ORIGINAL RESEARCH ARTICLE

Association between mortality and implantable cardioverter-defibrillators by aetiology of heart failure: a propensity-matched analysis of the WARCEF trial

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Abstract

Aims There is debate on whether the beneficial effect of implantable cardioverter-defibrillators (ICDs) is attenuated in patients with non-ischaemic cardiomyopathy (NICM). We assess whether any ICD benefit differs between patients with NICM and those with ischaemic cardiomyopathy (ICM), using data from the Warfarin versus Aspirin in Reduced Cardiac Ejection Fraction (WARCEF) trial.

Methods and results We performed a post hoc analysis using WARCEF (N = 2293; ICM, n = 991 vs. NICM, n = 1302), where participants received optimal medical treatment. We developed stratified propensity scores for having an ICD at baseline using 41 demographic and clinical variables and created 1:2 propensity-matched cohorts separately for ICM patients with ICD (N = 223 with ICD; N = 446 matched) and NICM patients (N = 195 with ICD; N = 390 matched). We constructed a Cox proportional hazards model to assess the effect of ICD status on mortality for patients with ICM and those with NICM and tested the interaction between ICD status and aetiology of heart failure. During mean follow-up of 3.5 ± 1.8 years, 527 patients died. The presence of ICD was associated with a lower risk of all-cause death among those with ICM (hazard ratio: 0.640; 95% confidence interval: 0.448 to 0.915; P = 0.015) but not among those with NICM (hazard ratio: 0.984; 95% confidence interval: 0.641 to 1.509; P = 0.941). There was weak evidence of interaction between ICD status and the aetiology of heart failure (P = 0.131).

Conclusions The presence of ICD is associated with a survival benefit in patients with ICM but not in those with NICM.

Keywords Heart failure with reduced ejection fraction; Implantable cardioverter-defibrillator; Non-ischaemic cardiomyopathy; Propensity score matching

Introduction

The 2013 American College of Cardiology/American Heart Association Guidelines for the Management of Heart Failure (HF) and the 2016 European Society of Cardiology Guidelines for the Diagnosis and Treatment of Acute and Chronic HF recommend implantable cardioverter-defibrillator (ICD) implantation for prevention of death in patients with HF with reduced ejection fraction.[1,2] While there is considerable evidence that ICDs prevent death in patients with ischaemic cardiomyopathy (ICM),[3,4] the evidence for patients with non-ischaemic cardiomyopathy (NICM) is less robust.

The Defibrillators in Non-Ischaemic Cardiomyopathy Treatment Evaluation (DEFINITE) trial[5] did not show a significant survival benefit for ICD, though there was a trend towards mortality reduction. Similarly, although the Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT) demonstrated improved mortality with ICD therapy for patients with cardiomyopathy, the subgroup analysis for non-ischaemic patients showed attenuated benefit.[4] More recently, the Danish Study to Assess the Efficacy of ICDs in Patients with Non-Ischaemic Systolic Heart Failure on Mortality (DANISH) trial[6] failed to show a survival benefit for ICDs compared with optimal medical therapy. However, updated meta-analyses[7–11] continue to suggest a survival benefit for ICD implantation among patients with NICM, a recommendation that is reflected in current guidelines. For these reasons, there is considerable interest in additional analyses of whether the impact of having an ICD may differ depending on HF aetiology.[12]

The Warfarin versus Aspirin in Reduced Cardiac Ejection Fraction (WARCEF) trial, a large randomized, clinical trial of patients with HF with reduced ejection fraction that tested the effect of warfarin vs. aspirin on death and stroke, provides an important opportunity to address this critical question. We conducted an analysis using WARCEF data to further elucidate the relation between ICD status and mortality for HF patients with ICM and NICM, using a propensity score-based approach to limit confounding.

