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ORIGINAL PAPER

Cardioverter–defibrillator does not improve short-term survival among patients with non-ischemic cardiomyopathy and reduced left ventricular ejection fraction

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Abstract

Introduction The DANISH trial raised doubts about the effectiveness of primary prevention of sudden cardiac death by ICD implantation among patients with non-ischemic heart failure. We sought to analyse data from the EVITA-HF registry to give an answer from real-world registry data to the DANISH trial.

Methods 1804 patients were identified from the EVITA-HF registry with chronic heart failure (CHF) due to ischemic or dilated heart disease and reduced left ventricular ejection fraction of ≤ 35%. The patients were divided into two groups: Patients with newly implanted cardioverter–defibrillator (ICD group; mean age 66 ± 12 years, 77% male) and without ICD (no-ICD group; mean age 66 ± 14 years, 77% male). The subgroups were compared with regard to mortality and predictive parameters affecting survival.

Results Cardiovascular risk factors were similar among patients in the non-ICD group ($n = 1473$) compared to ICD group ($n = 331$). After 1-year follow-up patients with ischemic heart disease showed a significant improved survival in the ICD group compared to non-ICD group [92.1% vs. 80.6%, HR 0.37 (0.22–0.62)]. Patients with non-ischemic cardiomyopathy did not show a difference with regard to survival between the ICD and the non-ICD group [93.7% vs. 93.1%, HR 0.92 (0.43–1.97)]. The data were stable in a Cox-regression model.

Conclusion In a real-world setting, no benefit was evident for patients with non-ischemic cardiomyopathy and reduced left ventricular ejection fraction by adding ICD therapy in a short-term follow-up of 12 months in contrast to patients with ischemic cardiomyopathy.

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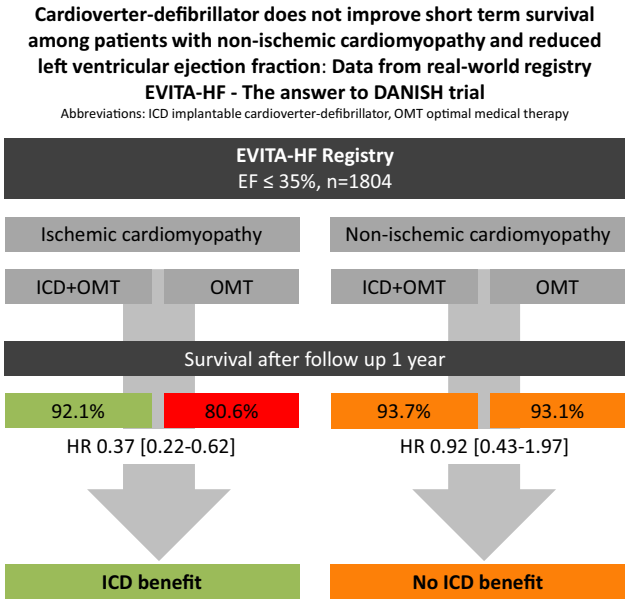
Graphic abstract



Keywords Non-ischemic cardiomyopathy · Sudden cardiac death · Primary prevention · Implantable cardioverter–defibrillator

Introduction

Implantable cardioverter–defibrillators (ICD) are a proven therapy for primary prevention of sudden cardiac death (SCD) among patients with impaired left ventricular ejection fraction and optimal pharmacological therapy. The 2015 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death [1] differentiate between ischemic and non-ischemic origin of heart failure and assess the ischemic origin to have stronger evidence to benefit from ICD implantation for primary prevention of SCD compared to non-ischemic origin. Among patients with non-ischemic heart failure, only the SCD-HeFT [2] trial examining a heterogenous cohort of patients with ischemic and non-ischemic heart failure showed a benefit for ICD implantation to prevent SCD in setting without CRT systems. Other randomized trials as DEFINITE [3] (pharmacological therapy with ACE inhibitor and betablockers vs. pharmacological therapy + ICD) failed to show reduction of overall death among patients with non-ischemic heart failure.

Despite the heterogeneous scientific data, the number of ICD implantation among patients with non-ischemic cardiomyopathy has, for example, more than doubled in France within a decade [4].

In 2016, the randomized DANISH [5] trial showed that ICD implantation among patients with non-ischemic heart failure and optimal pharmacological therapy including aldosterone antagonists did not result in an overall survival benefit. However, subgroups as patients younger than 59 years or patients with lower NT-proBNP levels showed a survival benefit by adding an ICD therapy. Two meta-analyses showed a benefit for adding ICD therapy among patients with dilated cardiomyopathy: in February 2017, Shun-Shin et al. published a meta-analysis [6] including the data of DANISH, MADIT I, MADIT II, CAT, Definite, Dinamit, Companion, SCD-HeFT, IRIS, and others. In July 2017, Wolff et al. [7] published a pooled analysis including 2292 patients out of randomized-controlled trials and stated that (1) the DANISH trial was the study that adhered the most to the guideline recommendations, (2) with the highest percentage of CRT therapy, and (3) no benefit for ICD therapy.

