ABSTRAKTER PRESENTERT PÅ VÅRMØTET

Prevalence of diabetes before and after first diagnosis of coronary artery disease

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Objectives: Diabetes is associated with coronary artery disease (CAD), and cardiovascular disease is the main cause of death in diabetes patients. In this study we have investigated the prevalence of known and undiagnosed diabetes in patients with initial myocardial infarction, percutaneous coronary intervention or coronary artery bypass graft as well as the incidence of subsequent cardiovascular events for a period of up to five years.

Material and method: Patients < 80 years of age who were hospitalised at Sørlandet Hospital Arendal with initial CAD between 2007–16, were included. The follow-up was mainly based on annual visit at the outpatient clinic, and median follow-up time was three years.

Results: Of the 1 259 patients included, 178 (14%) had diabetes at the time of hospitalisation, 49 (4%) had undiagnosed diabetes and 102 patients (8%) developed diabetes during the follow-up period (defined by $HbA_{1c} \geq 6.5\%$). Approximately half of those with diabetes had an $HbA_{1c} \leq 7\%$ during follow-up. The risk of subsequent cardiovascular events developing was higher in patients with diabetes than in patients without diabetes (age- and gender-adjusted HR 1.5; 95% CI: 1.1–2.1, p=0.005).

Conclusion: The prevalence of diabetes in patients with a first diagnosis CAD is high (14%) in comparison to that of general population (5%). High risk of subsequent cardiovascular events in patients with diabetes suggests better monitoring for the development of diabetes and good prophylactic treatment of patients with diabetes and CAD.

Number of pregnancies and subsequent phenotype in a cross-sectional cohort of women with arrhythmogenic cardiomyopathy

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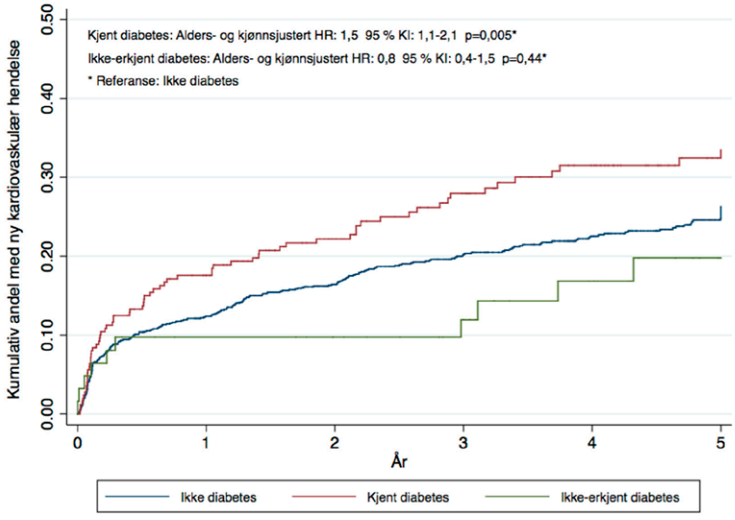
Aims: We aimed to assess the relation between number of pregnancies and cardiac structure, function and arrhythmic events in women with arrhythmogenic cardiomyopathy (AC).

Methods and result: We included female AC-patients in a cross-sectional study. Number of pregnancies and pregnancy related symptoms were recorded. Ventricular arrhythmias were defined as aborted cardiac arrest, sustained ventricular tachycardia or appropriate implantable cardioverter defibrillator therapy. Right and left ventricular dimensions



and function, including strain analyses, were assessed by echocardiography and magnetic resonance imaging. We created a new AC severity score to grade the severity of AC disease.

