

# ABSTRAKTER PRESENTERT PÅ VÅRMØTET

## High penetrance and similar disease progression in probands and family members with arrhythmogenic cardiomyopathy



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Aims: We aimed to assess structural progression in arrhythmogenic

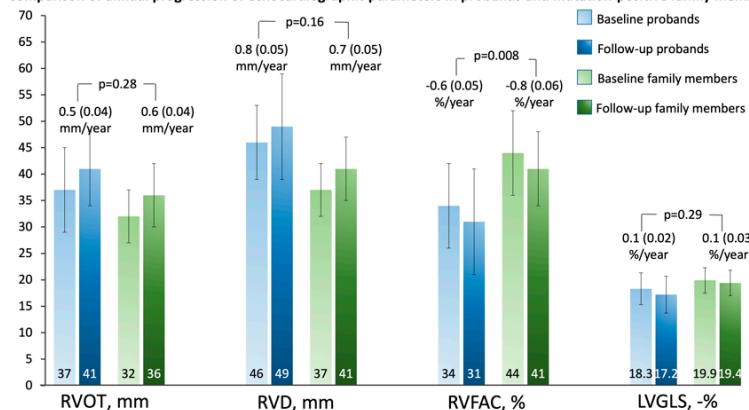
cardiomyopathy (AC) patients and mutation positive family members in a longitudinal cohort study.

Methods: Structural progression was defined as development of new Task Force imaging criteria from inclusion to follow-up and progression rates as annual changes in imaging parameters.

Results: We included 144 AC patients and family members (48% female, 47% probands, 40±16 years old). At genetic diagnosis and inclusion, 58% of family members had penetrant AC disease. During 7.0 (IQR 4.5 to 9.4) years of follow-up, 47% of family members without AC at inclusion developed AC criteria. In mixed model analysis of 598 echocardiographies, probands and family members had a similar progression rate of right ventricle (RV) outflow tract diameter (0.5mm/year vs. 0.6mm/year, p=0.28) and left ventricle global longitudinal strain (0.1%/year vs. 0.1%/year, p=0.29) while RV fractional area change progression rate was even higher in family members (-0.6%/year vs -0.8%/year, p=0.008) (Figure). Structural progression was associated with higher incidence of ventricular arrhythmic events adjusted for age, sex and proband status (HR 21.24, 95% CI [2.47, 182.81], p<0.01).

Conclusion: Disease penetrance was high in family members with AC both at genetic diagnosis and at last follow-up. Structural progression was similar in probands and family members and associated with higher incidence of ventricular arrhythmic events.

Comparison of annual progression of echocardiographic parameters in probands and mutation-positive family members



## Autoantibodies against methylglyoxal modified ApoB100 and ApoB peptide are associated with less coronary artery atherosclerosis in long-term type 1 diabetes.



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**Background and aims:** Advanced glycation end products (AGEs) are increased in diabetes. These modifications are recognized by the immune system, resulting in formation of anti-AGE-specific autoantibodies. The association of these immune responses with atherosclerosis in type 1 diabetes remains to be clarified. We investigated the association between circulating autoantibodies against methylglyoxal (MGO) modified ApoB100 and ApoB100 peptide 5 (MGO-p5) and coronary atherosclerosis in type 1 diabetes.

**Materials and Methods:** We measured autoantibodies against MGO-ApoB100 and MGO-p5 in plasma from 103 type 1 diabetes patients with a diabetes duration > 45 years and 63 controls. In 88 type 1 subjects and 60 controls without diagnosed coronary artery disease coronary atherosclerosis was assessed by computer tomography coronary angiography (CTCA). IgM and IgG levels recognizing MGO-Apo B100 and MGO-p5 were determined by enzyme-linked immunosorbent assay (ELISA).

**Results:** Anti-MGO-ApoB100 and MGO-p5 IgM levels were higher in the diabetes group with no coronary artery stenosis ( $n=14$ ) compared to those with significant ( $>50\%$ ) stenosis ( $n=36$ ), 96.2 (71-126.7) median (IQR) vs. 54 (30.2-85.4),  $p=0.03$ , for anti-MGO-ApoB100 and 77.4 (58-106) vs 36.9 (28.9-57.4) for anti-MGO-p5,  $p=0.01$ . Levels of anti-MGO-ApoB100 and anti-MGO-p5 were associated with the degree of coronary artery stenosis ( $r=-0.18$ ,  $p=0.04$ ) and ( $r=-0.27$ ,  $p<0.001$ ), and anti-MGO-p5 with calcium score ( $r=-0.27$ ,  $p=0.006$ ) in type 1 diabetes. In logistic regression analysis anti-MGO-ApoB100 and anti-MGO-p5 were significantly associated with stenosis after adjusting for confounders, OR 0.2 (0.05-0.6) (95% CI),  $p=0.01$  and OR 0.22 (0.06-0.75),  $p=0.02$ , respectively.

