Strain echocardiography improves prediction of arrhythmic events in ischemic and non-ischemic dilated cardiomyopathy

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This study was supported by the South-Eastern Norway regional health authority.

(2013/573/REK sor-ost).

Declaration of interest: none.

Abstract

Background:

Recent evidence suggests that an implantable cardioverter defibrillator (ICD) in non-ischemic cardiomyopathy (NICM) may not offer mortality benefit. We aimed to investigate if etiology of heart failure and strain echocardiography can improve risk stratification of life threatening ventricular arrhythmia (VA) in heart failure patients.

Methods:

This prospective multi-center follow-up study consecutively included NICM and ischemic cardiomyopathy (ICM) patients with left ventricular ejection fraction (LVEF) <40%. We assessed LVEF, global longitudinal strain (GLS) and mechanical dispersion (MD) by echocardiography. Ventricular arrhythmia was defined as sustained ventricular tachycardia, sudden cardiac death or appropriate shock from an ICD.

Results:

We included 290 patients (67±13 years old, 74% males, 207(71%) ICM). During 22±12 months follow up, VA occurred in 32(11%) patients. MD and GLS were both markers of VA in patients with ICM and NICM, whereas LVEF was not (p=0.14). MD independently predicted VA (HR: 1.19; 95% CI 1.08-1.32, p=0.001), with excellent arrhythmia free survival in patients with MD <70ms (Log rank p<0.001). Patients with NICM and MD <70ms had the lowest VA incidence with an event rate of 3%/year, while patients with ICM and MD >70 ms had highest VA incidence with an event rate of 16%/year.

Conclusion:

Patients with NICM and normal MD had low arrhythmic event rate, comparable to the general population. Patients with ICM and MD >70ms had the highest risk of VA. Combining heart failure etiology and strain echocardiography may classify heart failure patients in low, intermediate and high risk of VA and thereby aid ICD decision strategies.

Key words:

Heart failure; speckle-tracking echocardiography; risk assessment; ventricular arrhythmia

‡ Abbreviations

GLS: Global longitudinal strain

ICD: Implantable cardioverter defibrillator

ICM: Ischemic cardiomyopathy

LV: Left ventricle

LVEF: Left ventricular ejection fraction

MD: Mechanical dispersion

NICM: Non-ischemic dilated cardiomyopathy

SCD: Sudden cardiac death

VA: Ventricular arrhythmia

1. Introduction

Assessment of left ventricular (LV) function based on ejection fraction (EF), has traditionally been the most used method to estimate clinical outcome after myocardial infarction.[1] Heart failure with reduced EF (HFrEF) is defined as heart failure symptoms and EF below 40% irrespective of etiology, and is associated with increased risk of death and life threatening arrhythmias. [2] Implantable cardioverter defibrillators (ICD) improve survival from life threatening arrhythmias in patients with EF below 30-35%, and is indicated as primary prevention therapy in both ischemic and non-ischemic heart failure with EF below 35%. [3, 4] However, recent data indicate limited survival benefit of ICD as primary prevention in non-ischemic heart failure. Selecting patients for ICD therapy is still challenging, data is insufficient and the indications differ between centers in Europe. [5, 6] Parameters beyond LVEF are needed for more appropriate selection of patients for primary preventive ICD.

Longitudinal strain by echocardiography can assess both regional and global (GLS) LV function, and is superior compared to EF in evaluating LV function [7, 8]. Importantly, GLS is a better predictor of clinical outcome than EF in patients with relatively preserved systolic function, constituting the majority of patients after myocardial infarction. [9-11] Mechanical dispersion (MD) by strain echocardiography, reflecting contraction heterogeneity, is a marker of ventricular arrhythmias with good ability to predict arrhythmic events independently of EF. [12-14].

This study was a part of the IMPROVE study (clin trials: NCT02286908), a prospective, observational, multicenter, follow up study with aim to explore the predictive value of strain echocardiography in risk prediction of patients with heart disease. The aim of the present study was to prospectively investigate if strain echocardiography including GLS and MD can help risk stratification of ventricular arrhythmia and sudden cardiac death in a

modern population of patients with moderate and severe heart failure due to either ischemic cardiomyopathy (ICM) or non-ischemic dilated cardiomyopathy (NICM).

