





Patients with NSTEMI have fewer symptoms and higher quality of life three months after admission for acute chest pain

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Background: A substantial proportion of patients admitted for possible non-ST elevation acute coronary syndrome (NSTE-ACS) who are not diagnosed with non-ST elevation myocardial infarction (NSTEMI) suffer from conditions (e.g. chronic myocardial injury [CMI]) that may imply serious cardiac risk and impaired quality of life. It is unknown what predicts quality of life and recurrence of symptoms in chest pain patients.

Purpose: To investigate which demographic and clinical characteristics, including discharge diagnosis, that predict recurrent symptoms and quality of life three months after hospitalization for acute chest pain.

Methods: A total of 1506 patients ≥18 years admitted with suspected NSTE-ACS at Haukeland University Hospital, Bergen, Norway, were included in the WESTCOR study. The final diagnosis was adjudicated by two independent cardiologists based on all clinical data including routine cTnT (5th gen, Roche Diagnostics). Three months after discharge patients received questionnaires assessing general health (SF-12v1), angina-related health (SAQ-7) and dyspnea (Rose Dyspnea Scale). In all, 774 (51.3%) patients responded and were included in the analyses. Univariable and multivariable regression models were applied to identify predictors of symptoms and quality of life scores after adjusting for a subset of candidate predictors. A subgroup analysis was undertaken in patients with stable troponin concentrations (N=658).

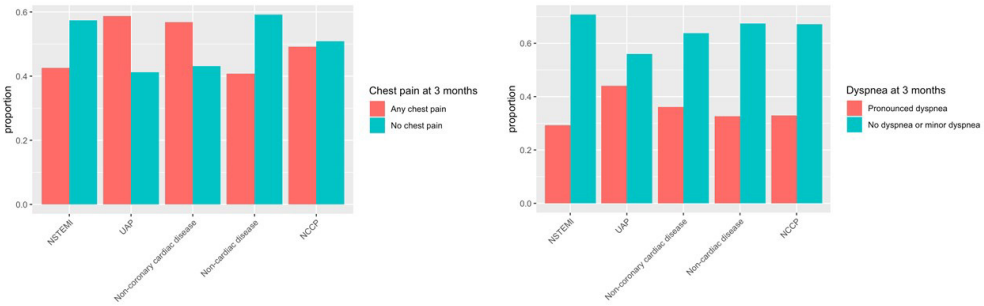
Results: Based on the discharge diagnosis the patients were grouped as NSTEMI (14.2%), unstable angina pectoris (UAP) (16.9%), non-coronary cardiac disease (6.6%), non-cardiac disease (6.3%) and non-cardiac chest pain (NCCP) (56.0%). After three months the NSTEMI patients had the highest quality of life scores and the lowest prevalence of symptoms (angina and dyspnea), while the inverse was true for the UAP patients (Fig 1). Revascularized patients had a better quality of life compared to those

Multivariable regression models of the association between predictors and scores of SAQ-7 and SF-12v1 instruments

	SAQ7-Angina Frequency β (P-value)	SAQ7-Quality of Life β (P-value)	SAQ7-Physical Limitation β (P-value)	SAQ7-Summary β (P-value)	Physical component-12 β (P-value)	Mental component-12 β (P-value)
Age	NS	NS	-0.18 (<0.001)	NS	NS	NS
Female gender	NS	NS	NS	NS	NS	NS
Prior MI	NS				NS	-0.11 (0.045)
Prior CABG	NS	NS	-0.10 (0.034)	NS	NS	
Hypertension	NS	-0.09 (0.013)	NS	NS	-0.23 (<0.001)	NS
Current smoking		-0.10 (0.005)	-0.09 (0.038)	NS	-0.13 (0.051)	-0.13 (0.008)
Reduced renal function (eGFR < 60 ml/min/1.73m^2	NS		-0.10 (0.043)	NS		
BMI					-0.18 (0.010)	
Revascularization	0.19 (0.002)	0.12 (0.010)		0.19 (0.005)	NS	
UAP	-0.18 (0.007)	-0.09 (0.045)	NS	-0.20 (0.008)	-0.16 (0.039)	
Non-coronary cardiac disease		NS	-0.10 (0.037)	-0.12 (0.037)		
	R^2=0.058 P < 0.001	R^2=0.055 P < 0.001	R^2=0.108 P < 0.001	R^2=0.072 P < 0.001	R^2=0.131 P < 0.001	R^2=0.037 P = 0.006

NS: not significant

Prevalence of symptoms three months after discharge



treated conservatively (P<0.001). Adjusted multivariable analysis also demonstrated that revascularization (β=0.19, P=0.002) and a diagnosis of UAP (β=-0.18, P=0.007) succeeded to predict angina frequency. Additionally, current smoking and hypertension were also associated with worse quality of life outcomes (Table 1). NCCP patients had high median prevalence of symptoms after three months, with 50% of the group reporting chest pain in the last four weeks, and 33% reporting dyspnea. In the subgroup analysis, current smoking predicted worse quality of life in all domains (all P<0.05) except SAQ7-Angina frequency.

Conclusions: Three months after hospitalization for chest pain revascularized patients had better quality of life and less symptoms compared to other patient groups. A diagnosis of UAP predicted recurrent symptoms and impaired quality of life in patients, suggesting that closer monitoring should be considered in order to minimize re-hospitalization.

Plaque and remodeling markers in coronary thrombi

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Background: Matrix Metalloproteinases (MMPs) and their inhibitors are considered to be of importance in development of atherosclerotic coronary artery disease. MMP-9 has been associated with unstable atherosclerotic plaques and rupture, as well as left ventricular remodeling after myocardial infarction (MI), whereas MMP-2 seems to be more related to progression of stable plaques. MMP activity is modulated by Tissue Inhibitors of Metalloproteinases (TIMPs). TIMP-1 has been associated with cardiac remodeling post MI, and TIMP-2 has been discussed to inhibit plaque development and destabilization. The extracellular MMP Inducer, EMMPRIN, stimulates both MMPs and TIMPs, and has been found upregulated on the surface of monocytes in patients with acute MI, and associated with MMP-9 activity.

Purpose: To study whether genes encoding MMP-2, MMP-9, TIMP-1, TIMP-2 and EMMPRIN are expressed in coronary thrombi and in circulating leukocytes from STEMI patients, and whether these are related to the degree of myocardial injury measured by troponin T, and time from symptoms to PCI.

Methods: Intracoronary thrombi were aspirated from 33 patients with ST-elevation myocardial infarction (STEMI) treated with primary PCI. The thrombi were snap-frozen in RNA-later solution for gene expression analyses. Peripheral blood samples with Pax-gene tubes were drawn at end of the PCI procedure. RNA was isolated from the thrombi and leukocytes, and the actual genes relatively quantified by RT PCR. Peak troponin T was collected from clinical records.