**Conclusions:** Our findings may suggest that high levels of anti-MGO ApoB100 IgM and anti-MGO-p5 IgM can be protective in coronary atherosclerosis in long-term type 1 diabetes.

## Exercise is associated with impaired left ventricular function in patients with Lamin A/C mutations.



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**Background:** Lamin A/C dilated cardiomyopathy is a malignant and highly penetrant inheritable cardiomyopathy. Competitive sports have been associated with adverse events in these patients, but data on recreational exercise are lacking.

We aimed to explore associations between exercise exposure and disease severity in patients with lamin A/C genotype.

**Methods:** Consecutive lamin A/C genotype positive patients answered a questionnaire on exercise habits from age 7 years until genetic diagnosis. We recorded exercise hours  $> 3$  metabolic equivalents, and calculated cumulative lifetime exercise. Patients were grouped in active or sedate based on lifetime exercise hours above or below median. We performed echocardiography, 12-lead ECG, Holter monitoring, and biomarkers including NT-proBNP. We defined LVEF  $< 45\%$  as a clinically significant impairment of left ventricular function.

**Results:** We included 69 patients (age  $42 \pm 14$  years, 41% probands, 46% female) with median lifetime exercise 4160 [IQR 1041-6924] hours. Active patients were more frequently probands (53% vs. 29%,  $p=0.04$ ), had lower LVEF ( $43 \pm 13\%$  vs.  $51 \pm 11\%$ ,  $p=0.006$ ), and higher NT-proBNP (78 [IQR 32-219] pmol/l vs. 30 [IQR 13-64] pmol/l,  $p=0.03$ ) compared to sedate patients, while age did not differ ( $45 \pm 13$  years vs.  $40 \pm 16$  years,  $p=0.16$ ). LVEF  $< 45\%$  was observed at younger age in active patients (Log rank  $p=0.007$ ). When adjusted for age and sex odds for LVEF  $< 45\%$  increased (OR adjusted

2.6[95%CI; 1.26-5.19], p=0.01) per tertile increment in lifetime exercise

**Conclusions:** Physically active lamin A/C patients had worse systolic function compared to sedate which occurred at younger age. Our data indicate exercise restriction beyond competitive sports.

## Late adverse effects of residual platinum concentrations on cardiac function in testicular cancer survivors: a 30-year follow-up study



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**Background:** Cisplatin-based chemotherapy (CBCT) is essential in the treatment of testicular cancer (TC), and platinum can be detected in TC survivors decades after cessation of treatment.

CBCT has been implicated as a risk factor in cardiovascular morbidity and mortality.

**Purpose:** Our study aimed to assess the relationship between residual serum platinum concentrations and changes in cardiac function and morphology in TC survivors 30 years after CBCT.

**Methods:** Seventy TC survivors diagnosed and treated with CBCT (1980-1994) were recruited from the longitudinal Norwegian Cancer Study in Testicular Cancer Survivors. Serum platinum concentration was measured twenty years after CBCT. Patients were then allocated to either a

high or low platinum concentration group. Echo-cardiography was performed in all subjects.

**Results:** The participants were on average 60±9 years old. There was a trend towards smaller left ventricular (LV) volumes in the high residual platinum concentration group (Table). No intergroup difference in cardiac function was found. Six (9%) participants had reduced EF (<52%) and 14 (20%) participants had reduced LV global longitudinal strain (> -18.0%), however, there was no intergroup difference. Neither cumulative cisplatin dose nor residual serum platinum concentration showed any correlation with LV or right ventricular functional parameters.

**Conclusion:** Our 30-year follow-up study of testicular cancer patients could not demonstrate impact on cardiac function caused by cumulative cisplatin dose or residual serum platinum concentrations.