2. Methods

2.1 Study design and patient population

In this prospective, observational, multicenter, follow up study we consecutively included patients admitted with first time diagnosis of heart failure and LVEF < 40 % between July 2014 and January 2018. The study patients were included in the heart failure subgroup of the IMPROVE study (clin trials: NCT02286908). Time of inclusion was defined as the date of the last echocardiographic examination before discharge, performed when the patient was stabilized from the acute event. We classified patients into ischemic cardiomyopathy (ICM) or non-ischemic dilated cardiomyopathy (NICM) based on the coronary angiogram. Patients defined as non-ischemic dilated cardiomyopathy had no evidence of a stenotic epicardial coronary artery (> 50% diameter in the absence of collateral perfusion), or the extent of coronary artery disease was not considered sufficient to account for the reduced ventricular function. We excluded patients with paced ventricular rhythm, severe stenosis or regurgitation of any valve, poor echocardiographic image quality, ventricular arrhythmia on admission, Takotsubo cardiomyopathy and tachycardia induced/non-ischemic non-dilated cardiomyopathy (Figure 1).

Clinical parameters included medical history at inclusion, cardiovascular risk factors, cardiac symptoms, and physical examination performed during the hospital stay and from medical records. The study complied with the Declaration of Helsinki and was approved by the Regional Committee for Medical research (2013/573/REK sor-ost). All patients provided written informed consent.

2.2 Echocardiography

All patients underwent a comprehensive transthoracic two-dimensional echocardiographic examination at inclusion using the Vivid E9 or E95 ultrasound systems (GE Vingmed Ultrasound, Horten, Norway). Data were analyzed offline using EchoPAC software (GE Vingmed Ultrasound) blinded to clinical and electrocardiogram (ECG) data. LV ejection fraction (LVEF) was assessed by Simpson´s biplane method. [15] LV global longitudinal strain (GLS) was measured by speckle tracking analyses of 2-dimensional (2D) gray scale image loops with > 60 frames/s from 3 apical views and calculated as the average peak systolic strain in a 16-segment LV model. [16] LV mechanical dispersion was defined as the standard deviation of time from Q/R on surface ECG to peak negative strain during the entire cardiac cycle in the same 16 LV segments (supplemental Figure 1). [13] Color flow Doppler images were obtained of all heart valves to exclude subjects with severe regurgitation or stenosis of any valve. Mitral inflow was assessed in the apical four-chamber view, using pulsed–wave Doppler echocardiography, with the Doppler beam aligned parallel to the direction of flow and the sample volume at the level of the mitral valve leaflet tips. From the mitral inflow profile, the E-wave and A-wave peak velocities were measured. Doppler tissue imaging of the mitral annulus was obtained from the apical four-chamber view, using a sample volume placed in the septal mitral valve annulus for measurement of e´. [17] Tricuspid regurgitant jet velocity was measured during systole at leading edge of spectral waveform. E/A ratio, Left atrial volume index ml/m2 and E deceleration time were assessed. Restrictive filling patterns was defined as E/A >2. [18] Left atrial volume was measured according to guidelines [15] and indexed for BMI (Left atrial volume index).

2.3 Electrocardiography (ECG)

Twelve lead ECG was obtained at inclusion. QRS duration and QT intervals were measured from 12-lead ECG recorded at 25 mm/s. QT intervals were corrected by heart rate using Bazett's formula.

2.4 Follow up

We obtained data regarding all-cause mortality, sudden cardiac death (SCD), ventricular arrhythmia and appropriate shock from the ICD, until May 2018 from electronic medical records, synchronized with the Norwegian Cause of Death Registry.

2.5 Study outcome

The primary outcome was life threatening ventricular arrhythmias (VA), defined as the combined endpoint of SCD, appropriate shock from a primary preventive ICD and sustained ventricular tachycardia (consecutive ventricular beats at a rate of >100 beats per second lasting for >30 seconds) documented by 12-lead ECG, Holter monitoring, cardiac device, or aborted cardiac arrest. We calculated annual risk of primary outcome by dividing the total risk during the follow up period by years of follow up. We considered annual risk of primary outcome as "low" when < 4%, similar to the general population, "intermediate" when 4-8% annual events and high risk when ≥8% annual events.

The secondary outcome was mortality, defined as all-cause mortality and appropriate shock from a primary preventive ICD.