Results: Genes coding for the five different markers were present in 84-100% of the thrombi. Median peak troponin T was 3434 m/L. The expression of TIMP-1 in the thrombi correlated significantly to peak troponin T (r =0.393, p=0.026), and dividing peak troponin T values into quartiles, the median value of TIMP-1 mRNA in Q4 was 2.5-fold higher compared to Q1-3 (p= 0.107). Peak troponin T also correlated to the expression of TIMP-1 in circulating leukocytes (r=0.469, p=0.006), and in Q4 of troponin T, the median value was 1.6-fold higher compared to Q1-3 (p= 0.056). There were no significant correlations between the other measured genes and troponin T, and also no associations of any genes expressed in the thrombi or in circulating leukocytes to time from symptom to PCI (median 152 min).

Conclusion: Genes coding for MMP-2, MMP-9, TIMP-1, TIMP-2 and EMMPRIN were highly expressed in human coronary thrombi. The positive correlation between peak troponin T and the expression of TIMP-1 both in thrombi and in circulating leukocytes at time of PCI in patients with STEMI, may indicate that the role of TIMP-1 is important in cardiac remodeling immediately post-MI.

Prevalence and incidence rates of atrial fibrillation in Denmark 2004-2018

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Background: Atrial fibrillation (AF) is the most common cardiac arrhythmia and is associated with substantial morbidity and mortality. Its prevalence is currently rising partly due to popu-

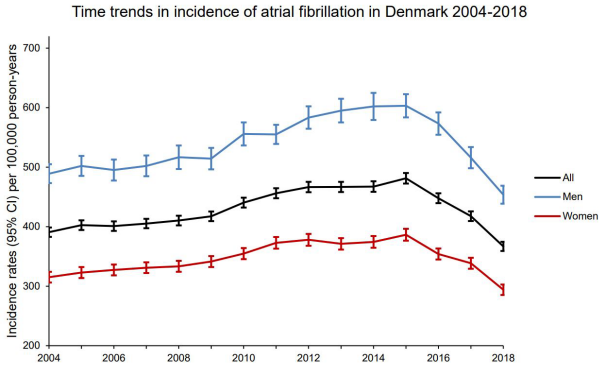
lation ageing. However, reported trends in incidence rates are conflicting, and the comparability of existing reports is limited due to methodological inconsistencies across studies.

Purpose: The main purpose of the current study was to investigate the prevalence of AF in the Danish adult population and time trends in incidence rates from 2004 through 2018. As a secondary purpose, the prevalence and incidence were compared to corresponding Norwegian estimates from 2004 through 2014 derived using the same methodology.

Methods: A register-based study was conducted including all individuals aged ≥18 years in Denmark from 2004-2018. AF cases were identified in the National Patient Register and the Cause of Death Register, which comprise information on all hospital contacts and deaths in Denmark, respectively. The prevalence of AF was calculated as the number of individuals alive at the end of the study period with at least one registered diagnosis from 1994 through 2018 divided by the number of Danish residents aged ≥18 years. Incidence rates were calculated as the number of annual AF cases with no previous diagnosis noted in the past 10 years divided by the person-time contributed by the population free of AF on 1 January in the same calendar year. All incidence rates were standardized according to a Nordic standard population. The comparison of the Danish and Norwegian incidence estimates focused solely on AF hospitalizations and deaths from 2004 through 2014.

Results: The cumulative prevalence of AF was 3.0% in the Danish adult population. The incidence increased from 391 per 100,000 person-years in 2004 to 481 per 100,000 person-years in 2015, after which it declined to 367 per 100,000 person-years in 2018 (Figure 1). On average, the incidence increased by 1.7% annually until 2015 (IRR: 1.017 (95% CI: 1.016-1.018); $p < 0.001$) and then declined by 8.5% (IRR: 0.915 (95% CI: 0.909-0.921); $p < 0.001$). Although the incidence rates generally were higher among men and older individuals, a similar time trend was observed in both men and women irrespective of age. Focusing solely on AF hospitalizations and deaths did not change the interpretation of the results. The comparable Norwegian estimates will be presented at the conference.

Conclusions: The prevalence of AF is currently around 3.0% in the Danish adult population, but the incidence rate has declined steeply since 2015. The observed decline in new cases is promising from a public health perspective and its underlying causes warrant further investigation.



Prognostic value of sST2 in heart failure patients with diabetes

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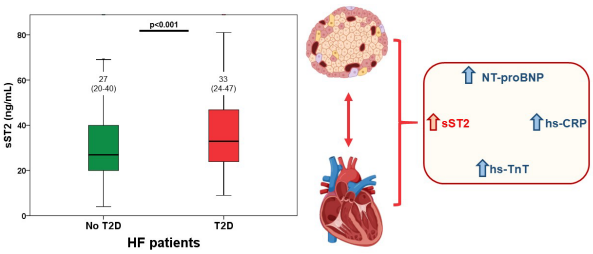
Background: Soluble suppression of tumorigenesis-2 (sST2) is released in response to inflammation and vascular injury, and holds prognostic value in heart failure (HF). Type 2 diabetes (T2D) is characterized by a pro-inflammatory status and is highly prevalent among HF patients, with adverse impact on outcomes. The clinical value of sST2 in HF patients with T2D has never been characterized.

Purpose: We aimed to assess sST2 clinical correlates and prognostic value in HF patients with T2D.

Methods: Individual data of 3476 patients with stable chronic HF from 5 cohorts from the BIOS (Biomarkers In Heart Failure Outpatient Study) dataset were analysed, with available N-terminal fraction of pro-B-type natriuretic peptide (NT-proBNP), high-sensitivity troponin T (hs-TnT), and sST2 levels.

Results: Mean age was 65±12 years (75% males). T2D was present in



1386 patients (40%), who had higher body mass index (BMI, 27 [24-30] vs. 26 [23-29] kg/m2, p<0.001), lower estimated glomerular filtration rate (eGFR, 56±22 vs. 60±19 mL/min/1,73 m2, p<0.001), higher sST2 (33 [24-47] vs. 27 [20-40] ng/mL, p<0.001), NT-proBNP (1735 [742-3963] vs. 1450 [514-3299] ng/L, p<0.001), hs-TnT (28 [16.2-51.5] vs. 17 [9-31] ng/L, p<0.001) and high-sensitivity C-reactive protein (hs-CRP, 6 [2-11] vs. 4. [2-9] mg/L, p=0.003) (Figure). Differences between sST2 levels in patients with or without T2D were influenced by hs-CRP (p for interaction=0.010) and hs-TnT (p=0.031), but not by NT-proBNP and eGFR. At multivariate linear regression analysis, NT-proBNP, hs-TnT and hs-CRP were independently associated with sST2 levels in both T2D and non-T2D patients. Compared with patients without T2D, those with T2D showed higher 1-year all-cause mortality (12% vs. 10%, p=0.034), cardiovascular mortality (9% vs. 7%, p=0.011), and HF hospitalization rate (22% vs. 12%, p<0.001). In a prognostic model including age, sex, eGFR, ischemic vs-non-ischemic aetiology, left ventricular ejection fraction class, New York Heart Association class, NT-proBNP, hs-TnT, and hs-CRP, sST2 retained independent prognostic value in both patients with or without T2D for 1-year all-cause and cardiovascular mortality, and 1-year HF hospitalization, with higher optimal cut-offs for mortality prediction in T2D vs. non-T2D (39 and 45 vs. 29 and 29 ng/mL respectively for 1-year all-cause and cardiovascular mortality).