## Feasibility and accuracy of real-time automatic quantification of left ventricular ejection fraction by hand-held ultrasound device



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**Background:** Automatic quantification of left ventricular (LV) ejection fraction (autoEF) by hand-held ultrasound devices (HUDs) may increase the benefit of focused cardiac ultrasound by inexperienced users. This has not yet been evaluated.

**Purpose:** To evaluate the feasibility and accuracy of autoEF for real-time quantification of LV function by HUDs. To assess the importance of image quality and the operators' experience for the accuracy of the method.

**Methods:** Patients referred with suspected heart failure (HF) were included. 5 general practitioners (GPs), 3 nurses and

**Table.**

	Low residual Pt concentration	High residual Pt concentration	p-value
Cumulative cisplatin dose, mg/m2	680±249	814±271	<0.05
Residual Pt concentration, ng/L	44±22	136±44	<0.001
3D LV end-diastolic volume, ml/m2	66±17	60±8	0.07
3D LV end-systolic volume, ml/m2	29±15	24±5	0.08
3D ejection fraction, %	57±9	59±6	0.24
LV global longitudinal strain, %	-19.2±3.3	-20.0±2.0	0.26
LV global circumferential strain, %	-21.1±4.2	-22.1±1.8	0.30
E/e'	10.6±4.4	9.2±2.2	0.10
TAPSE, mm	2.2±0.4	2.3±0.4	0.22
RV fractional area change, %	40±7	41±7	0.67

*Data are presented as mean±SD. The P-values were derived from the Student's t-test. LV, left ventricle; MV, mitral valve; Pt, platinum; RV, right ventricle; TAPSE, tricuspid annular plane systolic excursion.*

5 cardiologists performed the examinations. Each patient was examined by a nurse and a GP by HUD. Immediately thereafter, an HUD and echocardiographic reference examination was performed by a cardiologist. The GPs underwent 5 days of training prior to inclusion. The nurses were familiar with focused cardiac ultrasound from the outpatient HF clinic. AutoEF was measured in 4-chamber view only. Another cardiologist blinded to the reference measurements and operators evaluated each HUD recording on technical and qualitative parameters using a scale from 1 (poor) to 6 (very good).

Results: 87 patients (46% women) with mean age of 67.5 years were included. Mean BMI was 29 kg/m<sup>2</sup>, 95% CI (28, 30) and 24 (30%) had atrial fibrillation. Of 510 autoEF recordings, 255 (50%) were rejected during evaluation. AutoEF by HUD and reference EF was mean (SD) 53% (16.7) and 53% (7.3), respectively. Overall, the quality score for autoEF recordings was mean (SD) 4.4 (0.9). The proportions of accepted autoEF measurements were 75% for cardiologists and 33% for GPs. The difference compared to reference were lowest in the accepted recordings ( $p<0.001$ ).

Conclusion: The feasibility of real-time autoEF by HUD was only moderate. In the hands of the least experienced the use of automatic LV EF was inadequate. Sufficient training and good image quality is essential for autoEF by Huds.

## Echocardiographic deformation imaging in arrhythmogenic cardiomyopathy: combining strain pattern recognition with mechanical dispersion for optimal risk stratification



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Background Echocardiographic strain pattern recognition and right ventricular mechanical dispersion (RVMD) are valuable indices in risk assessment of patients with arrhythmogenic

cardiomyopathy (AC), but have never been externally validated and compared.

Objectives To validate, compare and combine strain pattern recognition and RVMD as markers of life-threatening ventricular arrhythmias (VA) in AC.

Methods AC probands and mutation-positive family members from two large referral centers were included in a retrospective study. Speckle tracking echocardiography was performed and deformation patterns of the subtricuspid area were scored as normal or abnormal, according to the presence of regional mechanical dysfunction. (panel A) RVMD was expressed as the standard deviation of the time from onset Q/R on ECG to peak negative strain in 6 segments. (panel B) VA was defined as sustained ventricular tachycardia, appropriate ICD therapy, or aborted cardiac arrest.