Methods

Study participants

The investigation conforms with the principles outlined in the Declaration of Helsinki. Details of the WARCEF trial have been published previously.[13] A total of 2305 patients with left ventricular ejection fraction ≤ 35% in sinus rhythm were randomly assigned to warfarin (target international normalized ratio 2.75, with an acceptable target range of 2.0 to 3.5) or aspirin (325 mg/day). Left ventricular ejection fraction was measured by radionuclide ventriculography, left ventriculography, or quantitative echocardiography. Based on those

findings and patients' past medical history, the aetiology of HF was determined by clinical judgement of each local site. Patients were enrolled at 168 centres in 11 countries between October 2002 and January 2010. The mean follow-up time was 3.5 ± 1.8 years. Patients who had a clear indication for warfarin or aspirin were not eligible. Additional eligibility criteria were a modified Rankin score of 4 or less (on a scale of 0 to 6, with higher scores indicating more severe disability) and planned treatment with a beta-blocker, an angiotensin-converting enzyme (ACE)-Inhibitor [or, if the side-effect profile with ACE-Inhibitors was unacceptable, with an angiotensin II receptor blocker (ARB)], or hydralazine and nitrates. Patients were ineligible if they had a condition that conferred a high risk of cardiac embolism, such as atrial fibrillation, a mechanical cardiac valve, endocarditis, or an intracardiac mobile or pedunculated thrombus.

For this analysis, we excluded 12 enrolled patients because of lack of data on either aetiology of HF or ICD status at baseline (*Figure 1*). Information regarding indications for ICD, and whether or not the patients received concurrent cardiac resynchronization therapy (CRT), was not recorded in WARCEF.

Assessment of outcomes

In the WARCEF trial, an independent endpoint adjudication committee, whose members were unaware of the treatment assignment, adjudicated major clinical outcomes. The committee adjudicated cause of death based on the standardized narrative reports on patients' status preceding death. If applicable and available, discharge summary; detailed report by physician, nursing staff, or family; autopsy report; death certificate; and other materials were considered as materials for adjudication. Post-mortem ICD interrogation was not always available but was considered in adjudication process if it was available. In the current analysis, the primary outcome was all-cause death, and the secondary outcomes were cardiovascular death and sudden death. Deaths were adjudicated as having a cardiovascular or non-cardiovascular cause, and cardiovascular deaths were then adjudicated as sudden or other types. The adjudication was not blinded to ICD status.

Statistical analysis

Baseline characteristics were assessed by ICD status and for ICM and NICM groups separately. Continuous variables are presented as mean ± SD and categorical variables as frequencies and percentages. They were considered balanced if the standardized bias was less than 0.25.[14] This is the difference in means (for continuous variables) or proportions (for each

Figure 1 Overview of the study cohort. ICD, implantable cardioverter-defibrillator.
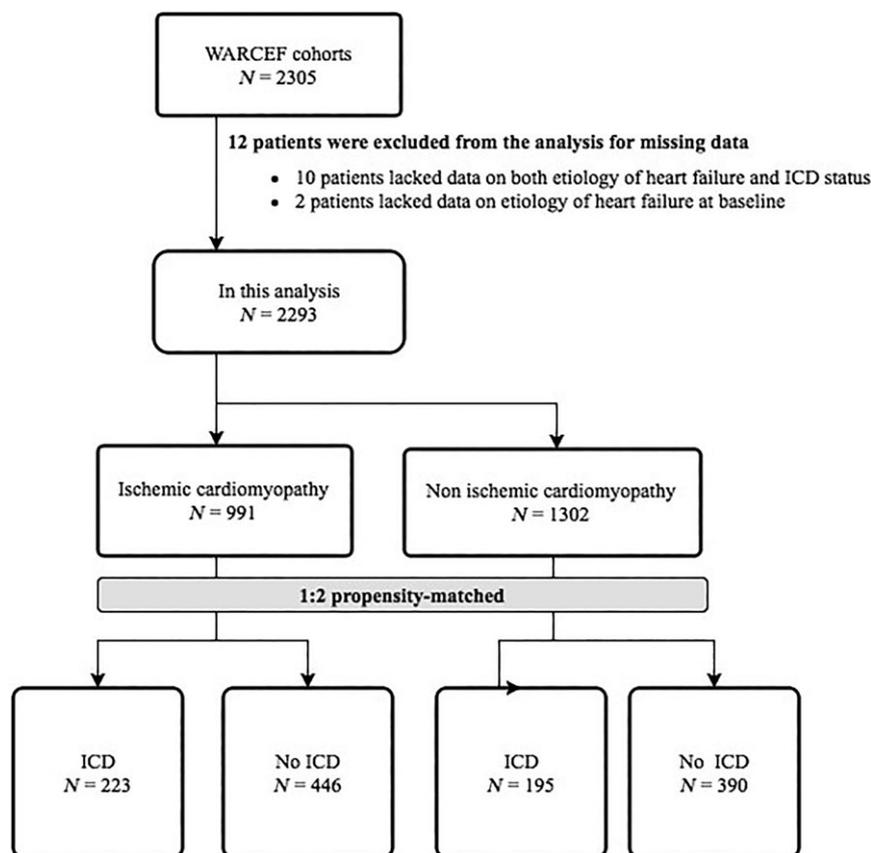
category of a categorical variable) divided by the pooled standard deviation.