We included 77 women (age 47±16, 43 probands and 34 AC mutation positive female relatives), 19±14 years after last pregnancy. Median number of pregnancies was 2 (0-4); 19 had no previous pregnancies, 16 had 1 pregnancy, 30 had 2, and 12 had ≥3 pregnancies. Presence of a definite AC diagnosis (p=0.36), severity of AC disease (p=0.53) and arrhythmic events (p=0.25) did not differ between groups of pregnancies. Number of pregnancies was related to increased right ventricular outflow tract diameter in single variable analyses (OR 1.76 (95%CI 1.08-2.87), p=0.02), but not when adjusted for body surface area and age (OR 1.56 (95%CI 0.91-2.66), p=0.11). The number of pregnancies was not associated with any other measures of cardiac structure and function.

Conclusion: Higher number of pregnancies did not seem to relate to a worse phenotype in women with AC.

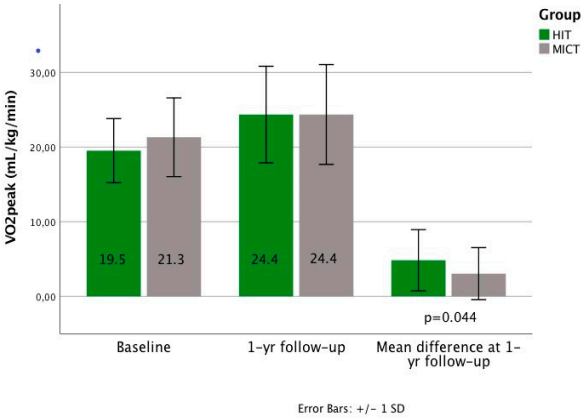


Figure 1: Clustered bars with mean of VO2peak at baseline, 1-yr follow-up and mean change at 1-yr follow-up

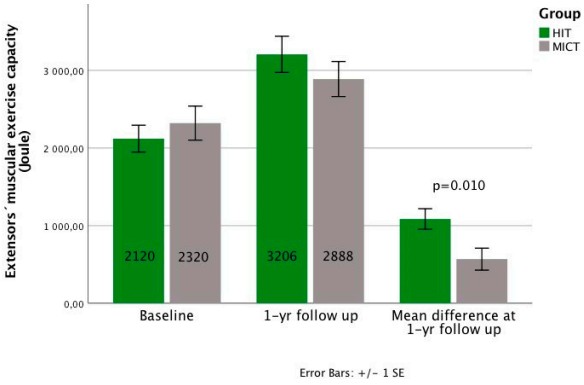


Figure 2: Clustered bars with mean of extensors´ muscular exercise capacity baseline, 1-yr follow-up and mean change at 1-yr follow-up

Effect of High-Intensity Interval Training in De Novo Heart Transplant Recipients - 1 Year Follow Up (The HITTS Study)

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Background: There is no consensus on how, when or at what intensity exercise should be performed and organized after heart transplantation (HTx). We have recently shown that high-intensity interval training (HIT) is safe, well tolerated and efficacious in maintenance HTx recipients, but studies on HIT in de novo HTx patients is non-existing.

Methods: Included patients were randomized 1:1, to HIT (4x4 min intervals at 85-95% of peak effort or regular moderate continuous training (MICT) (60-80% of peak effort).

Endpoints: The primary outcome is the effect of HIT vs MICT on the change in aerobic exercise capacity as assessed by VO_{2peak}. Metabolic/respiratory measures include VO_{2peak}, VE/VCO_2 slope and anaerobic threshold (AT). Secondary outcomes are: Isokinetic muscular strength, body composition, left ventricular function, hemodynamics, endothelial function, heart rate response, biomarkers, HRQoL, tolerability, safety and adverse events.

Results: At 1-yr follow-up there was a significantly ($p<0.05$) higher change (mean difference [95% CI]) in the HIT group compared to the MICT group for the following variables: VO_{2peak} (ml/kg/min): 1.8 [0.05, 3.5] (figure 1), AT (L/min): 0.28 [0.08, 0.46] and extensors´ muscular exer-

cise capacity (Joule): 517 [129, 905] (figure 2). The 1.8 ml/kg/min change equals approximately 0.5 MET which is regarded clinically meaningful and relevant.