We like to contribute to this discussion with a real-world perspective from the large EVITA-HF-registry including patients with chronic heart failure, a reduced ejection fraction of ≤ 35% and optimal pharmacological treatment with regard to mortality risk among patients with and without implanted ICD for primary prevention of SCD and ischemic and non-ischemic cardiomyopathy.

Methods

EVITA-HF was set up as a web-based registry using an electronic case report form (eCRF). Inclusion criteria were chronic heart failure since at least 3 months, and a

documented ejection fraction of ≤ 40%. Exclusion criteria were age younger than 18 years or missing consent of the patient. Patients were hospitalized (index hospitalization) in one of the 20 participating tertiary care heart centers. All centers offer the whole spectrum of diagnostic and treatment modalities in heart failure. Patients had to be included consecutively. Data management was performed at the Institut für Herzinfarktforschung Ludwigshafen at the University of Heidelberg, Germany. The registry received approval by the institutional ethics committees. Each patient gave informed written consent. The registry was supported by unrestricted grants from Medtronic, Novartis, and Sanofi Aventis.

The eCRF collected baseline information on demographics, presentation, medical history, clinical evaluation and diagnostics, pharmacological treatment and non-pharmacological interventions, quality of life, and adverse events during index hospitalization. In a subset of participating centers, a representative 1-year follow-up was performed by phone call and/or contact by the center or general practitioner. Thereby, information was obtained on vital status, adverse events, and interventions, since index discharge, current health status, pharmacological treatment, and quality of life. The follow-up information of survivors was regarded as 1-year status if obtained between 300 and 450 days after index discharge.

EVITA-HF was started in January 2009. As of December 2015, 4,282 patients had been included.

Population characteristics

The present analysis included patients documented in the registry with heart failure due to ischemic heart disease or dilated cardiomyopathy and a left ventricular ejection fraction ≤ 35%. Exclusion criteria were implanted defibrillator/CRT pacemaker at time of inclusion or indication for secondary prevention of cardiac sudden death. The cohort of 1804 patients was divided into a group with implantation of a defibrillator during index-hospital stay (ICD group; $n = 331$; 18.3%) vs. a group without implantation (no-ICD group; $n = 1473$; 81.7%). The reasons for the choice of ICD implantation were at the discretion of the hospitals following the guideline recommendations as NYHA class I or NYHA class IV without being listed for transplant, limited prognosis, or patient's choice.

Statistical analysis

Categorical data are shown as absolute numbers and percentages, continuous data as medians with interquartile range, and means with standard deviation. The Mann–Whitney U test was used to compare metric or ordinal data and the $\chi 2$ test to compare categorical data. One-year mortality at 366 days after index discharge was estimated and compared by methods of survival analysis (Kaplan–Meier curve, log-rank-test). The follow-up duration was defined as the time span from index discharge to the date of the follow-up contact. Unadjusted and adjusted hazard ratios with 95%-confidence intervals were calculated in Cox-regression models. All statistical comparisons were two-sided, with P values ≤ 0.05 being accepted as statistically significant. The statistical analysis was performed at the Institut für Herzinfarktforschung (Ludwigshafen) using SAS, version 9.3 (SAS Institute Inc., Cary, NC, USA).

Results

Patient Characteristics

Patients in the ICD group compared to non-ICD group were similar with regard to age (66 ± 12 vs. 66 ± 14 years; $p = 0.14$), but had in median a lower left ventricular ejection fraction [25 (20; 30) vs. 29% (23; 33]); $p < 0.001$). Measurement of ejection fraction was mainly (approx. 90%) performed by echocardiography.

The cause of heart failure was equally distributed between groups (ischemic: ICD group 59.8 vs. 58.6% non-ICD group; dilated/idiopathic: 40.2 vs. 41.4%; $p = 0.68$).

Cardiovascular risk factors did not differ between ICD group and non-ICD group: arterial hypertension (68.9 vs. 69.4%; $p = 0.86$), diabetes (39.3 vs. 36.8%; $p = 0.39$), renal insufficiency (28.7 vs. 26.7%; $p = 0.46$), and history of stroke (6.3 vs. 8.2%; $p = 0.25$). Patients in the ICD group reported more frequently a history of atrial fibrillation (33.8 vs. 28.3%; $p = 0.046$). Cancer (5.4 vs. 7.9%; $p = 0.12$) and dementia (0.0 vs. 1.1%; $p = 0.11$) did not differ between groups.