A propensity score matching approach was used to adjust for potential confounding in the comparison of patients who had or did not have implanted ICDs at randomization.[15,16] The goal is to assess whether any ICD benefit differs between NICM and ICM patients, rather than to measure ICD benefit in the overall population. We therefore match ICD to non-ICD patients within the NICM stratum and, separately, ICD to non-ICD patients within the ICM stratum.The propensity score model initially included 41 patient covariates, NICM vs. ICM status, and the interaction of this status with each of the covariates in a logistic regression model. To avoid overfitting, the final model included the subset of predictor variables that optimized the Akaike information criterion in a stepwise procedure.

We implemented the matching procedure with the R package MatchIt.[17] We first selected matched controls using random selection within a calliper width of SD 0.1 on the logit scale. That is, for each case, we considered the set of controls whose logit propensity score was within 0.1 SDs of the logit propensity score of the case and randomly selected two from the set as the matched controls. If no matches were available within the calliper, we used the nearest neighbour control to match the case. In this way, we were able to match all cases to controls within each stratum.

To assess the association between ICD status and outcomes by aetiology of HF and to determine whether aetiology of HF modulated the association between ICD status and mortality, we constructed Cox proportional hazards models including ICD, ICM, and their interaction as covariates separately for all-cause death, cardiovascular death, and sudden death. Time zero was defined as the time of randomization in the survival analyses. Robust variance estimators were used to adjust for any clustering caused by the matching. Two-tailed P values < 0.05 were considered statistically significant. All analyses were performed using SAS (version 9.4; SAS Institute, Cary, North Carolina) and R.

Results

Baseline characteristics

The flowchart for the analysis procedure is presented in *Figure 1*. Of the 2293 WARCEF participants, 418 had an ICD at time of enrolment (ICM, $N = 223$; NICM, $N = 195$)

(*Figure 1*). Before matching, ICM patients with ICDs were more likely to be from high-income countries (i.e. excluding Argentina and Ukraine); younger; have higher education, lower systolic blood pressure, alcohol consumption, ARB, lower sodium level; and less likely to have ACE-Inhibitor, as compared with ICM patients without ICDs. NICM patients with ICDs were more likely to be from high-income countries, have lower systolic blood pressure, and have a higher prevalence of past medical history of atrial fibrillation, have longer distance on 6 min walk test, and were more likely to take diuretics, as compared with NICM patients without ICDs (*Table 1*). We matched 205 ICM cases to controls and 189 NICM cases to controls using the calliper criterion and 18 ICM cases to controls and 6 NICM cases to controls using the nearest neighbour procedure. The standardized biases of all baseline covariates were less than 0.25 after matching (*Table 2*). Variables with high or moderate missingness include aldosterone blocker (32%), statin (21%), previous aspirin use (19%), 6 min walk (7%), and haemoglobin (6%). Missingness in other variables was negligible. Aldosterone blocker and 6 min walk entered the final propensity score model, with missing values imputed by mode and mean, respectively.