Conclusions**:** We have demonstrated that HIT is a safe and efficient method for exercise in de novo HTx recipients. HIT, compared to MICT, resulted in a clinically significantly higher change in exercise capacity as assessed by VO_{2peak} (25% vs. 15%), AT and muscular exercise capacity.

BEtablocker Treatment After acute Myocardial Infarction in revascularized patients without reduced left ventricular systolic function (BETAMI): rationale and design of a prospective, randomized, open, blinded end-point study.

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Background: Current guidelines on the use of β-blockers in post-acute myocardial infarction (MI) patients without reduced left ventricular ejection fraction (LVEF) are based on studies before the implementation of modern reperfusion and secondary prevention therapies. It remains unknown whether β-blockers will reduce mortality and recurrent MI in contemporary revascularized post-MI patients without reduced LVEF.

Design: BETAMI is a prospective, randomized, open, blinded end-point (PROBE) multi-center study in 10,000 MI patients designed to test the superiority of oral β-blocker therapy, compared to no β-blocker therapy. Patients with LVEF ≥40% following treatment with percutaneous coronary intervention or thrombolysis and/or no clinical signs of heart failure are eligible to participate. The primary end-point is a composite of all-cause mortality or recurrent MI obtained from national registries over a mean follow-up period of 3 years. Additional safety end-points include rate of ventricular arrhythmias, and hospitalizations for heart failure obtained from telephone

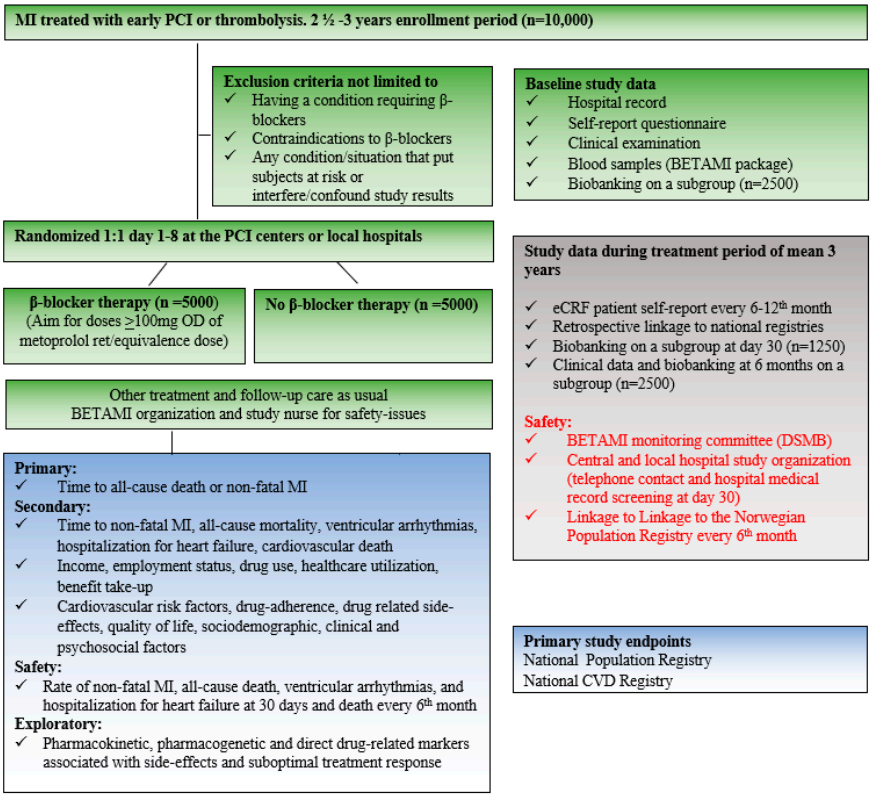

Figure. BETAMI flow-chart

contact with the patients, electronic Case Report Forms and the Population Registry 30 days, and every 6th months after randomization. Key secondary endpoints include recurrent MI, heart failure, cardiovascular and all-cause mortality, and clinical outcomes linked to β-blocker therapy including drug adherence, side-effects, cardiovascular risk factors, psychosocial factors, and health economy. Statistical analyses will be conducted according to the intention-to-treat principle. A pre-specified per-protocol analysis (patients truly on β-blockers or not) will also be conducted.