2.6 Statistical analysis

Categorical data were presented as numbers and percentage and continuous data as mean ± SD or as median (interquartile range) as appropriate. Comparisons of means were analyzed using Student´s t-test and Mann-Whitney U tests as appropriate. Proportions were compared using Chi-square test. Univariate logistic regression was used to identify markers of VA, and multivariate analysis included significant ($p<0.05$) variables from the univariate analyses (SPSS version 23.0, SPSS Inc., Chicago, IL, USA). Separate models were created for LVEF and GLS together with MD due to collinearity. Furthermore, separate models were created for LVEDV and QRS due to collinearity with MD. Kaplan–Meier survival analysis with follow up censored at 36 months was performed for patients stratified by etiology and with mechanical dispersion above and below 70ms and tested by log-rank tests. Reproducibility and repeatability of MD and GLS was tested in 50 randomly selected patients and expressed as intraclass correlation coefficients (ICC). A p-value < 0.05 was considered statistically significant.

3. Results

3.1 Clinical characteristics at inclusion

We screened 439 patients with LVEF < 40 % from three Norwegian centers participating in the IMPROVE study; Telemark hospital, Sorlandet hospital and Oslo University Hospital, Rikshospitalet. We excluded 149 (34%) with other etiologies than ICM or NICM (Figure1). The included population therefore included 290 heart failure patients. Of these, 207 (71%) had ICM and 83 (29%) NICM. At inclusion, ICM patients were older, had better LVEF, shorter QRS, lower mitral E/A ratio and left atrial volumes (all $p<0.01$) (Table 1).

A primary preventive ICD was implanted in 21 (10%) of ICM patients and in 21 (25%) of NICM patients (p<0.001) after 3 months on optimal medical treatment. [4]

In the total population, SCD occurred in 21 (7%) patients, 20/207 (10%) ICM and 1/83 (1%) NICM, (p=<0.01) and 4 patients received appropriate shocks from a primary preventive ICD (1/21 (5%) ICM and 3/21 (14%) NICM patients, p=0.04). Sustained ventricular tachycardia occurred in 7 (2%) patients in the entire study population 5/207 (2%) ICM and 2/83 (2%) NICM, (p=0.90) (Table 1).

3.2 Primary outcome, life-threatening VA

Patients were followed for a median period of 22 months (IQR: 20 months). No patients were lost to follow up.

The primary study outcome, life threatening arrhythmia (SCD, appropriate primary prophylactic ICD shock and sustained VT) occurred in 32 (11%) patients. These patients were more frequently males, had higher prevalence of AF, wider QRS and larger ventricular and atrial volumes (Table 2). Furthermore, patients with primary outcome had worse LV systolic function by LVEF and GLS and more pronounced MD (all p<0.05) (Table 2). GLS, MD and LVEF were univariate predictors of the primary outcome (Supplemental Table 3). MD was independently associated with the primary outcome when adjusted for age, gender, atrial fibrillation and LV endsystolic volume (LVESV) in a multivariate analysis (p<0.01) (Table 2). By including GLS in the model, both MD (p=0.01) and GLS (p= 0.04) were associated with primary outcome, while LVEF was not an independent marker when replacing GLS (p=0.14).

MD was related to QRS duration (R 0.43, p<0.001). QRS was a marginally significant predictor for the primary outcome in univariate analyses (p=0.05). A multivariate analysis

adding QRS duration to the significant univariate variables and excluding MD, did not demonstrate QRS as a predictor of outcome, (HR: 1.00; 95% CI 0.99-1.02,p=0.27). Similarly, LVEDV was also correlated to MD (R=0.14, P=0.02) and a marginally significant predictor for the primary outcome in univariate analysis (0.05), but was not significant in the multivariate analysis when excluding MD and LVEF (HR: 1.00; 95% CI 1.00-1.01, p=0.09) (suppl Table 3).

Mitral E/A ratio and left atrial volume index predicted the primary outcome in univariate analyses, but did not remain significant in multivariate analyses (supplemental Table 3). A restrictive filling pattern was not a predictor for arrhythmic outcome. However, restrictive filling combined with a dilated left atrium predicted arrhythmic outcome (Table 2).

Reproducibility for MD by intraclass correlation coefficient (ICC) was 0.85 (95%CI 0.74-0-92), and repeatability was 0.93 (95%CI 0.91-0.94) for single measures and 0.96 (95%CI 0.95-0.97) in average measures.