Primary outcome: All-cause death

Kaplan–Meier curves for all-cause death are presented in *Figure 2*. Results from the Cox models are presented in *Table 3*. There were 279 deaths in the current analysis (205 deaths among those without ICD and 74 deaths among those with ICD). For the 585 patients with NICM in the matched cohort, a total of 102 (17.4%) died during the follow-up. These include 31 (15.9%) of the 195 patients with ICDs at baseline and 71 (18.2%) of the 390 matched patients who did not have ICDs. ICD status did not predict mortality [hazard ratio (HR): 0.984; 95% confidence interval (CI): 0.641 to 1.509; $P = 0.941$].

Of the 669 patients with ICM in the matched cohort, 177 (26.5%) died during follow-up. These included 43 (19.3%) of the 223 patients with ICDs at baseline and 134 (30.0%) of the 446 matched patients who did not have ICDs. Having an ICD at baseline was significantly associated with lower mortality (HR: 0.640; 95% CI: 0.448 to 0.915; $P = 0.015$). There was a weak evidence of interaction between ICD status and the aetiology of HF ($P = 0.131$).

Secondary outcomes: Cardiovascular and sudden death

Of 279 deaths, a total of 184 (65.9%) were classified as cardiovascular (133 deaths among patients without ICD and 51 deaths among those with ICD). The relation between ICD status and cardiovascular mortality was similar to its relation

with all-cause mortality, though it did not achieve statistical significance in either subgroups (for ICM, HR: 0.713, 95% CI: 0.473 to 1.075, $P = 0.107$; for NICM, HR: 0.967, 95% CI: 0.578 to 1.618; $P = 0.898$; interaction $P = 0.365$).

A total of 97 deaths were classified as sudden (77 deaths among those without ICD and 20 deaths among those with ICD). The association between having ICD and sudden death was not significant among patients with ICM but was significant among patients with NICM (for ICM, HR: 0.673, 95% CI: 0.385 to 1.176, $P = 0.164$; patients with NICM, HR: 0.246, 95% CI: 0.077 to 0.781; $P = 0.017$; interaction $P = 0.124$).

Discussion

In this retrospective, propensity-matched analysis of the WARCEF trial, we found that the presence of ICD at baseline was associated with a lower risk of all-cause death among those with ICM but not among those with NICM. There was weak evidence of an interaction effect for ICD status and whether a patient had NICM or ICM. These findings are consistent with prior studies showing that the benefit of ICDs is more pronounced in patients with ICM, but ICDs may be less effective in patients with NICM.

Our findings are broadly consistent with the recent literature[6,12] suggesting that the effect of ICD may be attenuated in patients with NICM. Compared with ICM, NICM is known to be associated with a better left ventricular reverse remodelling,[18] a better clinical outcome,[19] and a lower background risk for ventricular arrhythmia.[20,21] Besides these differences between ICM and NICM, the evidence for the primary prevention of ICD among patients with NICM is less robust.[4–6] The recent DANISH trial, which randomized 1116 patients with NICM to receive conventional therapy or an ICD, demonstrated no significant association between the presence of ICD and all-cause mortality among NICM patients (HR: 0.87; 95% CI: 0.68 to 1.12; $P = 0.28$). Similarly to the WARCEF population, the rates of optimal medical therapy in DANISH trial participants were high. Studies have consistently shown that the optimal medical therapies, such as ACE-Inhibitors,[22] ARBs,[23] beta-blockers,[24] mineralocorticoid-receptor antagonists,[25] or combinations of these medications,[26] all reduce the rate of cardiovascular death or sudden death. It is, therefore, possible that sudden death in medically optimized HF patients may be less common, leading to diminished benefit from ICDs.