Conclusions: The results from the BETAMI trial may have the potential of changing current clinical practice for treatment with β-blockers following MI in patients without reduced LVEF.

Relationship between left ventricular ejection fraction and mortality after myocardial infarction complicated by heart failure or left ventricular dysfunction

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Background: Identifying risk factors for specific modes of death in patients with HF or LV dysfunction after MI may help to avert events. We sought to evaluate LVEF as a prognosticator of specific death modes.

Methods and results: In an individual patient data meta-analysis of four merged trials (CAPRICORN, EPHESUS, OPTIMAAL, and VALIANT), Cox modelling was performed to study the association between baseline LVEF from 19740 patients and types of death during follow-up.

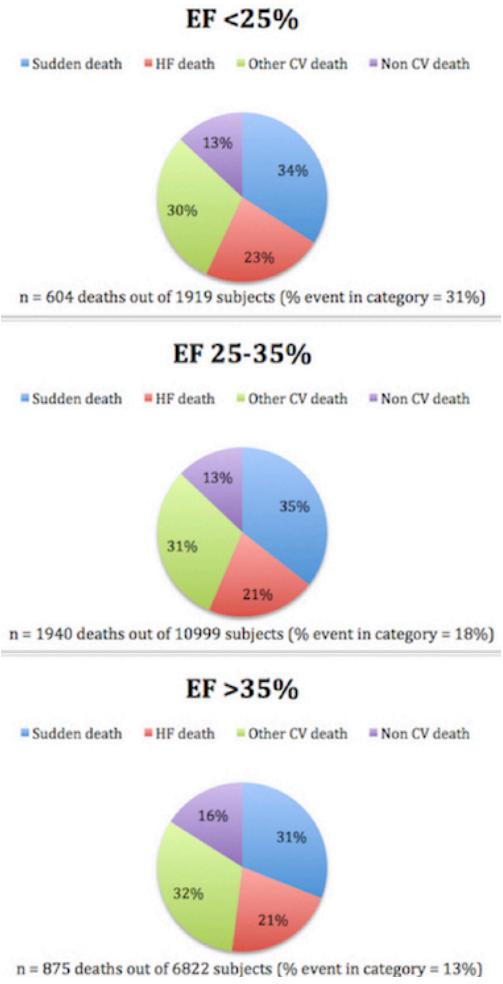

Figure 1. EFand mode of death

Over a median follow-up of 707 days 3419 deaths occurred.

The distribution pattern for mode of death was similar across LVEF categories (<25%, 25-35%, >35%). In multivariable models adjusted for age, sex, Killip class, systolic BP, diabetes, hypertension, renal failure, COPD, PAD, medication use, eGFR, Hb and sodium, the risk of all types of death increased with decreasing LVEF. Each 5% decrease in LVEF was associated with a 23% increased risk of sudden death (HR 1.23, 95% CI 1.14-1.33), a 26% increased risk of HF death (HR 1.26, 95% CI 1.15-1.39), a 13% increased risk of other CV death (HR 1.13, 95% CI 1.04-1.24), and a 14% increased risk of non CV death (HR 1.14, 95% CI 1.00-1.29).

Conclusions: In patients with HF or LV dysfunction after MI, low LVEF was an ubiquitous risk marker associated with death regardless of type.

It consequently deserves great attention beyond the risk of sudden death and may be a marker not just specific to sudden death. Mode of death was fairly equally represented throughout the categories of increasingly compromised LVEF.