Medication

Patients in the ICD group showed more intensive pharmacological heart failure treatment compared to patients in the non-ICD group at time of admittance to hospital (see Tables 1, 2). At the end of index-hospital stay, the pharmacological treatment was optimized in both group leading to equal rates with regard to betablockers, but still, a higher rate for ACE inhibitors/ARB, diuretics, and aldosterone antagonists in the ICD group remained (see Table 2).

At 1-year follow-up, both groups showed equal rates of betablockers and ACE inhibitors/ARB and higher rates of aldosterone antagonists and diuretics in the ICD group.

Rhythm analysis

The rate of patients with sinus rhythm (74.5 vs. 73.4%; $p = 0.66$) and atrial fibrillation (21.2 vs. 21.9%; $p = 0.79$)

Table 1 Patient baseline characteristics

	ICD group ($n=331$)	No-ICD group ($n=1473$)	*P* value
Proportion of patients	18.3	81.7	–
Age, years; median (IQR)	68 (58;74)	69 (58;76)	0.14
mean ± SD	66 ± 12	66 ± 14	0.14
Male gender	77.3	76.7	0.81
LVEF; median (IQR)	25 (20; 30)	29 (23; 33)	<0.001
Cause of cardiomyopathy			
Ischemic	59.8	58.6	0.68
Dilated/idiopathic	40.2	41.4	0.68
Implanted pacemaker	7.9	6.5	0.38
Comorbidities and risk factors			
Hypertension	68.9	69.4	0.86
History of stroke	6.3	8.2	0.25
Diabetes mellitus	39.3	36.8	0.39
Chronic renal insufficiency	28.7	26.7	0.46
History of atrial fibrillation	33.8	28.3	0.046
COPD	14.2	14.8	0.78
Cancer	5.4	7.9	0.12
Dementia	0.0	1.1	0.11

Data are presented as percentages of patients unless otherwise stated

HF heart failure, *CI* confidence interval, *COPD* chronic obstructive pulmonary disease, *IQR* interquartile range, *SD* standard deviation

at time of inclusion did not differ between ICD group and non-ICD group (see Table 3).

In the ICD group, the QRS width was wider [126/min (100; 154) vs. 110 (95; 131); $p<0.001$] with a higher rate of left bundle branch block (49.4 vs. 26.5%; $p<0.001$). In the Holter ECG analysis, the mean heart rate [78/min (69; 88) vs. 79 (70; 89); $p=1.00$] as well as the burden of ventricular ectopy [0.2 per hour (0.0; 14.7) vs. 2.5 (0.0; 32.8); $p=0.17$] were equal between groups.

The rate of implanted pacemakers did not differ between groups (7.9 vs. 6.5%; $p=0.38$; see Table 1).

Laboratory parameters

In the ICD group, patients showed less anemia according to WHO definition compared to non-ICD group (25% vs. 34%; $p<0.001$) and had lower levels of CRP [0.60 (0.34; 1.67) vs. 1.40 (0.50; 3,40); $p<0.001$]. The renal function [GFR 64 (49; 81) vs. 66 (48; 84); $p=0.47$], the cholesterol level [172 (140; 209) vs. 170 (138; 201); $p=0.25$], and the NT-pro BNP levels [2847 (1219; 5172) vs. 2622 (853; 7373); $p=0.92$] did not differ between groups (see Table 4).

Follow-up

Among the ICD group, 99.7% of the patients were discharged from hospital alive with 100% of them having a defibrillator implanted, 44% with a left ventricular lead for cardiac resynchronization. Among the non-ICD group, 98.0% of patients left the hospital alive ($p=0.038$).

After a median follow-up of 12.6 months (12.0; 14.6) in the ICD group and 12.6 months (12.0; 14.3) in the non-ICD group: 97.6% ($n=322$) vs. 93.6% ($n=1357$) were available for assessment ($p=0.005$).

The overall death rate was significantly lower in the ICD group compared to non-ICD group [7.2% vs. 14.3%; HR 0.48 (0.31–0.74)].