Conclusions: sST2 is higher in HF patients with T2D and likely linked to a pro-inflammatory status. sST2 maintains its prognostic value both in diabetic and non-diabetic HF patients, independently of NT-proBNP, hs-TnT and hs-CRP.

Psoriasis severity and the risk of left ventricular remodelling in psoriasis patients treated with infliximab

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Background: Psoriasis is an immune mediated skin disorder with a great variation in disease severity. Chronic inflammation predisposes to subclinical cardiac damage like left ventricular (LV) remodelling. However, the association of psoriasis severity with LV remodelling is not known.

Purpose: To assess LV remodelling in patients with moderate to severe psoriasis treated with infliximab.

Methods: Psoriasis severity was assessed by the Psoriasis Area Severity Index (PASI) before initiation of treatment with the tumour necrosis factor α inhibitor infliximab in 53 patients (age 47±15 years, 30% women, body mass index (BMI) 29.2±5.5 kg/m^2). Echocardiography was preformed after a mean follow-up of 4.9±3.8 years and compared to 99 control subjects (age 47±11 years, 28 % women, BMI 29.9±3.9 kg/m^2). LV remodelling was assessed from LV relative wall thickness and LV mass index by echocardiography.

Results: Both psoriasis patients and controls had high prevalence of hypertension (66% vs. 61%, p=0.54) and obesity (34% vs. 33% p=0.94). Psoriasis patients were more likely to be smokers than controls (37% vs. 17%, p=0.005), but other cardiovascular risk factors were similarly distributed. Psoriasis patients had higher LV relative wall thickness (0.38±0.09 vs. 0.34±0.07, p=0.001), but lower LV mass index (36.1±9.6 g/m^2.7 vs. 40.3±9.8 g/m^2.7, p=0.014), compared to controls. Having psoriasis remained associated with higher LV relative wall thickness (β 0.25, p=0.002) and lower LV mass index (β-0.20, p=0.02) in multivariable analyses after adjustment for age, sex, smoking, hypertension and BMI. In psoriasis patients mean PASI decreased from 16.1±11.5 to 0.8±0.8 during infliximab treatment, p<0.001. Higher PASI at start of treatment was associated with a higher LV relative wall thickness at follow-up (Table), but not with higher LV mass index in univaria-

Table. Multivariable associations of LV relative wall thickness in psoriasis patients

	Psoriasis (n=53)			
	Univariable		*Multivariable* R^2 0.49, p<0.001	
	β	p	β	p
PASI	**0.35**	**0.009**	**0.36**	**0.006**
Age, years	0.49	<0.001	0.55	<0.001
Hypertension	0.33	0.02	0.10	0.40
Women	-0.14	0.31	0.08	0.52
Smoking	-0.21	0.14	--	--
BMI, kg/m^2	0.08	0.59	--	--

BMI, body mass index; LV, left ventricular; PASI, psoriasis area severity index

ble analyses. After adjusting for sex, age and hypertension, higher PASI at start of treatment (β 0.36, p=0.006) still predicted greater LV relative wall thickness at follow-up in psoriasis patients (Table).

Conclusion: Higher psoriasis severity before infliximab treatment predicted presence of adverse LV remodelling after 4.9 years treatment despite nearly complete clinical remission.

QRS fragmentation is associated with increased risk of ventricular arrhythmias

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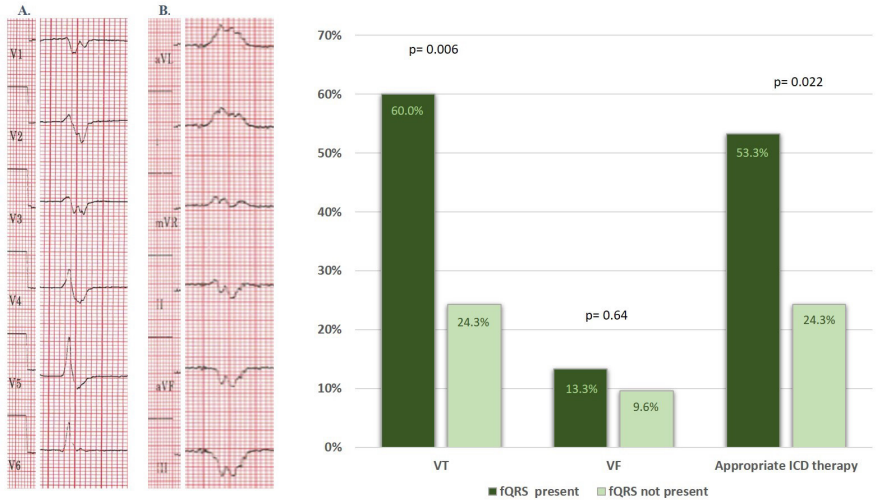
Background: Fragmentation of the QRS complex (fQRS) on ECG is defined as the presence of additional spikes within the QRS complex. fQRS has been associated with myocardial conduction abnormalities, but whether it predicts ventricular arrhythmias (VA) is uncertain.

Purpose: To assess the association between the presence of fQRS on standard 12-leads ECG and the risk of VA.

Methods: In a prospective observational study, we included 243 patients treated with implantable cardioverter-defibrillator (ICD). Baseline ECG was analyzed for fQRS by a trained physician blinded for outcome data. fQRS was defined according to Das (ref) as the presence of an additional R wave (R'), notching in the S wave nadir, or >1 R' in 2 contiguous leads. For wide QRS (≥120ms), fQRS was defined as >2 R waves (R''), >2 notches in the R or S wave in 2 contiguous leads (Figure). Patients were followed at regular ICD controls, and incident ventricular tachycardia (VT), ventricular fibrillation (VF) and treatment with antitachycardia pacing (ATP) or DC-shock were recorded.