Use of a novel single molecule ultra sensitive cTnI assay as an early rule out marker for NSTEMI: The WESTCOR study

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Background**:** Approximately 15% of patients investigated for suspected NSTE-ACS are diagnosed with NSTEMI. The aim of this study is to assess the diagnostic accuracy and the ability of a ultra sensitive troponin assay to rule out NSTEMI in unselected patients presenting with acute chest pain.

Methods**:** 979 patients with suspected NSTE-ACS were consecutively included from Sept. 2015 to Feb. 2017. Serum samples were collected at 0 (cTn0), 1 (475 patients), 3 and 8-12 hours. The final diagnosis was adjudicated by two independent cardiologists based on all available clinical, laboratory (i.e. hs-cTnT (Roche Diagnostics) used in clinical routine) and imaging data. The 0 and 1 hour samples were additionally measured for hs-cTnI (Abbott Diagnostics) and an ultra sensitive cTnI assay (us-cTnI(sgx)) (Singulex Clarity System). The prognostic performance of the baseline measurements with/without 1-hour-delta value as predictors of NSTEMI where compared between the assays with AUC-ROC. The us-cTnI(sgx) combinations that would rule out low numbers of NSTEMI and high numbers of patients with non-cardiac chest pain were compared to the current ESC rule out algorithms for hs-cTnT and hs-cTnI(Abbott).

Results**:** The prevalence of NSTEMI was 13%, UAP 11% and non-cardiac chest pain 58% (Table 1). The ROC- AUCs did not differ significantly between the assays (data not shown). Table 1 shows that larger percentages of non-cardiac chest pain patients may be ruled out using the us-cTnI(sgx) 0 and 1 hour samples, compared to the hs assays (same sensitivity for NSTEMI).

Table 1. Rule out algorithms for us-cTnI

	NSTEMI	UAP	Non-ACS cardiac disease	Non-cardiac chest pain	Other diseses	Total
Complete cohort	**N=129**	**N=110**	**N=77**	**N=567**	**N=96**	**N=979**
cTnI(Sgx)$_0$ < 2 ng/L	1 (0.8)	30 (27.3)	6 (7.8)	289 (51.0)*	34 (35.4)	360 (36.8)
1 hour cohort	N=67	N=56	N=29	**N=279**	**N=44**	**N=475**
cTnI(Sgx)$_0$ < 2 ng/L or cTnI(Sgx)$_0$ < 4 and $\Delta_{0\text{-}1}$ < 3 ng/L	0	35 (62.5)	8 (27.6)	225 (81.5)**	25 (56.8)	293 (62.3)
cTnI(Sgx)$_0$ < 2 ng/L or cTnI(Sgx)$_0$ < 6.0 and $\Delta_{0\text{-}1}$ < 3 ng/L	1 (1.5)	40 (71.4)	10 (34.5)	251 (91.3)**	31 (70.5)	333 (70.9)
cTnI(Sgx)$_0$ < 2 ng/L or cTnI(Sgx)$_0$ < 8.67 and $\Delta_{0\text{-}1}$ < 3 ng/L	1 (1.5)	43 (76.8)	14 (48.3)	258 (93.8)**	36 (81.1)	352 (74.9)

** hs-cTnT < 5 ng/L and hs-cTnI$_{(Abbott)}$ < 2 ng/L had a rule out rate for NSTEMI of 1.5% and 2.3% and ruled out 42.9% and 32.9% of non-cardiac chest pain patients, respectively*

*** hs-cTnT$_0$ < 5 ng/L or hs-cTnT$_0$ < 12 ng/L and $\Delta_{0\text{-}1}$ < 3 ng/L and hs-cTnI$_0$ < 2 ng/L or hs-cTnI$_0$< 5 ng/L and $\Delta_{0\text{-}1}$ < 2 ng/L had a rule out rate for NSTEMI of 1.5% and ruled out 85.9% and 74.9% of non-cardiac chest pain patients, respectively.*

Conclusion: The us-cTnI assay shows similar overall diagnostic performance for NSTEMI compared to the high sensitive assays. The ability to rule out patients with non-cardiac chest pain without reducing the sensitivity for NSTEMI seems superior for us-cTnI.