Separated in ischemic and non-ischemic origin, patients with ischemic cardiomyopathy showed a survival benefit from ICD therapy [7.9% vs. 19.4%; HR 0.37 (0.22–0.62), see Fig. 1], whereas patients with non-ischemic cardiomyopathy did not benefit from ICD [6.3% vs. 6.9%; HR 0.92 (0.43–1.97); see Fig. 2]. The mortality was higher in the non-ICD group of patients with ischemic cardiomyopathy compared to non-ischemic cardiomyopathy. In the subgroups of females, males, elderly (≥ 75 years), diabetic and non-diabetic patients, patients without COPD as well as patients with and without renal insufficiency ICD therapy was associated with lower mortality (see Table 5).

In a Cox-regression model adjusted for age, gender, chronic kidney disease, left ventricular ejection fraction, NYHA class, and QRS duration, the benefit of ICD therapy was confirmed for patients with ischemic cardiomyopathy (adjusted HR 0.40; 0.23–0.69), but not for patients with non-ischemic cardiomyopathy (adjusted HR 0.71; 0.32–1.55) (see Fig. 3).

Discussion

The published data of the EVITA-HF registry are to our knowledge the first real-world analysis that compares mortality between patients with ischemic and non-ischemic cardiomyopathy by adding ICD within 12 months of follow-up after the randomized DANISH trial [5] has been published.

The cohort of the EVITA-HF registry and the subgroups with and without implanted ICD were typical cohorts of patients with heart failure and did not differ with regard to origin of cardiomyopathy. Both cohorts were consequently treated with heart failure medication that is proven by medication at time of discharge of index-hospital stay as well as at time of 1-year follow-up. The ICD group showed a more consequent pharmacological treatment, but showed a lower systolic left ventricular ejection fraction (EF), more often left bundle branch block (LBB) and thus a high percentage with 44% of patients having a CRT defibrillator implanted. A cox-regression analysis confirmed that the differences in the EF, prevalence of LBB, and CRT systems did not influence the results of the non-adjusted analysis.

Table 2 Medication at time of inclusion and at follow-up

	ICD group ($n=331$)	No-ICD group ($n=1473$)	P value
Medication at time of admission			
Betablocker	81.5	71.8	< 0.001
ACE inhibitor/ARB	82.7	72.9	< 0.001
Aldosterone antagonist	50.3	33.3	< 0.001
Diuretics	77.6	62.2	< 0.001
Glycosides	19.1	11.6	0.007
Antiarrhythmics class III	8.1	4.4	0.041
Antiarrhythmics class IV	2.9	2.5	0.82
IK_f blocker	0.6	1.2	0.47
Platelet inhibitors	56.6	52.2	0.28
Oral anticoagulation	22.0	20.7	0.70
Statin	58.5	49.2	0.002
Insulin	16.8	12.8	0.16
Oral antidiabetics	20.8	16.2	0.14
Antidepressant medication	4.0	5.4	0.47
Medication at end of index-hospital stay	$n=330$	$n=1444$	
Betablocker	90.0	91.8	0.28
ACE inhibitor/ARB	94.2	90.2	0.020
Aldosterone antagonist	74.5	62.2	<0.001
Diuretics	89.1	79.7	<0.001
Glycosides	21.2	14.3	0.002
Antiarrhythmics class III	12.1	8.9	0.068
Antiarrhythmics class IV	0.9	0.7	0.82
IK_f blocker	1.8	3.3	0.17
Platelet inhibitors	59.7	63.7	0.18
Oral anticoagulation	35.2	31.5	0.20
Statin	64.8	63.3	0.59
Insulin	17.3	14.7	0.22
Oral antidiabetics	21.0	16.6	0.059
Antidepressant medication	4.8	6.4	0.28
Medication at 1 year follow-up	$n=178$	$n=771$	
Betablocker	89.9	89.2	0.80
ACE inhibitor/ARB	88.2	86.8	0.61
Aldosterone antagonist	66.7	54.5	0.003
Diuretics	85.9	72.6	< 0.001
Glycosides	19.8	12.6	0.013
Antiarrhythmics class III	6.8	4.5	0.22
IKf blocker	2.3	3.6	0.36

Data are presented as percentages of patients unless otherwise stated

ARB angiotensin-receptor blocker; IK_f blocker, ion-channel f blocker

The patients receiving an ICD therapy seemed to be well selected, as out of the total cohort, "only" 18.3% of the patients received an ICD therapy. These could favour a better outcome in the ICD group.

Comparing the outcome of patients with and without implanted ICD, the results are in line with published data and accepted guidelines: ischemic cardiomyopathy [8–12] and patients without cancer [13] are in favour of adding ICD therapy. In our cohort, older patients showed a greater benefit of ICD therapy that is in line with the DEFINITE trial [3], but stands in contrast to DANISH trial [5] both investigating patients with non-ischemic cardiomyopathy.