3.3 Life threatening VA according to etiologies of heart failure

The primary outcome combined endpoint of SCD, appropriate shock from a primary prophylactic ICD and sustained ventricular tachycardia was 11% in total population and equally frequent in ICM and NICM (13% in ICM and 7% in NICM, Log rank p=0.11). The annual event rate was 6% (7% for ICM and 4% for NICM patients). Survival free from life threatening arrhythmia was significantly better in patients with MD < 70 ms compared to patients with MD > 70 ms. (Figure 2a. Log rank p<0.001). Patients with NICM and MD < 70 ms had the lowest life-threatening VA incidence (3/63 (5%)), with a yearly event rate of 3 %, comparable with the yearly death rate at 1% in the general Norwegian population aged 63-66

years and were defined as low risk group. Patients with ICM and MD < 70 ms also had a low VA incidence, with a yearly event rate of 4%, not statistically different from patients with NICM and MD < 70 ms (p=0.50). Patients with NICM and MD > 70 ms had intermediate prognosis and a VA incidence of 3/20 (15%) with a yearly event rate of 8%. Intermediate risk was found by survival analyses when combining NICM patients with MD > 70 ms and ICM patients with MD < 70 ms. Combined, these patients had an annual event rate of 5%. Prognosis was most unfavorable in ICM patients with MD >70 ms, demonstrating a VA incidence of 15/51 (29%) and an annual event rate of 16% (Figure 2b. Log rank p<0.001).

Subgroup analyses of patients with LVEF < 35 % (n= 226 (78%)) showed similar results with both MD and GLS independently associated with life-threatening VA in multivariate analyses (MD (p=0.02) and GLS (p<0.01) adjusted for age, sex and etiology of heart failure (data not shown).

3.4 Secondary outcome, all-cause mortality and appropriate shock from a primary preventive ICD

All-cause mortality occurred in 27 (9%) and included 21 SCD, 3 deaths from malignancies, 1 from infection, 1 from severe aortic stenosis and 1from unknown causes. All-cause mortality was more frequent in ICM (26/207 (13%)) compared to NICM (1/83 (1%) Log rank p<0.01).

The secondary outcome of mortality (including all-cause mortality and appropriate shock from primary preventive ICD) occurred in 31/290 (11%) patients during the follow up period, and was more frequent in ICM patients 27/207 (13%) compared to NICM 4/83 (5%) (Log rank p=0.02, Figure 2c). Annual mortality outcome rate was 6 % in the total population (7% ICM and 2% NICM) and the mortality outcome rate in NICM patients was only slightly higher compared to the age matched general population (1% annual mortality) (Figure 2c).

4. Discussion

This is the first prospective study to show that MD and GLS improve prediction of VA and SCD independently of LVEF in patients with moderate and severe heart failure, irrespective of etiology. Importantly, classification of patients in risk groups by etiology of heart failure and MD may add important information when considering a primary prophylactic ICD in high-risk individuals, but may also help to identify individuals with low mortality benefit.

4.1 Incidence of arrhythmic events and mortality

The primary outcome occurred in 11% of patients with an annual event rate of 6%. The recent Danish trial (Defibrillator implantation in patients with nonischemic systolic heart failure) observed a 2.3% annual arrhythmic rate including events with SCD, VA and cardiac arrest.[6] Our findings support a low event rate in NICM patients with 4% annual primary (arrhythmic) outcome. The secondary outcome occurred in 11% with annual event rates of 6%. This event rate is in line with other studies including heart failure patients e.g. the Sudden cardiac death heart failure trial (SCD-HeFT) reporting almost 7 % annual all-cause mortality.[19]

Risk stratification by etiology and strain echocardiography

At present, LVEF guides the choice of ICD treatment in patients with heart failure, despite well-known limitations. [2, 20] In particular, choosing patients for primary preventive ICD based on LVEF < 35% is challenging and the method suffers from insufficient sensitivity. In addition, the use of primary preventive ICD in patients with NICM has been questioned due to low mortality benefit in several recent studies. [5, 6] A number of studies, including findings from our group, have demonstrated that both GLS and MD predict clinical outcome

better than LVEF in patients with acute myocardial infarction (AMI) and heart failure. [12, 13] In this prospective study, we confirm that MD > 70 ms is associated with higher risk of VA and SCD with improved precision compared to LVEF. Pronounced mechanical dispersion reflects inhomogeneous myocardial contractions, and has been shown to predict risk of ventricular arrhythmias in multiple cardiac diseases including AMI and several cardiomyopathies.[14] Our study adds to previous knowledge by presenting a risk stratifying strategy in patients with heart failure by combining etiology of heart failure with MD cut off values. We stratified patients in low, intermediate and high risk for life threatening VA. Our results indicate that ICM and MD > 70 ms constitute a particular high-risk population that should be closely monitored for arrhythmias and support previous findings of MD as a good predictor of arrhythmic events in both patients with ICM and NICM. [14]