Results: In total, 168 baseline ECG recordings (69%) were interpretable for fQRS, while the remaining were uninterpretable mainly due to low quality and low QRS voltage. The included patients were aged 66 ±11 years, 14% female, with BMI 27±4 kg/m2 and left ventricular ejection fraction (LVEF) 42±11%. Twenty-two percent had diabetes mellitus (DM), 40% atrial fibrillation, 61% history of myocardial infarction (MI), 81% heart failure and 18% in New York Heart Association Class ≥3. fQRS was present in 16 (10%) patients who had comparable baseline characteristics to those without fQRS, except lower prevalence of DM (p=0.05). Patients with versus without fQRS had comparable QRS duration (p=0.72), QRS axis (p=0.28), corrected QT duration (QTc) (p=0.35) and heart rate (p=0.66). During mean 3.2±0.7 years follow-up 65 (28%) patients had ≥1 VA, including 60 with VT, 21 with VF, and 59 with appropriate ICD-therapy. Presence of fQRS was associated with a 4-fold increased risk of VA (OR 4.15, [95%CI 1.38-12.4], p=0.011). This association persisted after adjusting for age, gender, DM, MI, LVEF and QRS duration (OR 3.99, [95%CI 1.16-13.65], p=0.03). fQRS was strongly associated with incident VT (OR 4.66 [95%CI 1.55-14.0], p= 0.006, which persisted after adjustment [p=0.018]), while there was no significant association with incident VF (OR 1.45, [95% CI 0.29-7.09], p= 0.64) (Figure). fQRS associated with incident



FIGURE

Left panel: Examples of fQRS in: **A.** ECG with narrow QRS: fQRS present in anterior leads; **B**. ECG with wide QRS: fQRS present in lateral leads.

Right panel: Proportion of patients with ventricular arrhythmias and appropriate ICD therapy stratified by the presence or absence of fQRS.

VA irrespective of ICD indication (primary versus secondary, p-for-interaction=0.80). fQRS was superior to established ECG variables in predicting VA, including QRS-duration, QTc, and presence of Q-waves.

Conclusions: Interpretation of fQRS in standard ECG is feasible in 70%. fQRS is associated with increased risk of VA, independent of established risk factors, and is an easily available tool that may be useful in identifying patients at increased risk of VA.

Risk factors, subsequent disease onset and prognostic impact of myocardial infarction and atrial fibrillation

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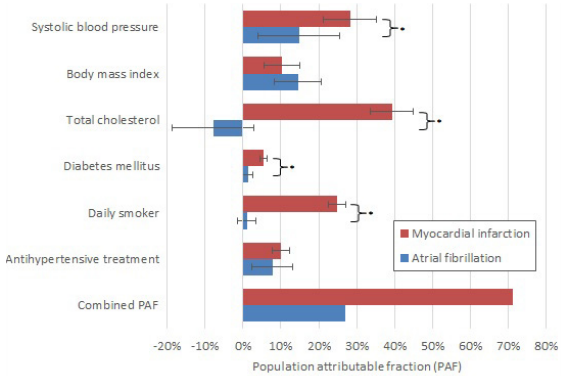
Background: Myocardial infarction (MI) is a known risk factor for incident atrial fibrillation (AF), while AF frequently complicates acute MI. Although both diseases share common cardiovascular risk factors, the direction and strength of the association of the risk factors with disease onset, subsequent disease incidence and mortality are not completely understood.

Purpose:Our goal was to define the temporal relationship of MI and AF and the association of cardiovascular risk factors with disease incidence in order to determine whether common clinical risk factors show different associations with incident MI or AF. We further aimed to investigate predictors of subsequent disease onset and the impact of subsequent disease diagnosis on mortality.

Methods: In pooled multivariable Cox regression analyses we examined temporal relations of disease onset and identified predictors of MI, AF and subsequent all-cause mortality in 108,363 individuals (median age 46.0 years, 48.2% men) free of MI and AF at baseline from six European population-based cohorts.



Results: Over a maximum follow-up of 10.0 years 3558 (3.3%) individuals were diagnosed exclusively with MI, 1922 (1.8%) with AF but no MI, and 491 (0.5%) individuals developed both MI and AF. Association of male sex, systolic blood pressure, antihypertensive treatment and diabetes mellitus appeared to be stronger with incident MI than with AF, whereas increasing age and body mass index showed a higher risk for incident AF. Total cholesterol and daily smoking were significantly related to incident MI but not AF. The combined population attributable fraction of the cardiovascular risk factors was over 70% for incident MI, whereas it was only about one quarter for incident AF. Subsequent MI after incident AF (hazard ratio1.68, 95% CI 1.03-2.74) and subsequent AF after MI (hazard ratio 1.75, 95% CI 1.31-2.34) both significantly increased overall mortality risk.

Conclusions: Subsequent diagnosis of MI and AF was associated with a significant increase in mortality, irrespective of the first event. We found different associations of common cardiovascular risk factors with incident MI and AF indicating distinct pathophysiological pathways in disease development.

Risk prediction of atrial fibrillation and its complications in the community using high-sensitivity cardiac Troponin I: Results from the BiomarCaRE Consortium

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Aims-Atrial fibrillation (AF) is becoming increasingly common and is associated with serious complications. Traditional cardiovascular risk factors (CVRF) do not explain all AF cases. Blood-based biomarkers reflecting cardiac injury may help close this gap. High-sensitivity troponin I (hsTnI) has emerged as a potential predictor.

Methods-We investigated the predictive ability of hsTnI for incident AF in 29,227 participants (median age 52.6 years, 51.2% men) across four different European community cohorts of the Biomarkers for Cardiovascular Risk Assessment in Europe (BiomarCaRE) consortium in comparison to CVRF and established biomarkers (high-sensitive C-reactive protein (hsCRP), N-terminal pro B-type natriuretic peptide (NT-proBNP)).

Results-During a median follow-up of 13.8 (lower and upper quartiles 4.5, 21.3) years, 1,509 (5.2%) participants developed AF. Those in the highest fourth of hsTnI values at baseline (≥5.1 ng/L) had a 2.71-fold (95% confidence interval (CI) 2.31, 3.17; P<0.01) risk for developing AF compared to those in the lowest fourth (≤2.1 ng/L). In multivariable-adjusted Cox proportional hazard models no statistically significant association was seen between hsTnI and AF, whereas NT-proBNP (hazard ratio (HR) per two-fold increase in NT-proBNP 1.64; 95% CI 1.56, 1.72; P<0.001) as well as hsCRP (HR ratio per two-fold increase in hsCRP 1.05; 95% CI 1.01, 1.10; P=0.01) were statistically significantly related to incident AF. Inclusion of hsTnI did not improve model discrimination over CVRFs (C-index CVRF 0.7914 vs. C-index CVRF, hsTnI 0.7927; 95% CI -0.0004, 0.0031; P=0.130). Higher hsTnI concentrations were associated with AF complications such as stroke (HR 1.25; 95% CI 1.03, 1.51; P=0.02), heart failure (HR 1.27; 95% CI 1.12, 1.44; P<0.001) and cardiovascular events (HR 1.24; 95% CI 1.08, 1.42; P<0.001) as well as overall mortality (HR 1.15; 95% CI 1.05, 1.25; P<0.001) in those who were diagnosed with AF.