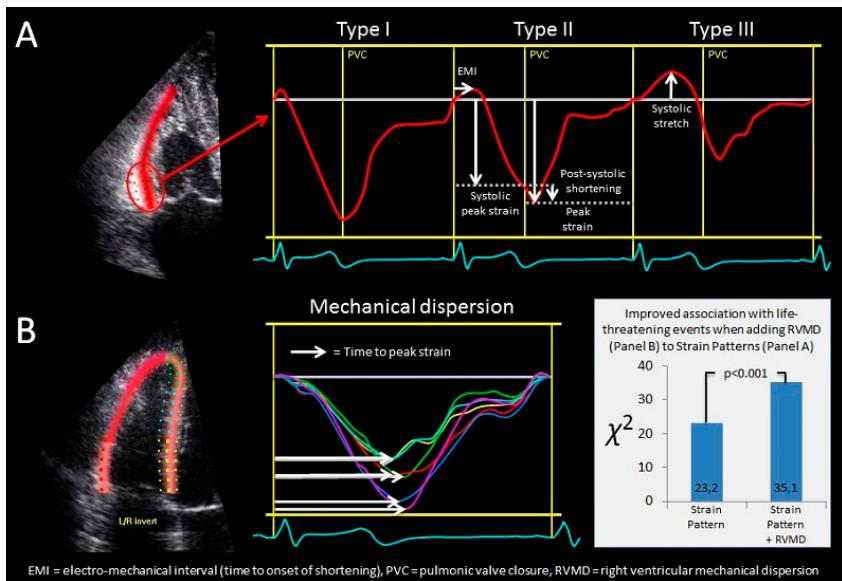
Results 160 subjects (80 matched patients from each center) were included (43% probands, 55% female, age 41±17 years). VA had occurred in 60 (38%) subjects. Patients with VA had higher prevalence of abnormal strain patterns (80% vs. 42%,  $p<0.001$ ) and greater RVMD (51±32 vs. 28±18ms,  $p<0.001$ ). Abnormal strain patterns and RVMD were markers of VA independently of each other (adjusted OR 2.7, 95% CI[1.1-6.4],  $p=0.02$ , and 1.3, 95%CI[1.1-1.6],  $p=0.002$  by 10ms increments, respectively). The association with VA improved when combining both methods. Incremental value was found when adding RVMD to pattern recognition (NRI 0.57,  $p<0.001$  and IDI 0.04,  $p=0.01$ ). By using the optimal cut-off for RVMD of 24ms, a two-step approach detected VA with a negative predictive value of 0.90, 95% CI[0.78-0.95].

Conclusions Strain pattern recognition and RVMD were both useful in risk stratification in AC patients. Combining the methods improved risk stratification in high risk individuals for VA. Furthermore, a two-step approach, by calculating RVMD in cases with normal strain patterns, accurately identified low risk individuals.

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Secondary outcomes are change in LV function by global longitudinal strain and LVEF by echocardiography, and cardiovascular biomarkers.

Conclusion: PRADA II is the first randomized, placebo-controlled study of Sacubitril/Valsartan in the cardio-oncology setting and may provide important new insights in preventive cardioprotective strategies in cancer patients receiving anthracyclines with or without trastuzumab. The trial will further enable identification of patients at higher risk of developing cardiotoxicity and those most likely to respond to cardioprotective therapy.



Kirkels figure 1.

## The feasibility and reliability of automatic quantitative analyses of mitral annular plane systolic excursion by hand-held ultrasound devices



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Aims: Mitral annular plane systolic excursion (MAPSE) is an established measure of left ventricular (LV) function. We aimed to study the feasibility, accuracy and reliability of automatic measurements of MAPSE when performed by hand-held ultrasound device (HUD).

Methods and results: Twenty patients were included at a university hospital. A standard echocardiographic examination was performed by either a cardiologist or a sonographer. Four grey scale recordings of the LV 4-chamber view were included. Subsequently, the 4-chamber view was recorded four times using a hand-held ultrasound device (HUD). A cardiologist blinded to all other data measured MAPSE on reference images in septal and lateral mitral annulus using anatomical motion mode. MAPSE was automa-

tically measured from live grey-scale recordings recorded by the HUD. From the initial 80 pairs, the automatic method failed in 8 recordings, leaving 72 pairs for comparison. The automatic method underestimated mean MAPSE with difference  $\text{mean} \pm \text{SD } 1.1 \pm 1.4 \text{ mm}$  ( $9.6 \pm 2.2 \text{ mm}$  (HUD) vs  $10.7 \pm 2.6$  (reference)). The difference was significant. There was a larger difference in the lateral measurements of  $\text{mean} \pm \text{SD } 10.5 \pm 2.4$  versus  $\text{mean} \pm \text{SD } 12.1 \pm 3.0$ . The within measurements coefficient of variation was  $\text{mean} \pm \text{SD } 9.6 \pm 7.6\%$  in automatic versus  $7.1 \pm 3.5\%$  in reference ( $p$ -value for the difference 0.24). The intraclass correlation for the absolute agreement between the methods was 0.78 for mean values. The absolute value of the measurement did not influence its accuracy. Lower and upper limits of agreement for mean values were -1.5 and 4 mm. Intrarater and interrater correlation was 0.94 and 0.98, respectively.