4.2 Identification of high-risk NICM patients by strain echocardiography

We showed that patients with NICM had a low risk of life threatening VA, particularly when combined with MD < 70 ms, supporting findings from the DANISH study. [6] Nevertheless, some NICM patients have increased risk of VA, as also shown in our study, and risk has been linked to regional fibrosis [21-23]. MD has been associated to arrhythmic risk in NICM [12] and to cardiac arrhythmic risk and fibrosis by cardiac magnetic resonance (CMR) in patients with hypertrophic cardiomyopathy. [24] Importantly, we were able to identify a subgroup of NICM patients with MD > 70 ms with increased risk of events, and possible benefit from primary preventive ICD. Importantly, these patients should not be evaluated as low risk individuals, but remain in ICD evaluation according to previous guidelines.

We used the cut off value of MD 70 ms in our study. This value has relatively consistently been shown to discriminate patients with high risk of ventricular arrhythmias and was also confirmed in a recent meta-analysis. [14]

4.3 Clinical implications

We showed that ICM patients with MD > 70 ms had particularly high VA risk. These patients should be evaluated for primary prevention ICD, as stated in current guidelines. Importantly, NICM patients with MD > 70 ms were also at intermediate risk of VA and should receive full attention for primary prevention ICD. In contrast, patients with NICM and MD < 70 ms had a low risk of VA, and the risk was comparable to the general population which may help reassuring patients in this category. Our findings demonstrate clinically important differences in event rate when classifying patients based on the etiology of heart failure combined with MD values.

4.4 Study limitations

Our study was a prospective follow up study. Interventions and decisions on ICD implantations were not randomized nor controlled. We did not include CMR data in the present study and can therefore not show possible relationship to fibrosis.

Repeatability is a challenge in all echocardiographic measurements.[25] (Measurement of GLS with semiautomated methods and ease of obtaining automated MD may improve robustness, and the ICC values for MD in our study were excellent. Furthermore, measurements of MD vary between different software [26]. All our analyses were performed with the same software limiting software dependent variation. However, the presented absolute values and cut offs of MD may vary from values measured by other software.

5. Conclusions

In patients with heart failure with reduced ejection fraction, life-threatening VA occurred in 11% of patients, clearly demonstrating the continued need for primary prevention ICD. However, we demonstrated important subgroup differences based on etiology of heart failure and level of mechanical dispersion. We identified a low risk group of patients with NICM and MD < 70 ms who may not benefit from an ICD implantation in line with results from the DANISH study. Patients with ICM and MD > 70 ms had highest risk of of life threatening arrhythmia and should adhere to guidelines for primary prevention ICD.

Funding

This study is funded by the South-Eastern Norway regional health authority (2013/573/REK sor-ost).

Conflict of interest

All authors declare no conflicts of interest.

Acknowledgements

We thank all the participants in the study.

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Figure legends

Figure 1: Flow chart demonstrating inclusion of patients and outcome.

439 patients with LVEF < 40% were screened (top). NICM and ICM patients (n=290) were included. Primary outcome: Combined endpoint of sustained ventricular arrhythmia, SCD, and shock from a primary preventive ICD. Secondary outcome: Combined endpoint of all cause-mortality and appropriate shock from a primary preventive ICD. LVEF = Left ventricular ejection fraction. NICM = Non-ischemic dilated cardiomyopathy. ICM=Ischemic cardiomyopathy. SCD = Sudden cardiac death. VA = Ventricular arrhythmia.

Figure 2: Kaplan Meier demonstrating freedom from primary (a+b) and secondary (c) outcome in 290 NICM and ICM patients.

2A) Primary outcome. Patients categorized by etiology and mechanical dispersion above or below 70 ms.