In a subgroup, analysis of DANISH patients younger than 59 years and patients with low NT-proBNP levels showed a benefit of ICD therapy. In our cohort, the subgroup analysis of patients with an NT-proBNP/BNP level below the median

Table 3 Heart rhythm parameters at inclusion

	ICD group ($n=331$)	No-ICD group ($n=1473$)	*P* value
Heart rhythm			
Sinus rhythm	74.5	73.4	0.66
Atrial fibrillation/Atrial flutter	21.2	21.9	0.79
Paced rhythm	7.0	5.4	0.26
Other arrhythmia	0.9	1.5	0.41
Holter ECG			
Heart rate (1/min); median (IQR)	78 (69; 88)	79 (70; 89)	1.00
Ventricular ectopy (1/h); median (IQR)	0.2 (0.0; 14.7)	2.5 (0.0; 32.8)	0.17
QRS width (ms); median (IQR)	126 (100; 154)	110 (95; 131)	<0.001
Left bundle branch block (intrinsic)	49.0	26.5	<0.001

Data are presented as percentages of patients unless otherwise stated

Table 4 Laboratory parameter at time of inclusion

	ICD group ($n=331$)	No-ICD group ($n=1473$)	*P* value
Hemoglobin	13.7 (12.7; 14.8)	13.5 (12.0; 14.7)	0.003
Anemia (WHO definition) (%)	24.9	34.1	0.001
GFR (ml/min)	64.0 (49.2; 80.7)	65.7 (48.1; 83.7)	0.47
GFR < 60 ml/min (%)	42.3	40.6	0.57
Sodium (mmol/l)	139 (137; 142)	139 (137; 141)	0.59
Potassium (mmol/l)	4.3 (4.0; 4.6)	4.3 (3.9; 4.6)	0.46
Cholesterol (mg/dl)	172 (140; 209)	170 (138; 201)	0.25
CRP (mg/dl)	0.60 (0.34; 1.67)	1.40 (0.50; 3.40)	<0.001
NT-pro BNP samples available (%)	50.8	56.8	0.045
NT-pro BNP (pg/ml)	2847 (1219; 5172)	2622 (853; 7373)	0.92

GFR glomerular filtration rate, *CRP* c-reactive protein

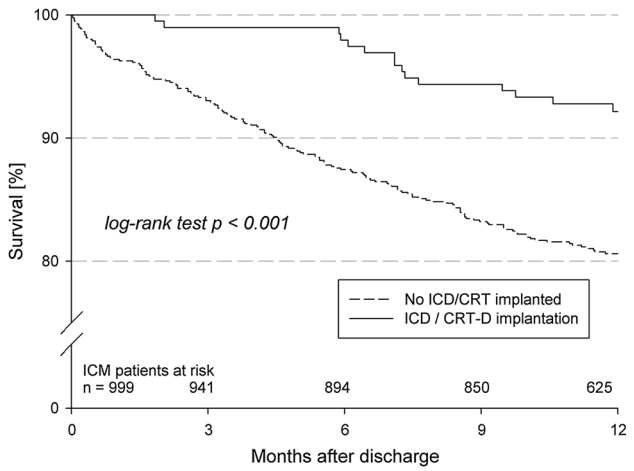


Fig. 1 Kaplan–Meier curve for patients with ischemic heart disease with and without implanted ICD during a follow-up of 12 months (non-corrected analysis)

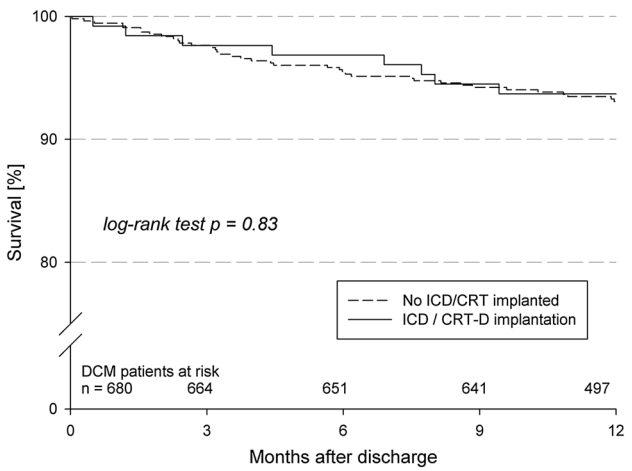


Fig. 2 Kaplan–Meier curve for patients with non-ischemic cardiomyopathy with and without implanted ICD during a follow-up of 12 months (non-corrected analysis)

(1912/500 pg/ml) was not meaningful due to a small sample size of 23 patients in the ICD group (vs. 246 patients in the non-ICD group) and also in the group of patients younger than 59 year patients (ICD group $n=53$ with a calculated higher mortality compared to patients without an ICD $n=278$: 12.3 vs. 3.9%; HR 3.29; 1.19–9.04).