Conclusion-hsTnI as a biomarker of myocardial injury does not improve prediction of AF incidence beyond classical CVRFs. However, it is associated with AF complications and mortality after AF onset probably reflecting underlying subclinical cardiovascular impairment.

Role of inflammation and comorbidities in the association of heart failure with incident cancer in the HUNT3 cohort

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Background: Conflicting data exist regarding the risk of cancer in patients with heart failure (HF). It was first reported that incident cancer is more common among patients with than without HF, whereas more recent studies indicate that this association is primarily driven by comorbidities. HF, cancer, and comorbidities, such as chronic kidney disease (CKD) and chronic obstructive pulmonary disease (COPD), share numerous risk factors, including a state of chronic low-grade inflammation reflected by elevated circulating levels of pro-inflammatory cytokines. The objective of this analysis was to assess whether chronic low-grade inflammation, as measured by levels of high-sensitivity C-reactive protein (hsCRP), and comorbidities mediate the association of HF with incident cancer.

Methods: We used data from the 3rd wave of the Nord-Trøndelag Health Study (HUNT3), a population-based study that enrolled 50,803 individuals ≥18-year-old between October 2006 and June 2008 in the Nord-Trøndelag County (Norway), from the Cancer Registry of Norway and from the administrative health care records of the same region. Associations between baseline characteristics and the development of cancer were assessed using Cox proportional hazards regression models, using time from HUNT3 enrollment as the time scale. Analyses were performed using R statistical software, version 4.0.2.

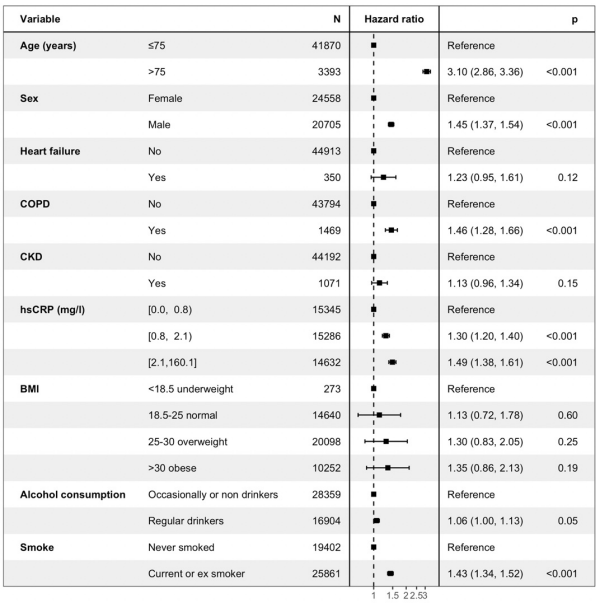
Results: In HUNT3, hsCRP was measured in 47,571 individuals at the time of enrollment. Of these, we excluded 2,308 patients because of missing information, leaving a cohort of 45,263 subjects. Figure 1 shows the characteristics of the study population at baseline stratified by hsCRP tertiles. The prevalence of cardiovascular disease, comorbidities, and obesity was progressively higher with increasing concentrations of hsCRP.

During a median follow-up of 12 years, there were 66/408 cases of incident cancer in patients with HF at baseline and 5,024/47,163 in subjects without HF, with a more than 2-fold (HR 2.30; 95%CI 1.80-2.93; p<0.001) increase in risk of developing cancer. After adjusting for age and sex, the excess risk decreased to 43% (HR 1.43; 95%CI 1.12-1.82). When including hsCRP in the model, the HF-related risk of cancer was 33%

(HR 1.33; CI 1.04-1.70; p=0.022). Furthermore, when body mass index, CKD, COPD, and smoking and drinking habits were included in the model, the risk of cancer in HF patients compared to individuals without HF was no longer significant (HR 1.23; 95%CI 0.94-1.60; p=0.127). Age, male sex, hsCRP, COPD, obesity, and smoking habits were all associated with an increased risk of cancer (Figure 2).

Conclusions: The increased risk of cancer in HF patients compared with the general population is at least in part explained by concomitant inflammation and comorbidities.

	Overall	hsCRP [0.0, 0.8)	hsCRP [0.8, 2.1)	hsCRP [2.1, 160.1]
n	**47571**	**15958**	**16073**	**15540**
Sex male, N (%)	21539 (45.3)	7257 (45.5)	7801 (48.5)	6481 (41.7)
Age at screening [years], Mean (SD)	52.48 (15.85)	49.03 (15.17)	53.83 (15.33)	54.62 (16.46)
HF, N (%)	408 (0.9)	62 (0.4)	115 (0.7)	231 (1.5)
Myocardial infarction, N (%)	1478 (3.1)	372 (2.3)	503 (3.1)	603 (3.9)
Angina, N (%)	1729 (3.6)	419 (2.6)	610 (3.8)	700 (4.5)
Stroke, N (%)	1231 (2.6)	270 (1.7)	424 (2.6)	537 (3.5)
Kidney disease, N (%)	1135 (2.4)	286 (1.8)	415 (2.6)	434 (2.8)
Chronic bronchitis, emphysema or COPD, N (%)	1565 (3.3)	296 (1.9)	448 (2.8)	821 (5.3)
Diabetes, N (%)	2018 (4.2)	459 (2.9)	693 (4.3)	866 (5.6)
Smoking, N (%)				
Never smoked	19874 (43.0)	7594 (48.7)	6585 (42.2)	5695 (37.8)
Current or ex-smoker	26397 (57.0)	7987 (51.3)	9037 (57.8)	9373 (62.2)
Alcohol consumption, N (%)				
Regular drinkers	17199 (37.2)	6346 (40.7)	5901 (37.8)	4952 (32.9)
Occasionally or non-drinkers	29080 (62.8)	9261 (59.3)	9712 (62.2)	10107 (67.1)
BMI group, N (%)				
18.5-25 normal	15277 (32.3)	7809 (49.1)	4314 (26.9)	3154 (20.4)
<18.5 underweight	296 (0.6)	176 (1.11)	62 (0.39)	58 (0.38)
25-30 overweight	20999 (44.3)	6539 (41.1)	8003 (50.0)	6457 (41.9)
>30 obese	10788 (22.8)	1393 (8.75)	3639 (22.7)	5756 (37.3)



Subclinical cardiac organ damage in patients with moderate to severe psoriasis treated with infliximab

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Background: Psoriasis is an immune mediated disease that has been associated with elevated risk of cardiovascular (CV) disease. Comorbidities, psoriasis treatment and presence of subclinical cardiac organ damage can modulate CV risk in psoriasis.