Conclusion: Automatic quantification of LV systolic longitudinal function by HUD was feasible and reliable even though the automatic method yielded a small underestimation. The automatic method showed excellent repeatability and could be compared with other methods. In the future automatic quantification for LV function by HUDs may be a possible diagnostic tool at the patient's point of care.

## Rationale and Design of the Prevention of cArdiac Dysfunction during Adjuvant breast cancer therapy (PRADA II) trial: A Randomized, Placebo-controlled, Multicenter Trial



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**Background:** Cardiotoxicity due to anthracycline-containing chemotherapy and/or trastuzumab during breast cancer treatment may lead to ventricular dysfunction and to dose-reduction or halt in potentially life-saving cancer therapy. This reduction in left ventricular ejection fraction (LVEF) may be attenuated by angiotensin blockade. In chronic systolic heart failure, neprilysin inhibition with Sacubitril/Valsartan is superior to traditional angiotensin blockade, but whether it can prevent reduction in LVEF after anthracycline-containing chemotherapy has not been evaluated previously.

The primary hypothesis of the PRADA II trial is that Sacubitril/Valsartan compared to placebo can prevent reduction in LVEF associated with anthracycline-containing chemotherapy.

**Methods:** PRADA II (ClinicalTrials.gov Identifier: NCT03760588) is a randomized, placebo-controlled, double blind, multi-center clinical trial. 300 breast cancer patients from four university hospitals in Norway, scheduled to receive chemotherapy with anthracycline epirubicin with or without trastuzumab, will be randomized 1:1 to Sacubitril/Valsartan or placebo. The target dose is 97/103 mg b.i.d. The patients will be examined with cardiovascular magnetic resonance (CMR), echocardiography, cardiovascular biomarkers and functional testing at baseline, at end of anthracycline treatment and at 18 months (Figure 1). The primary outcome is change in LVEF by CMR.

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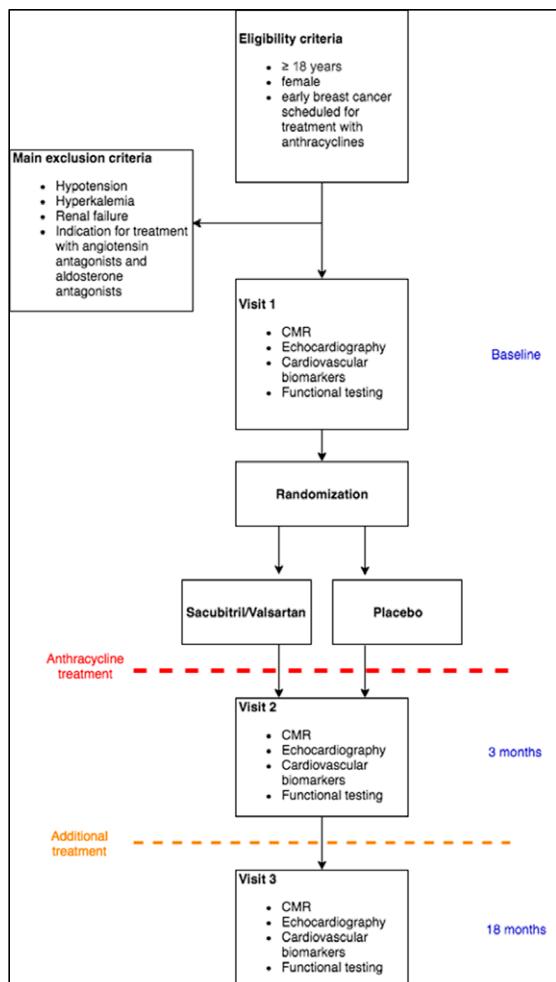


Figure 1: Flow chart of the PRADA II trial