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

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

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

Methods: 990 patients with suspected NSTE-ACS were consecutively included from Sept.

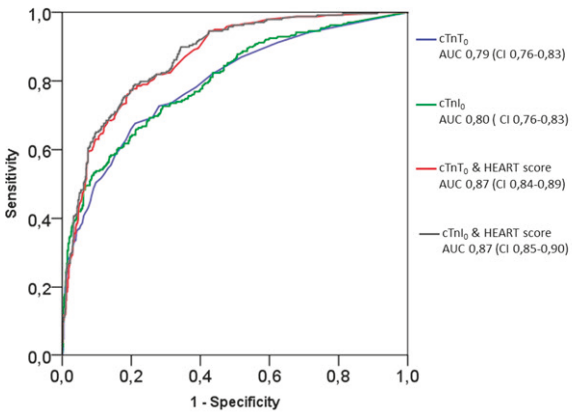

Figure 1. ROC-AUC for cTn0 and cTn0 and HEART-Score combined in ACS vs. non-ACS patients

*Table 1. Number of patients that were ruled out by the ESC troponin algorithms and the ESC algorithms and HEART-score combined (percentages in brackets). * $cTnT_0 < 5$ ng/L or $cTnT_0 < 12$ ng/L and $\Delta_{0-1} < 3$ ng/L. ** $cTnI_0 < 2$ ng/L or $cTnI_0 < 5$ ng/L and $\Delta_{0-1} < 2$ ng/L.*

	NSTEMI	UAP	Non-ACS cardiac disease	Non-cardiac chest pain	Other diseases	Total
Complete cohort	N=130	N=110	N=79	N=574	N=97	N=990
Single sample						
$cTnT_0 < 5$ ng/L	2 (1.5)	19 (17.3)	6 (7.6)	246 (42.9)	28 (28.9)	301 (30.4)
$cTnI_0 < 2$ ng/L	3 (2.3)	10 (9.1)	3 (3.8)	189 (32.9)	18 (18.6)	223 (22.5)
Single sample and HEART ≤ 3						
$cTnT_0 < 5$ ng/L	1 (0.8)	5 (4.5)	5 (6.3)	212 (36.9)	23 (23.7)	246 (24.8)
$cTnI_0 < 2$ ng/L	1 (0.8)	3 (2.7)	2 (2.5)	151 (26.3)	13 (13.4)	170 (17.2)
1 hour cohort	N=67	N=56	N=30	N=283	N=45	N=481
Two samples						
cTnT*	1 (1.5)	32 (57.1)	8 (26.7)	243 (85.9)	28 (62.2)	312 (64.9)
cTnI**	1 (1.5)	31 (55.4)	6 (20.0)	212 (75.2)	19 (42.2)	269 (56.0)
Two samples and HEART ≤ 3						
cTnT*	1 (1.5)	3 (5.4)	3 (10.0)	178 (62.9)	19 (42.2)	204 (42.4)
cTnI**	1 (1.5)	3 (5.4)	1 (3.3)	154 (54.4)	10 (22.2)	169 (35.1)

2015 to Feb. 2017. Serum samples were collected at 0 (cTn0), 1 (n=481; results were not reported to clinical care), 3 and 8-12 hours. The final diagnosis was adjudicated by two independent cardiologists based on all available clinical, laboratory (i.e. hs-cTnT (Roche Diagnostics) used in clinical routine) and imaging data. All samples were measured by the hs-cTnT and hs-cTnI (Abbott Diagnostics) assays. All patients were evaluated by the HEART-Score and a value of > 3 was regarded as a significant clinical risk that would overrule the biochemical ESC rule out criteria.