It may be surprising that in our analysis, ICD status predicted mortality in patients with ICM, but its association on sudden death was not found to be statistically significant. Conversely, ICD status did not predict mortality in patients with NICM in our analysis but did have a strong association with sudden death. However, these results regarding sudden death must be interpreted with caution, as the adjudication

Table 1 Patient characteristics before propensity score matching

Characteristics	Ischaemic			Non-ischaemic		
	ICD (n = 223)	No ICD (n = 768)	Standardized bias	ICD (n = 195)	No ICD (n = 1107)	Standardized bias
Treatment arm						
Warfarin	108/223 (48.4)	380/768 (49.5)	0.021	104/195 (53.3)	546/1107 (49.3)	0.08
Demographics						
Middle-income countries (Argentina or Ukraine)	3/223 (1.3)	98/768 (12.8)	0.377	3/195 (1.5)	103/1107 (9.3)	0.284
Age, years	61.1 ± 10.0	63.8 ± 10.2	0.271	58.1 ± 12.2	59.1 ± 11.8	0.09
Age categories						
<60	92/223 (41.3)	265/768 (34.5)	0.141	107/195 (54.9)	558/1107 (50.4)	0.089
60–74	114/223 (51.1)	374/768 (48.7)	0.048	72/195 (36.9)	432/1107 (39.0)	0.043
>74	17/223 (7.6)	129/768 (16.8)	0.259	16/195 (8.2)	117/1107 (10.6)	0.078
Male sex	199/223 (89.2)	655/768 (85.3)	0.114	154/195 (79.0)	829/1107 (74.9)	0.095
Race or ethnic group						
Non-Hispanic White	177/223 (79.4)	604/768 (78.6)	0.018	139/195 (71.3)	809/1107 (73.1)	0.04
Non-Hispanic Black	26/223 (11.7)	65/768 (8.5)	0.111	41/195 (21.0)	198/1107 (17.9)	0.081
Hispanic	13/223 (5.8)	72/768 (9.4)	0.127	9/195 (4.6)	72/1107 (6.5)	0.078
Other	7/223 (3.1)	27/768 (3.5)	0.021	6/195 (3.1)	28/1107 (2.5)	0.034
Educational level						
< High school	73/221 (33.0)	376/767 (49.0)	0.321	72/195 (36.9)	469/1106 (42.4)	0.111
High school graduate or some college	109/221 (49.3)	284/767 (37.0)	0.251	95/195 (48.7)	455/1106 (41.1)	0.153
College graduate or postgraduate	39/221 (17.6)	107/767 (14.0)	0.104	28/195 (14.4)	182/1106 (16.5)	0.057
Body measurement and vital statistics						
Height, cm	172.4 ± 8.9	171.5 ± 9.0	0.099	172.9 ± 9.5	171.4 ± 9.5	0.166
Weight, kg	86.5 ± 16.5	84.6 ± 17.6	0.111	89.0 ± 21.5	86.5 ± 20.8	0.118
Body mass index mean	29.1 ± 5.2	28.7 ± 5.4	0.07	29.7 ± 7.2	29.3 ± 6.3	0.067
Body mass index distribution						
<25	50/222 (22.5)	186/766 (24.3)	0.041	52/193 (26.9)	271/1098 (24.7)	0.052
25–30	88/222 (39.6)	325/766 (42.4)	0.057	57/193 (29.5)	411/1098 (37.4)	0.164
>30	84/222 (37.8)	255/766 (33.3)	0.096	84/193 (43.5)	416/1098 (37.9)	0.116
Systolic BP, mmHg	119.1 ± 19.3	124.4 ± 17.6	0.29	119.9 ± 18.6	125.3 ± 19.4	0.278
Pulse, beats/min	69.6 ± 10.1	71.2 ± 11.6	0.141	71.9 ± 11.3	73.0 ± 12.5	0.119
Past medical history/co-morbidities						
Hypertension	141/216 (65.3)	492/748 (65.8)	0.01	107/187 (57.2)	623/1076 (57.9)	0.014
Diabetes mellitus	92/223 (41.3)	283/768 (36.8)	0.091	50/195 (25.6)	297/1107 (26.8)	0.027
Atrial fibrillation	13/223 (5.8)	23/768 (3.0)	0.152	17/195 (8.7)	33/1107 (3.0)	0.299
Peripheral vascular disease	42/223 (18.8)	119/768 (15.5)	0.091	14/195 (7.2)	86/1107 (7.8)	0.022
Prior stroke or TIA	29/223 (13.0)	104/768 (13.5)	0.016	19/195 (9.7)	142/1106 (12.8)	0.094
Alcohol and smoking						
Smoking status						
Current smoker	35/222 (15.8)	138/767 (18.0)	0.059	38/195 (19.5)	196/1106 (17.7)	0.046
Former smoker	148/222 (66.7)	417/767 (54.4)	0.249	92/195 (47.2)	520/1106 (47.0)	0.003
Never smoked	39/222 (17.6)	212/767 (27.6)	0.231	65/195 (33.3)	390/1106 (35.3)	0.04
Alcohol consumption						
Current consumption, >2 oz/day	65/223 (29.1)	179/768 (23.3)	0.136	48/195 (24.6)	279/1106 (25.2)	0.014
Previous consumption, >2 oz/day	71/223 (31.8)	149/768 (19.4)	0.299	45/195 (23.1)	241/1106 (21.8)	0.031
Never consumed alcohol	87/223 (39.0)	440/768 (57.3)	0.366	102/195 (52.3)	586/1106 (53.0)	0.014