Table 5 Mortality risk groups

	ICD group ($n=322$)	No-ICD group ($n=1357$)	P value/HR (95%-CI)	P for interaction
Patients with available FU	97.6 (322/330)	93.6 (1357/1450)	0.005	
Length of FU [months]; median (IQR)	12.6 (12.0; 14.6)	12.6 (12.0; 14.3)	0.80	
Total	7.2	14.3	0.48 (0.31–0.74)	
Female gender	2.7	13.9	0.19 (0.05–0.77)	0.14
Male gender	8.5	14.4	0.56 (0.36–0.89)	
Age ≥ 75 yrs	8.5	22.5	0.33 (0.15–0.76)	0.19
Age < 75 yrs	6.9	10.7	0.63 (0.38–1.05)	
EF ≤ 30%	7.4	15.8	0.44 (0.28–0.70)	0.75
EF 31–35%	6.4	11.4	0.54 (0.17-1.74)	
Ischemic cardiomyopathy	7.9	19.4	0.37 (0.22–0.62)	0.054
Non-ischemic cardiomyopathy	6.3	6.9	0.92 (0.43–1.97)	
COPD	8.5	21.0	0.39 (0.14–1.07)	0.63
No COPD	7.0	13.2	0.50 (0.31–0.81)	
Cancer	6.3	23.1	0.25 (0.03–1.87)	0.50
No cancer	7.3	13.6	0.51 (0.33–0.79)	
Atrial fibrillation	5.5	21.3	0.24 (0.10–0.54)	0.036
No atrial fibrillation	8.2	11.7	0.67 (0.40–1.11)	
Diabetes	9.3	18.0	0.49 (0.27–0.89)	0.88
No diabetes	5.9	12.2	0.45 (0.24–0.85)	
Chronic renal insufficiency	12.9	27.6	0.41 (0.22–0.74)	0.62
No renal insufficiency	4.9	9.5	0.51 (0.27–0.94)	

Data are presented as Kaplan–Meier estimates of 1-year mortality unless otherwise stated

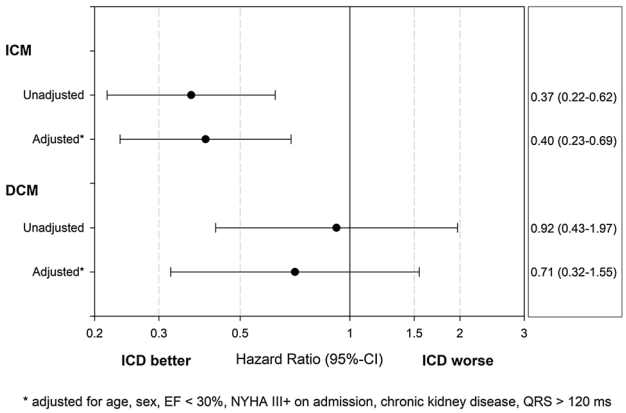


Fig. 3 Hazard ratio for mortality among patients with and without ischemic cardiac disease unadjusted and adjusted to ager, gender, NYHA class, ejection fraction, renal disease, and QRS width

Corresponding to findings of Amit et al. [14], we did not observe a difference of mortality between men and women. In our cohort, nearly half of the patients were treated with a CRT system that is known to be more favourable in outcome among women [8, 9] compared to ICD with a single ventricular lead [10, 11]. This could explain the discrepancy.

For the future, analysis of subgroups of patients with non-ischemic cardiomyopathy may identify patients with a high risk of SCD who may benefit from ICD and subgroups with a high risk of non-cardiac death that may not profit from an additional ICD therapy. Clinical and electrocardiographic scores [15, 16] and MRI characterization of arrhythmogenic substrate [17] are currently under scientific evaluation to differentiate beneficiaries from non-beneficiaries.

Limitations

The most important limitation of our study is the non-randomized design. The EVITA-HF registry shows the real world of mortality among patients with heart failure with and without implanted ICD for primary prevention of SCD. The results cannot be interpreted in a confirmatory sense.

Follow-up was limited to 1 year being much shorter compared to the randomized trials such as DANISH. A shorter follow-up may have advantages in non-randomized studies, because non-randomized groups have a higher probability that the prevalence of limiting diseases differs between analysed groups resulting in a higher mortality. The length of follow-up does not allow any conclusion about the long-term or life-long effect of an ICD therapy among patients with ischemic and non-ischemic cardiomyopathy.