2B) Primary outcome. Patients categorized according to risk groups. Low risk group (green): NICM patients with MD < 70 ms. Intermediate risk group (orange): Patients with NICM and MD > 70 ms and patients with ICM and MD < 70 ms. High risk group (red): Patients with ICM and MD > 70 ms. Blue line indicates survival rate in a general 63-66-year-old population. Patients in the high risk group had increased risk of primary outcome compared to the intermediate and low risk groups, Log rank $p<0.001$

2C) Secondary outcome. Patients with ICM (red) and NICM (green). ICM patients had increased risk of the secondary outcome compared to NICM patients, Log rank $p = 0.02$. Blue line indicates survival rate in a general 63-66-year-old population.

X-axis indicates days after inclusion. ICM=Ischemic cardiomyopathy; MD = mechanical dispersion; NICM = Non-ischemic dilated cardiomyopathy; SCD = Sudden cardiac death. VA = Ventricular arrhythmia.

* $p<0.05$ vs. other groups

Supplemental figure 1: Mechanical dispersion by strain echocardiography in patients with ischemic and non-ischemic dilated cardiomyopathy.

Speckle tracking echocardiography showing longitudinal strain curves in the four-chamber view from patients with ischemic (upper) and non-ischemic cardiomyopathy (lower). White horizontal arrows indicate contraction duration, defined as time from Q/R on the electrocardiogram to peak negative longitudinal strain. Mechanical dispersion was defined as the SD of contraction duration from 16 LV segments. Left panels demonstrate a more homogenous contraction pattern in a survivor, whereas in the non-survivor (right) mechanical dispersion is more pronounced.

Tables

Table 1

Baseline characteristics in 290 patients with LVEF < 40%. Comparison between 207 patients with ICM and 83 patients with NICM.

	All patients n = 290	ICM n = 207	NICM n = 83	P-value*
Age, years	67 ± 13	68 ± 12	63 ± 15	<0.01
Female, n (%)	74 (26)	47 (23)	27 (33)	0.08
Heart rate, bpm	76 ± 14	75 ± 14	78 ± 16	0.21
Systolic BP, mmHg	124 ± 21	123 ± 20	127 ± 24	0.12
Diastolic BP, mmHg	76 ± 12	75 ± 12	78 ± 14	0.04
NYHA class	2.2 ± 0.9	2.1 ± 0.9	2.4 ± 0.9	0.15
ECG parameters				
Atrial fibrillation, n (%)	28 (10)	17 (8)	11 (14)	0.16
QRS duration, ms	110 ± 26	106 ± 23	122 ± 28	<0.001
QTc interval, ms	462 ± 43	460 ± 41	465 ± 47	0.40
Primary prevention ICD, n (%)	42 (15)	21 (10)	21 (25)	<0.001
Secondary prevention ICD, n (%)	10 (3)	8 (4)	2 (2)	0.54
Sudden cardiac death, n (%)	21 (7)	20 (10)	1 (1)	0.01
Sustained VT, n (%)	7 (2)	5 (2)	2 (2)	0.90
Shock from primary ICD, n (%)	4 (10)	1 (1)	3 (4)	0.04
All cause mortality, n (%)	27 (9)	26 (13)	1 (1)	<0.01
Primary outcome, n (%)	32 (11)	26 (13)	6 (7)	0.11

Primay outcome annual event rate, n (%)	16 (6)	14 (7)	3 (4)	
Secondary outcome, n (%)	31 (11)	27 (13)	4 (5)	0.04
Secondary outcome annual event rate, n (%)	17 (6)	15 (7)	2 (2)	
Echocardiographic parameters				
LVEDV, ml	176 ± 60	159 ± 52	217 ± 59	<0.001
LVESV, ml	123 ± 49	110 ± 42	157 ± 50	<0.001
LVEF, %	31 ± 6	32 ± 6	28 ± 7	<0.001
LVEF <35%, n (%)	226 (78)	155 (75)	71 (86)	0.05
GLS, %	-10.5 ± 3.3	-10.7 ± 3.0	-10.1 ± 3.9	0.23
MD, ms	63 ± 19	63 ± 19	62 ± 19	0.70
E/e´	17.7 ± 10.5	16.6 ± 9.1	20.4 ± 12.8	0.02
Left atrial volume index, ml/m2	38.3 ± 14.2	36.3 ± 13.1	43.4 ±15.6	<0.01
Mitral E/A ratio	1.4 ± 0.9	1.3 ± 0.8	1.8 ± 1.2	<0.01
Restrictive filling n (%)	154 (54)	109 (58)	45 (54)	0.87
E/A ratio>2 and dilated left atrium	27 (9)	15 (7)	12 (15)	0.04