Purpose: To assess the prevalence and covariables of subclinical cardiac organ damage in patients with moderate-to-severe psoriasis on infliximab treatment.

Methods: Echocardiography was performed in 53 psoriasis patients (age 47±15 years, 30% women) and 99 control subjects (age 47±11 years, 28% women). Subclinical cardiac organ damage was defined as presence of left ventricular (LV) hypertrophy, concentric LV geometry and/or dilated left atrium. Psoriasis area and severity index (PASI) was used to assess the severity of psoriasis. Hypertension was defined as use of antihypertensive medication/history of hypertension and/or elevated ambulatory blood pressure ≥130/80 mmHg.

Results: Hypertension was the most common comorbidity, present in 66% of patients and 61% of control subjects (p=0.54). Smoking was more prevalent in psoriasis patients than controls (37% vs 17%, p=0.005), while other CV risk factors and antihypertensive treatment did not differ between groups. Subclinical cardiac organ damage was less prevalent in psoriasis patients than controls (51% vs. 73%, p=0.007, Figure). In the total study cohort, having psoriasis was associated with lower prevalence of subclinical cardiac organ damage independent of hypertension, smoking, age and sex

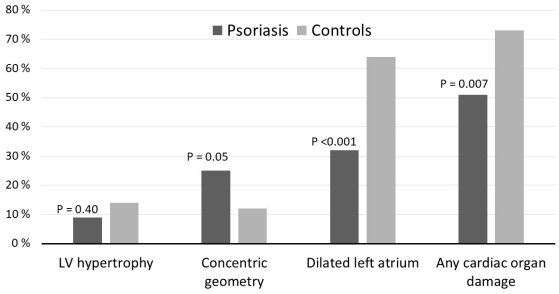

Figure 1. Subclinical cardiac organ damage in psoriasis patients and controls. LV: left ventricle

(odds ratio [OR] 0.30, 95% confidence interval [CI] 0.13-0.72, p=0.007) in logistic regression analysis. Among psoriasis patients, hypertension was associated with a near seven-fold increased risk of cardiac organ damage (OR 6.88 [95% CI 1.32-35.98], p=0.022) independent of age, sex and body mass index. PASI at start of treatment or current PASI was not associated with presence of subclinical cardiac organ damage.

Conclusion: Psoriasis patients on infliximab treatment had less subclinical cardiac organ damage compared with controls, suggesting that inhibition of CV inflammation may attenuate cardiac organ damage in psoriasis. Hypertension was the strongest covariable for subclinical cardiac organ damage in psoriasis patients.

The association of myocardial injury during chronic total occlusion percutaneous coronary intervention with lesion complexity and treatment strategy

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Background: Chronic total occlusion (CTO) percutaneous coronary intervention (PCI) is associated with procedural myocardial injury (PMI), and adverse long-term clinical outcomes [1-4].CTO lesion complexity is quantified using established scores[5-8], with high complexity known to determine the need for dissection and re-entry techniques and the retrograde approach, which are then associated with a higher incidence of procedural complications [9,10]. If CTO recanalization is unsuccessful, a modification procedure can be performed, with the intention to improve subsequent procedural success [11-14]. There are limited data on the association between PMI, CTO complexity and treatment strategy.

Purpose: To report the incidence of myocardial injury following CTO PCI, and assess whether this is associated with lesion complexity, crossing strategy, or the use of a modification procedure.

Methods: This is a retrospective analysis of consecutive elective CTO PCI procedures performed at a single centre in Norway between January 2020 and March 2021. High-sensitivity troponin T (hsTnT) was measured pre and 12-18 hours post-procedure. Myocardial injury defined as a post-procedure elevation of hsTnT >5x 99th percentile URL with a normal baseline value or a rise >20% with elevated pre-procedure hsTnT. CTO complexity was described using the J-CTO, PROGRESS, RECHARGE and EuroCASTLE scores [5-8]. Procedures were classified as technical successful or unsuccessful according to CTO academic research consortium (CTO-ARC) criteria [15], and further categorised according to final crossing strategy [antegrade wiring (AW), antegrade dissection re-entry (ADR), retrograde wiring (RW) or retrograde dissection re-entry (RDR)]. If unsuccessful they were further categorised as 'failure' or 'unplanned modification procedure'. A 'planned modification procedure' defined as intentional antegrade modification of the occlusive segment with no attempt to complete CTO crossing.

Results: We analysed 122 CTO PCI procedures. Mean J-CTO, PROGRESS, RECHARGE, EuroCASTLE scores were 2.7, 1.2, 3.0 and 3.1 respectively. Technical success during the index procedure was 75%. An unplanned or planned modification procedure was performed in 16% and 2% of cases, respectively. Technical failure occurred in 7% of cases. Myocardial injury occurred in 65% of all procedures (78% of failed procedures, 64% of successful procedures, 63% of unplanned and none of 3 planned CTO modifi-

Figure 1. Procedural myocardial injury according to CTO complexity scores

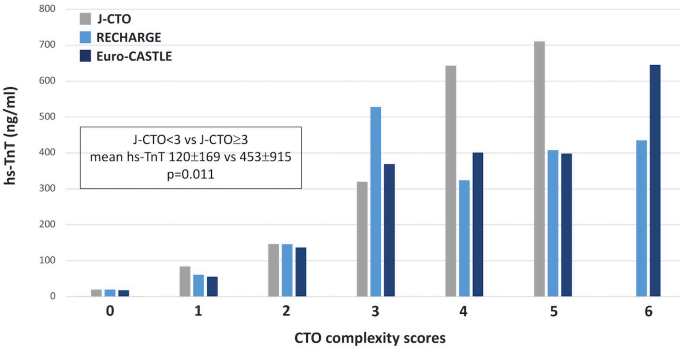

Table 1. Procedural myocardial injury according to treatment strategy and outcomes

CTO PCI treatment strategy	Mean J-CTO score	hs-TnT (mean±SD)
Technical success	2.4±1.2	291±757
All antegrade	2.1±1.2	130±158
Antegrade wiring (AW)	2.1±1.0	109±145
Antegrade dissection re-entry (ADR)	2.4±1.5	195±177
All retrograde	3.0±1.0	573±1187
Retrograde wiring (RW)	3.0±0.7	287±172
Retrograde dissection re-entry (RDR)	3.0±1.0	685±1380
Failure	3.3±0.9	675±709
Unplanned modification	3.0±1.2	393±695
Planned investment	4.0±0	21±10

cation procedures). The mean hs-TnT according to treatment strategy and outcomes are reported in Table 1. The relationship between the CTO complexity scores and hs-TnT are illustrated in Figure 1.