The EVITA-HF registry could not differentiate between cardiac and non-cardiac death and gave no information about

appropriate and inappropriate antitachycardic therapies. The differentiation of cardiac and non-cardiac death seems not to be of great importance as the DANISH trial showed a significant reduction of cardiac death by adding an ICD but a significant increase in overall deaths among patients with implanted ICD [5].

The non-ICD group had a disadvantage in treatment, because not one patient received a CRT pacemaker, whereas 26.5% of these patients in the non-ICD group showed an LBBB and low ejection fraction. This could explain the higher mortality in the subgroup of patients with ischemic cardiomyopathy, but does not affect the conclusion for patients with non-ischemic cardiomyopathy.

The EVITA-HF registry and the DANISH trial were initiated at a time when the new angiotensin-receptor neprilysin inhibitor that has proven to reduce mortality among patients with systolic heart failure [18, 19] was not available. Therefore, it is unknown which effect a treatment would have added.

Conclusions

In a real-world setting, no benefit was evident for patients with non-ischemic cardiomyopathy and reduced left ventricular ejection fraction by adding ICD therapy in a short-term follow-up of 12 months in contrast to patients with ischemic cardiomyopathy.

References

1. Priori SG, Blomström-Lundqvist C, Mazzanti A, Blom N, Borggrefe M, Camm J, Elliott PM, Fitzsimons D, Hatala R, Hindricks G, Kirchhof P, Kjeldsen K, Kuck KH, Hernandez-Madrid A, Nikolaou N, Norekvål TM, Spaulding C, Van Veldhuisen DJ (2015) 2015 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: the Task Force for the Management of Patients with Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death of the European Society of Cardiology (ESC). Eur Heart J 36(41):2793–2867
2. Bardy GH, Lee KL, Mark DB, Poole JE, Packer DL, Boineau R, Domanski M, Troutman C, Anderson J, Johnson G, McNulty SE, Clapp-Channing N, Davidson-Ray LD, Fraulo ES, Fishbein DP, Luceri RM, Ip JH (2005) Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT) Investigators: amiodarone or an implantable cardioverter-defibrillator for congestive heart failure. N Engl J Med 352:225–237
3. Kadish A, Dyer A, Daubert JP, Quigg R, Estes NA, Anderson KP, Calkins H, Hoch D, Goldberger J, Shalaby A, Sanders WE, Schaechter A, Levine JH (2004) Defibrillators in Non-Ischemic Cardiomyopathy Treatment Evaluation Investigators. Prophylactic defibrillator implantation in patients with nonischemic dilated cardiomyopathy. N Engl J Med 350:2151–2158
4. Boveda S, Narayanan K, Jacob S, Providencia R, Beganton F, Algalarrondo V, Defaye P, Perier MC, Sadoul N, Piot O, Klug D, Gras D, Fauchier L, Bordachar P, Babuty D, Deharo JC, Leclercq C, Marijon E; DAI-PP Investigators (2017) Temporal trends over a decade of defibrillator therapy for primary prevention in community practice. J Cardiovasc Electrophysiol 28(6):666–673. https://doi.org/10.1111/jce.13198
5. Køber L, Thune JJ, Nielsen JC, Haarbo J, Videbæk L, Korup E, Jensen G, Hildebrandt P, Steffensen FH, Bruun NE, Eiskjær H, Brandes A, Thøgersen AM, Gustafsson F, Egstrup K, Videbæk R, Hassager C, Svendsen JH, Høfsten DE, Torp-Pedersen C, Pehrson S, DANISH Investigators (2016) Defibrillator Implantation in Patients with Nonischemic Systolic Heart Failure. N Engl J Med 375(13):1221–1230
6. Shun-Shin MJ, Zheng SL, Cole GD, Howard JP, Whinnett ZI, Francis DP (2017) Implantable cardioverter defibrillators for primary prevention of death in left ventricular dysfunction with and without ischaemic heart disease: a meta-analysis of 8567 patients in the 11 trials. Eur Heart J. 38(22):1738–1746
7. Wolff G, Lin Y, Karathanos A, Brockmeyer M, Wolters S, Nowak B, Fürnkranz A, Makimoto H, Kelm M, Schulze V (2017) Implantable cardioverter/defibrillators for primary prevention in dilated cardiomyopathy post-DANISH: an updated meta-analysis and systematic review of randomized controlled trials. Clin Res Cardiol 106(7):501–513
8. Moss AJ, Hall WJ, Cannom DS, Klein H, Brown MW, Daubert JP, Estes NAM III, Foster E, Greenberg H, Higgins SL, Pfeffer MA, Solomon SD, Wilber D, Zareba W, for the MADIT-CRT Trial Investigators (2009) Cardiac-resynchronization therapy of the prevention of heart-failure events. N Engl J Med 361:1329–1338
9. Cleland JG, Daubert JC, Erdmann E, Freemantle N, Gras D, Kappenberger L, Tavazzi L, for the Cardiac Resynchronization-Heart Failure (CARE-HF) Study Investigators (2005) The effect of cardiac resynchronization on morbidity and mortality in heart failure. N Engl J Med 352:1539–1549
10. Tang ASL, Wells G, Talajic M, Arnold MO, Sheldon R, Connolly S, Hohnloser SH, Nichol G, Birnie DH, Sapp JL, Yee R, Healey JS, Rouleau JL, for the RAFT Investigators (2010) Cardiacresynchronization therapy for mild-to-moderate heart failure. N Engl J Med. 363:2385–2395
11. Moss AJ, Zareba W, Hall WJ, Klein H, Wilber DJ, Cannom DS, Daubert JP, Higgins SL, Brown MW, Andrews ML (2002) Prophylactic implantation of a defibrillator in patients with myocardial infarction and reduced ejection fraction. N Engl J Med 346:877–883
12. Bristow MR, Saxon LA, Boehmer J, Krueger S, Kass DA, De Marco T, Carson P, DiCarlo L, DeMets D, White BG, DeVries DW, Feldman AM, Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure (COMPANION) Investigators (2004) Cardiac resynchronization therapy with or without an implantable defibrillator in advanced chronic heart failure. N Engl J Med 350:2140–2150
13. Bilchick KC, Stukenborg GJ, Kamath S, Cheng A (2012) Prediction of mortality in clinical practice for medicare patients undergoing defibrillator implantation for primary prevention of sudden cardiac death. J Am Coll Cardiol 60(17):1647–1655
14. Amit G, Suleiman M, Konstantino Y, Luria D, Kazatsker M, Chetboun I, Haim M, Gavrielov-Yusim N, Goldenberg I, Glikson M, Israeli Working Group on Pacing and Electrophysiology (2014) Sex differences in implantable cardioverter-defibrillator implantation indications and outcomes: lessons from the Nationwide Israeli-ICD Registry. Europace. 16(8):1175–1180
15. Providência R, Boveda S, Lambiase P, Defaye P, Algalarrondo V, Sadoul N, Piot O, Klug D, Perier MC, Bouzeman A, Gras D, Fauchier L, Bordachar P, Babuty D, Deharo JC, Leclercq C,