(Continues)

Table 1 (continued)

Characteristics	Ischaemic			Non-ischaemic		
	ICD (n = 223)	No ICD (n = 768)	Standardized bias	ICD (n = 195)	No ICD (n = 1107)	Standardized bias
Status of heart failure						
NYHA classification						
Class I	26/223 (11.7)	102/767 (13.3)	0.049	27/193 (14.0)	160/1102 (14.5)	0.015
Class II	123/223 (55.2)	402/767 (52.4)	0.055	116/193 (60.1)	621/1102 (56.4)	0.076
Class III	73/223 (32.7)	254/767 (33.1)	0.008	48/193 (24.9)	305/1102 (27.7)	0.063
Class IV	1/223 (0.4)	9/767 (1.2)	0.073	2/193 (1.0)	16/1102 (1.5)	0.036
Ejection fraction, %	23.3 ± 6.8	25.0 ± 7.5	0.233	24.5 ± 7.3	24.7 ± 7.8	0.024
LVEF ≤ 20%	76/223 (34.1)	195/768 (25.4)	0.195	55/194 (28.4)	324/1106 (29.3)	0.021
Distance covered on 6 min walk, m	353.0 ± 126.6	341.4 ± 146.8	0.081	377.6 ± 124.4	352.8 ± 153.8	0.166
Baseline MMSE score	28.5 ± 2.0	28.4 ± 2.1	0.039	28.5 ± 2.0	28.6 ± 2.1	0.025
Baseline MLWHF score	37.5 ± 24.3	34.0 ± 22.5	0.153	32.9 ± 22.7	33.2 ± 24.4	0.011
Medications						
Aspirin or other antiplatelet agents	136/190 (71.6)	446/599 (74.5)	0.065	104/141 (73.8)	572/781 (73.2)	0.012
Warfarin or other oral anticoagulants	24/223 (10.8)	51/768 (6.6)	0.156	14/195 (7.2)	90/1107 (8.1)	0.035
ACE-Inhibitor	165/222 (74.3)	656/768 (85.4)	0.295	165/194 (85.1)	945/1105 (85.5)	0.013
ARB	57/221 (25.8)	112/768 (14.6)	0.298	32/193 (16.6)	174/1104 (15.8)	0.022
Beta-blocker	209/223 (93.7)	682/768 (88.8)	0.163	181/194 (93.3)	986/1105 (89.2)	0.135
Aldosterone blocker	85/146 (58.2)	283/472 (60.0)	0.035	80/130 (61.5)	362/594 (60.9)	0.012
Diuretic	185/223 (83.0)	614/768 (79.9)	0.076	168/194 (86.6)	884/1105 (80.0)	0.168
Statin	185/196 (94.4)	541/611 (88.5)	0.194	118/150 (78.7)	546/717 (76.2)	0.059
Lab data						
Creatinine, mg/dL	1.2 ± 0.3	1.2 ± 0.3	0.184	1.2 ± 0.3	1.1 ± 0.3	0.113
eGFR	64.5 ± 19.6	66.5 ± 19.9	0.099	69.2 ± 20.7	70.4 ± 21.0	0.054
Haemoglobin, g/dL	14.0 ± 1.8	14.1 ± 1.5	0.047	14.1 ± 1.5	14.1 ± 1.5	0.007
Sodium, mEq/L	138.2 ± 9.5	139.8 ± 3.2	0.294	139.6 ± 3.4	139.8 ± 3.3	0.062
WBC count, ×10^9/L	7.7 ± 2.0	7.5 ± 2.0	0.097	7.5 ± 2.4	7.4 ± 2.0	0.084