Results: The prevalence of NSTEMI was 13%, UAP 11%, non-ACS cardiac disease 8%, non-cardiac chest pain 58%, and 10% had other diseases. When a HEART score ≤ 3 were added as a clinical criterion to the ESC biochemical criteria, the number of ACS-patients who were incorrectly ruled out decreased 3-8.5 times (Table 1). Conversely, the percentages of non-cardiac chest pain patients who were correctly ruled out were 6-23% lower. Figure 1 shows the ROC-AUC of the cTn0 and HEART-Score in ACS vs. non-ACS patients.

Conclusion: The diagnostics accuracy of the ESC Cardiac algorithms for early identification of unselected chest pain patients with NSTE-ACS was markedly improved by the use of a clinical score.

Harmful effects of exercise intensity and exercise duration in arrhythmogenic cardiomyopathy

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Background: Vigorous exercise accelerates and aggravates arrhythmogenic cardiomyopathy (AC), but there is no data separating the harmful effects of exercise intensity and duration in these patients.

Purpose: To explore the impact of exercise duration and intensity on the prevalence of abnormal cardiac function in AC.

Methods**:** In a cross sectional study of AC patients diagnosed between 2008 and 2016, exercise history prior to diagnosis was recorded by standardized interviews. Exercise intensity was categorized according to the reported physical activity, and exercise >6 metabolic equivalents (METs) was defined as high intensity. Exercise duration was recorded as hours/week, and categorized as long if above median. By echocardiography, left ventricular (LV) dysfunction was defined as ejection fraction <54% (females) or 52% (males), or global longitudinal strain, defined as the average peak negative strain from 16 LV segments, worse than -18%. Right ventricular (RV) dysfunction was defined as fractional area change ≤40% or tricuspid annular plane systolic excursion <17mm, and RV dilation was defined as RV basal diameter >41mm or proximal RV outflow tract in parasternal short-axis view ≥32mm.

Results**:** We included 173 AC patients (53% probands, 44% female, age 41±16 years) with detailed exercise information for a median of 10 (range 3-70) years until the time of diagnosis. Median weekly exercise duration was 2.5 (range 0.2-20.0) hours, and mean exercise intensity was 6.7±1.8 METs. 91 subjects (52%) reported high intensity exercise. LV dysfunction was evident in 66 patients (38%), and was most prevalent in patients with high intensity and long duration exercise (Figure, panel A). High intensity exercise was associated with LV dysfunction independently of long duration (adjusted Odds Ratio (OR) 2.2 (95%CI 1.1-4.5), p=0.03). RV dysfunction was found in 104 patients (60%) and was associated with high intensity exercise (Figure, panel B), independently of long duration exercise (adjusted OR 2.6 (95%CI 1.2-5.3), p=0.01). RV dilation was observed in 127 patients (73%), and was associated with long duration exercise (Figure panel C), independently of high intensity exercise (adjusted OR 3.2 (95%CI 1.3-7.6), p=0.008).

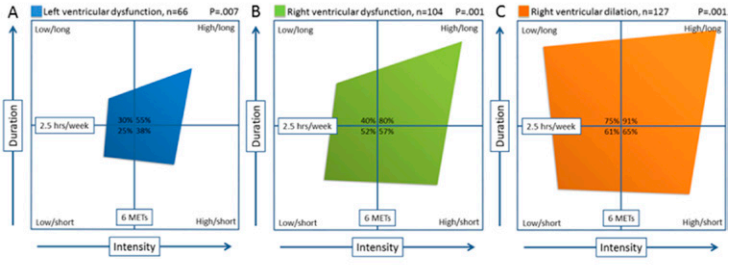

Figure – Modified radar plots of the distribution of LV dysfunction (A), RV dysfuncion (B) and RV dilation (C) in 173 AC patients cathegorized into four groups of exercise intensity high or low (above/below 6 METs) and exercise duration long or short (more/less than 2.5 hours per week). P-values by Chi-Square test.
AC = arrhythmogenic cardiomyopathy, LV = left ventricle, METs = metabolic equivalents, RV = right ventricle.