Marijon E, on behalf of the DAI-PP Investigators (2015) Prediction of nonarrhythmic mortality in primary prevention implantable cardioverter-defibrillator patients with ischemic and nonischemic cardiomyopathy. Am Coll Cardiol EP 1–2:29–37

16. Grett M, Christ M, Röing Gen Nölke JP, Trappe HJ (2017) ECG score to predict ICD therapies in patients with nonischemic cardiomyopathy and primary prophylactic CRT-D. Herzschrittmacherther Elektrophysiol. 28(1):48–53
17. Gao P, Yee R, Gula L, Krahn AD, Skanes A, Leong-Sit P, Klein GJ, Stirrat J, Fine N, Pallaveshi L, Wisenberg G, Thompson TR, Prato F, Drangova M, White JA (2012) Prediction of arrhythmic events in ischemic and dilated cardiomyopathy patients referred for implantable cardiac defibrillator: evaluation of multiple scar quantification measures for late gadolinium enhancement magnetic resonance imaging. Circ Cardiovasc Imaging 5(4):448–456
18. Solomon SD, Zile M, Pieske B, Voors A, Shah A, Kraigher-Krainer E, Shi V, Bransford T, Takeuchi M, Gong J, Lefkowitz M, Packer M, McMurray JJ (2012) Prospective comparison of ARNI with ARB on Management Of heart failUre with preserved ejectioN fracTion (PARAMOUNT) Investigators: the angiotensin receptor neprilysin inhibitor LCZ696 in heart failure with preserved ejection fraction: a phase 2 double-blind randomised controlled trial. Lancet 380(9851):1387–1395
19. Böhm M, Young R, Jhund PS, Solomon SD, Gong J, Lefkowitz MP, Rizkala AR, Rouleau JL, Shi VC, Swedberg K, Zile MR, Packer M, McMurray JJ (2017) Systolic blood pressure, cardiovascular outcomes and efficacy and safety of sacubitril/valsartan (LCZ696) in patients with chronic heart failure and reduced ejection fraction: results from PARADIGM-HF. Eur Heart J 38(15):1132–1143