Conclusions: Myocardial injury is common during CTO PCI, particularly with more complex anatomy, requiring the retrograde approach or an unplanned modification procedure. A prospective analysis of whether myocardial injury can be avoided using a planned investment procedure in high complexity cases is currently being conducted.

The associations of serum homoarginine to long-term prognosis in patients with chronic coronary syndrome and non-obstructive coronary artery disease

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Background: Although generally at lower risk than those with obstructive CAD, patients with non-obstructive CAD (NOCAD) are heterogeneous concerning long-term prognosis. Notably, reversible ischemia due to vascular dysfunction is a frequent finding in NOCAD patients (1). The endogenous, non-proteinogenic amino acid homoarginine (hArg) increases the availability of nitric oxide (NO) and thereby the NO-dependent vasodilatation (2). Several studies have reported a strong inverse relation between serum hArg levels and cardiovascular disease (CVD) risk among patients with obstructive CAD. However, the prognostic implications of serum hArg levels in NOCAD patients have not been explored previously.

Purpose: We evaluated serum hArg as a predictor of long-term risk of CVD mortality among patients with NOCAD.

Methods: 1046 patients with chronic coronary syndrome (CCS) underwent elective coronary angiography during 2000-2004, with the findings of NOCAD. Serum hArg was measured by liquid chromatography-tandem mass spectrometry in samples that had been frozen and stored at -80°C. The association of serum hArg to CVD mortality risk was visualized in a generalized additive regression plot and further explored using Cox regression. The models included age, sex, body mass index, hypertension, diabetes, smoking status, serum LDL cholesterol and estimated glomerular filtration rate as independent covariables. We evaluated model discrimination and risk classification by calculating C-statistics and net reclassification improvement (NRI >0), respectively.

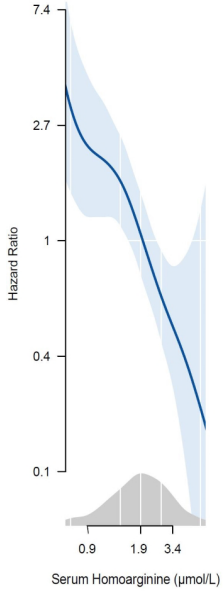

Fig 1. The association of serum Homoarginine with long- term risk of CVD mortality by multivariable generalized additive regression.

Results: Median (25th-75th percentiles) age at inclusion was 57 (51-65) years, 48.5 % were women and median (25th-75th percentiles) level of serum hArg was 1.87 (1.47-2.38) µmol/L. During median (25th- 75th percentiles) 14.1 (13.2-15.4) years of follow-up 5.7 % of the patients died from CVD. The multivariable adjusted hazard ratio (95% confidence interval) per SD increment of (log transformed) hArg was 0.53 (0.40-0.70) in relation to CVD mortality. The multivariable model without biomarker provided a C- statistics for CVD mortality of 0.79 which increased to 0.82 by the addition of serum-hArg to the model (Δ area =0.03, P= 0.01). Further, serum hArg provided a high NRI (95% CI) of 0.53 (0.40-0.70), P<0.001.

Conclusion: We demonstrated a strong inverse relationship between serum hArg and long-term risk of CVD mortality among patients with NOCAD. Our study adds to previous literature linking low hArg with vascular dysfunction and adverse CVD prognosis. The potential clinical usefulness of serum hArg measurements for the identification of a high-risk phenotype in NOCAD warrants further evaluation.

The role of IL-6 receptor trans-signalling in ischemia-reperfusion injury, infarct healing and future adverse events in patients with ST-Elevation Myocardial Infarction

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Background: Inflammation has emerged as a new treatment target in patients with coronary artery disease, and inflammation seems to play an important role in the ischemia/reperfusion injury in ST-elevation myocardial infarction (STEMI). The pro-inflammatory cytokine interleukin-6 (IL-6) has been shown to be associated with myocardial injury and poor prognosis in patients with STEMI.

Purpose: The aim of the study was to further elucidate possible associations between the IL-6 trans-signalling system and final infarct size, myocardial function, adverse remodelling, and future cardiovascular events in patients with STEMI.

Methods: A total of 272 patients with first-time STEMI included in the POSTEMI study on ischaemic postconditioning, with symptom duration <6 hours and treated with percutaneous coronary intervention (PCI), were included. Blood samples for analysis of IL-6 and IL-6 receptor (IL-6R) were collected before PCI, immediately after PCI, at day 1 (median 18.3 hours after PCI), and at 4 months follow-up. Cardiac magnetic resonance imaging (CMR) was performed in the acute phase, median 2 days after admission, and repeated after 4 months. Clinical events and all-cause mortality were registered during 12 months' and 70 months' follow-up, respectively.

Results: There was a significant increase in IL-6 levels from admission to day 1 with a subsequent decline from day 1 to 4 months (Figure 1A). No significant change in IL-6R levels were found from admission to day 1 (Figure 1B). There was no difference between patients treated by postconditioning compared to routine PCI. High levels of IL-6 (> median) at all sampling points were significantly associated with increased infarct size and reduced left ventricular ejection fraction (LVEF) measured by CMR. Additionally, high levels of IL-6 (> median) at day 1 were associated with lower myocardial salvage, more presence of microvascular obstruction and larger increase in indexed LV end diastolic volume (LVEDVi). IL-6R measured during hospitalisation was significantly associated with change in LVEDVi, but did not associate with infarct size, LVEF or myocardial salvage. High levels of IL-6 (>75th percentile) at all sampling points were associated with an increased risk of having an adverse clinical event during the first year and with long-term all-cause mortality (Figure 2), whereas there was no association between IL-6R and adverse clinical events.

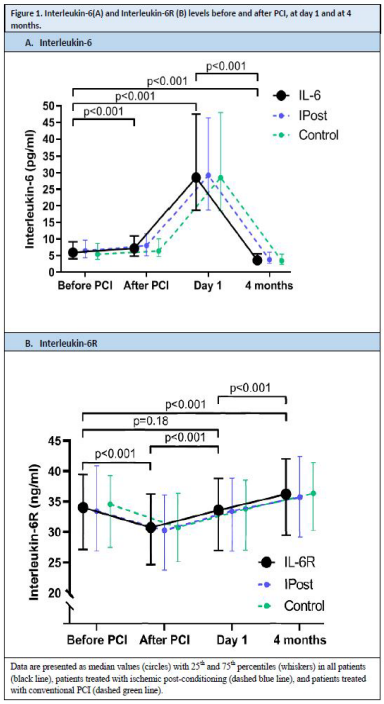
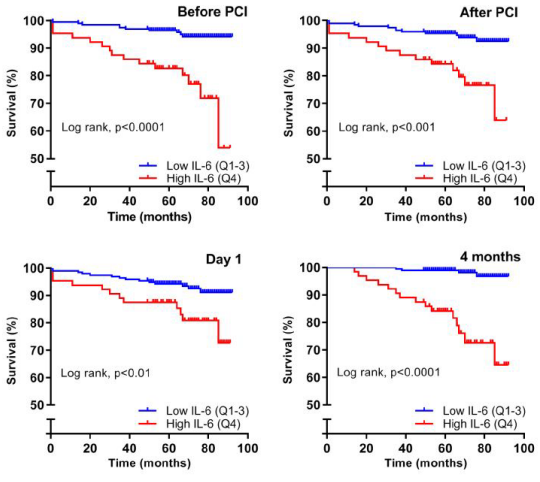


Figure 1. Interleukin-6(A) and Interleukin-6R (B) levels before and after PCI, at day 1 and at 4 months.