Conclusions**:** High intensity exercise was a strong and independent marker of LV and RV dysfunction, and long duration exercise was a strong and independent marker of RV dilation. These important insights add to our understanding of the harmful effects of exercise in AC, and may guide exercise advice to these patients.

Cardio-oncology; more than left ventricular systolic dysfunction

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Introduction**:** A rare but severe complication of treatment for chronic myeloid leukaemia (CML) with dasatinib (a protein kinase inhibitor) is pulmonary hypertension (PHT). There is limited evidence on how these patients should be followed.

Case Report**:** A 29-year-old female with paroxysmal atrial fibrillation was referred to our institution for shortness of breath. The patient had been diagnosed with CML in 2008 and managed with imatinib which was changed to dasatinib in 2011. On examination a holosystolic murmur was noted over the heart. Echocardiography revealed a pulmonary artery systolic pressure of 110mmHg and markedly dilated right ventricle with paradoxical septal motion and impaired function (Figure 1, panels A, B and C). Further diagnostic work up excluded pulmonary embolism, pulmonary- and connective tissue disease. Invasive right heart catheterization confirmed severe precapillary PHT with mean pulmonary arterial pressure of 46mmHg and pulmonary vascular resistance of 10 WU. On six minutes walk test the patient achieved a distance of 395m. Dasatinib was discontinued and replaced by bosutinib to treat her CML. Therapy for PHT was commenced with tadalafil and macitentan. Four months later her symptoms had greatly improved. Echocardiography showed a marked reduction in pulmonary artery systolic pressure to 60mmHg (Figure 1, panels D, E and F). Repeat right heart catheterization confirmed the improvements. Her six minutes walk improved by 25%.

Discussion**:** Novel effective anti-cancer agents are constantly being introduced into oncology, however, little is known about potential adverse cardiovascular effects. While the field of cardio-oncology commonly has been focusing on left ventricular dysfunction, this case of extreme drug-induced precapillary PHT and imminent right ventricular failure illustrates the rather broad spectrum which cardio-oncology constitutes.

Conclusion**:** This case of severe precapillary PHT is an important reminder of the rare but severe complication of treatment with dasatinib and the need for multidisciplinary management in cardio-oncology.

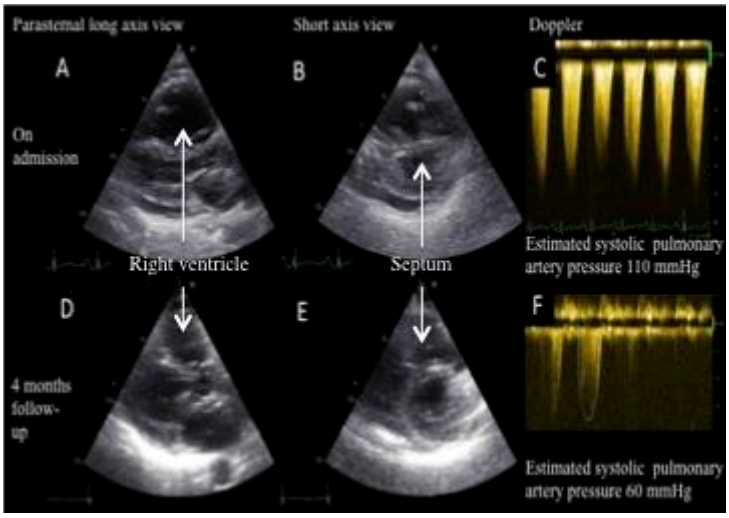

Figure 1: Echocardiography images showing a (A) markedly dilated right ventricle with (B) paradoxical septal motion and (C) elevated systolic pulmonary artery pressure after treatment with dasatinib with improvements on follw-up four months later (panels D, E and F).