Values are mean ± SD or numbers (n). P-values are calculated from unpaired Student´s t-test, Mann Whitney U test and Chi square when appropriate. BP = blood pressure; Bpm = beats per minute; E = early transmitral flow velocity; e´= early diastolic myocardial velocity; ECG = electrocardiogram; GLS; global longitudinal strain ICD= implantable cardioverter defibrillator; ICM= ischemic cardiomyopathy; LVEDV = left ventricular end-diastolic volume; LVEF = left ventricular ejection fraction; LVESV = left ventricular end-systolic volume; MD; mechanical dispersion, NICM; non ischemic cardiomyopathy; NYHA = New

York Heart Association functional classification; QTc = heart rate corrected QT interval; VT = ventricular tachycardia * P-values for the comparison of ICM and NICM patients

Table 2

Characteristics of patients with LVEF <40%, comparing patients with and without life threatening ventricular arrhythmia (primary outcome)

	No life threatening VA n = 252	**Life threatening VA n = 32**	**P-value*** Student -test	**Multivariate HR (95% CI)**	**P-value**
Age, years	66 ± 13	70 ± 14	0.11	1.03 (0.99-1.06)	0.15‡*
Female, n (%)	72 (29)	2 (6)	<0.01	0.23(0.05-1.00)	0.05‡*
ICM, n (%)	175 (69)	26 (81)	0.17		
Heart rate, bpm	76± 15	76± 13	0.90		
Systolic BP, mmHg	125± 22	122± 18	0.46		
Diastolic BP, mmHg	76± 15	74± 10	0.36		
NYHA class	2.2 ± 0.9	2.4 ± 0.9	0.14		
ICD, n (%)	39 (15)	10 (31)	0.09		
ECG parameters					
Atrial fibrillation, n (%)	18 (7)	8 (26)	0.001	1.70 (0.66-4.40)	0.27‡
QTc interval, ms	462± 41	460 ± 58	0.83		
QRS duration, ms	109±26	120±25	0.05		
Echocardiographic parameters					
LVEDV, ml	173 ± 60	198 ± 61	0.02		
LVESV, ml	121 ± 48	145 ± 53	<0.01	1.00 (1.00-1.30)	0.35‡
LVEF, %	31 ± 6	28 ± 7	<0.01	0.88 (0.90-1.02)	0.14‡
GLS, %	-10.7 ± 3.1	-9.3 ± 3.8	<0.01	1.14 (1.00-1.30)	0.04‡

MD, ms	62 ± 17	75 ± 30	0.01	1.02 (1.00-1.03)	0.01‡*
E/e´	18.0 ± 10.9	18.7 ± 8.4	0.75		
Mitral E/A ratio	1.4 ± 0.9	1.9 ± 1.2	0.03	1.56 (1.08-2,25)	0.02*
Left atrial volume index	37.3 ± 14.1	45.0 ± 13.2	<0.01	1.01 (0.99-1.05)	0.26*
Restrictive filling n(%)	131(55)	19 (59)	0.39		
EA ratio >2 and dilated left atrium n (%)	20 (8)	6 (19)	0.02	2.75 (0.92-8.15)	0.07*

P-values are calculated from unpaired Student´s t-test, Mann Whitney U test and Chi square when appropriate. BP= blood pressure; Bpm; beats per minute; E= early transmitral flow velocity; e= early diastolic myocardial velocity; ECG = electrocardiogram; GLS = global longitudinal strain; HR = hazard ratio; Ischemic cardiomyopathy; ICD = Implantable cardioverter defibrillator; LVEDV = left ventricular end diastolic volume; LVEF = left ventricular ejection fraction; LVESV = left ventricular end systolic volume; MD = mechanical dispersion; NYHA= New York Heart Association functional classification; QTc = heart rate corrected QT interval; VA= ventricular arrhythmia

Hazard ratio (HR) by multivariate regression. HR is calculated for 5 % decrease in EF, 1 % worsening of GLS and 10 ms increase in MD. MD, GLS and LVEF are adjusted for significant univariate variables.

‡Model 1: Multivariate analyses including age, sex, AF, MD and GLS or LVEF or LVESV. (GLS, LVEF and LVESV were not included together due to collinearity).

*Model 2: Multivariate analyses including age, sex, MD, left atrial volume index, and mitral E/A ratio or the categorical variable “EA ratio >2 and dilated left atrium”.