Data are presented as median values (circles) with 25th and 75th percentiles (whiskers) in all patients (black line), patients treated with ischemic post-conditioning (dashed blue line), and patients treated with conventional PCI (dashed green line).

Figure 2. All-Cause Mortality according to IL-6 levels in patients with STEMI



Kaplan-Meier plots of all-cause mortality at median follow-up at 70 months according to levels of IL-6 (> or < 75th percentile), measured before and after PCI, at day 1 and at 4 months.

Conclusion: Patients with high IL-6 levels during the acute phase of STEMI had larger infarct size, reduced myocardial salvage, reduced LV function and worse clinical outcome than patients with lower levels of IL-6. High levels of IL-6 measured after 4 months were associated with larger infarct size, reduced LVEF and increased all-cause mortality. IL-6R was significantly associated with increase in LVEDVi. The results add important information to the role of IL-6 in myocardial injury in acute STEMI and the IL-6 pathway as a potential treatment target.

The validity of heart failure diagnoses at hospital-discharge and ambulatory evaluation visits: insights from two Norwegian local hospitals

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Background: The validity of heart failure (HF) diagnoses made in hospitals has been debated and low positive predictive values (PPV) may represent a bias in epidemiological research.

Purpose: To validate primary and secondary HF diagnoses at discharge or during ambulatory evaluation in general hospitals aiming to obtain confirmed HF diagnoses to develop a HF-prediction risk score.

Methods: We extracted data on all patients with a HF diagnosis by ICD-10 codes (I50 HF, I42 cardiomyopathy and I11 hypertension with HF) in any position from the hospitals' electronic medical records from Oct. 2006 to Dec. 2018. One experienced cardiologist scrutinized all journals for events being either a valid HF event, unlikely, or uncertain due to lacking information, according to the 2016 ESC HF guidelines. In cases where first event was unlikely or uncertain subsequent events were judged for valid HF.

Results: A total of 3411 patients with at least one HF diagnosis were assessed (mean age 79.7±10.6 yrs, 49.1% men); 3089 after in-hospital stays and 322 after ambulatory consultations. Overall, 2174 were deemed as valid HF diagnosis with a PPV of 63.7%; PPV was higher when HF diagnosis was based on in-hospital diagnoses and when HF was the primary diagnosis (Table).

Conclusions: Only 64% of all HF diagnoses were likely HF according to present guidelines, with higher precision for in-hospital diagnoses and HF in the primary position. This underscores the importance to use validated HF-diagnoses for HF prediction risk score development.

Table. Positive Predictive Value (PPV) of a heart failure (HF) diagnosis being valid according to sex, whether HF was primary or secondary diagnosis, and location of HF diagnosis.

	Verified heart failure		Unlikely heart failure	Uncertain	Total
	n	PPV (95% CI)	n	n	N
All HF diagnoses	2174	63.7 (62.1 – 65.4)	815	422	3411
Sex					
Men	1110	66.3 (64.0 – 68.6)	391	173	1674
Women	1064	61.3 (58.9 – 63.6)	424	249	1737
Diagnoses order					
Primary	941	75.8 (73.3 – 78.1)	221	80	1242
Secondary	1233	56.8 (54.7 – 58.9)	594	342	2169
Location of HF diagnosis					
In-hospital stay	2034	65.8 (64.1 – 67.5)	409	646	3089
Ambulatory evaluation	140	43.5 (38.0 – 49.1)	13	169	322

Additive prognostic value of cardiac biomarkers in patients with chronic obstructive pulmonary disease and heart failure

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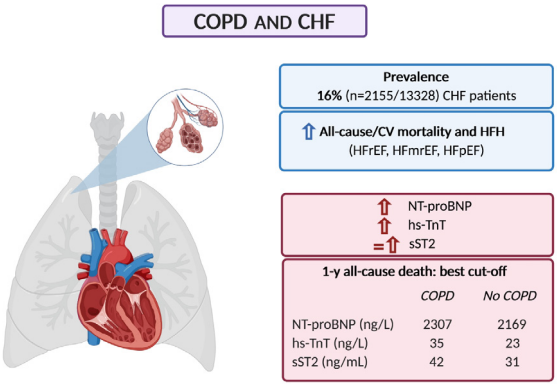
Background: Chronic obstructive pulmonary disease (COPD) is a frequent comorbidity in patients with heart failure (HF). We assessed the influence of COPD on circulating levels and prognostic value of 3 HF biomarkers: N-terminal pro-B-type natriuretic peptide (NT-proBNP), high-sensitivity

troponin T (hs-TnT), and soluble suppression of tumorigenesis-2 (sST2).

Methods: Individual data from patients with chronic HF, known COPD status and NT-proBNP, hs-TnT, sST2 values (n=13328) were analysed.

Results: As compared to patients without COPD, those with COPD (n=2155, 16%) were older (age 71 years [64-77] vs. 66 [57-75]; p<0.001), more frequently men (79% vs. 74%; p<0.001), had more severe dyspnoea (43% in New York Heart Association [NYHA] class III-IV vs. 31%; p<0.001), slightly worse renal function (median estimated glomerular filtration rate [eGFR] 58 mL/min/1.73 m2 [43-73] vs. 60 [46-77]; p<0.001), higher NT-proBNP (1508 ng/L [650-3363] vs. 1239 ng/L [479-2911]; p<0.001), hs-TnT (22 ng/L [13-38] vs. 17 ng/L [9-30]; p<0.001), and sST2 (31 ng/mL [23-45] vs. 29 [21-43]; p=0.040). In both the COPD and no-COPD subgroups, the best cut-offs of the 3 biomarkers refined the prediction of 1- and 5-year all-cause and cardiovascular mortality and 1- to 12-month HF hospitalization over a prognostic model including age, sex, ischemic aetiology, eGFR, HF categories, NYHA III-IV, beta-blocker use and the NT-proBNP cut-off alone.



Conclusions: Among patients with HF, those with COPD have higher circulating cardiac biomarkers. Patient classification based on COPD-specific cut-offs refines risk reclassification for all-cause and cardiovascular mortality and HF hospitalization and might be helpful for decision making and management.