ACE-Inhibitor, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; BP, blood pressure; eGFR, estimated glomerular filtration rate; ICD, implantable cardio-defibrillator; LVEF, left ventricular ejection fraction; MLWHF, Minnesota Living with Heart Failure questionnaire; MMSE, Mini-Mental Scale Examination; NYHA, New York Heart Association; TIA, transient ischaemic attack; WBC, white blood cell.

Table 2 Patient characteristics after propensity matching

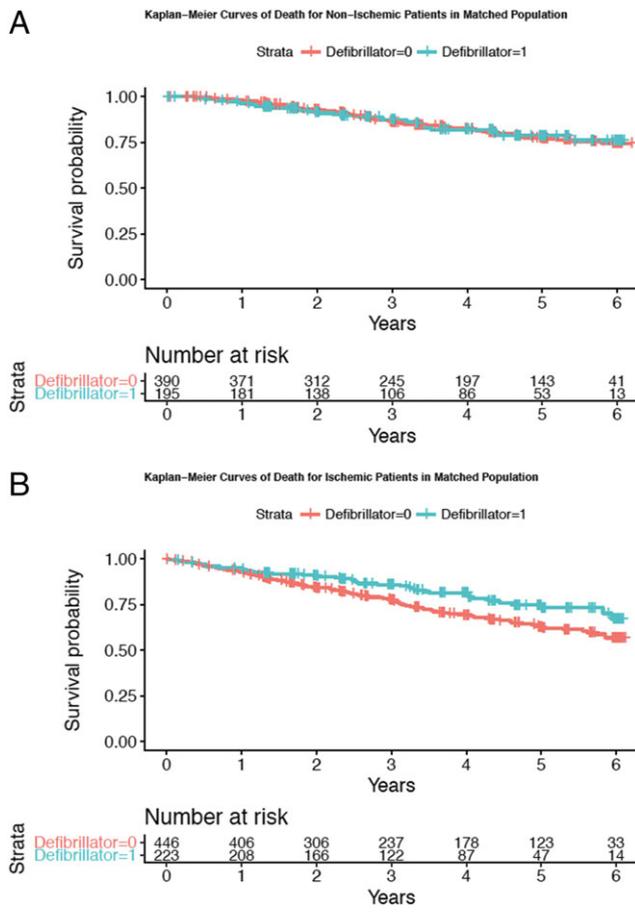| Variable	Ischaemic			Non-ischaemic		
	ICD (n = 223)	No ICD (n = 446)	Standardized bias	ICD (n = 195)	No ICD (n = 390)	Standardized bias
Treatment arm						
Warfarin	108/223 (48.4)	223/446 (50.0)	0.031	104/195 (53.3)	184/390 (47.2)	0.123
Demographics						
Middle-income countries (Argentina or Ukraine)	3/223 (1.3)	9/446 (2.0)	0.051	3/195 (1.5)	6/390 (1.5)	0
Age, years	61.1 ± 10.0	62.4 ± 9.6	0.135	58.1 ± 12.2	57.0 ± 11.7	0.091
Age categories						
<60	92/223 (41.3)	171/446 (38.3)	0.06	107/195 (54.9)	228/390 (58.5)	0.073
60–74	114/223 (51.1)	224/446 (50.2)	0.018	72/195 (36.9)	137/390 (35.1)	0.037
>74	17/223 (7.6)	51/446 (11.4)	0.126	16/195 (8.2)	25/390 (6.4)	0.07
Male sex	199/223 (89.2)	395/446 (88.6)	0.021	154/195 (79.0)	302/390 (77.4)	0.037
Race or ethnic group						
Non-Hispanic White	177/223 (79.4)	358/446 (80.3)	0.022	139/195 (71.3)	277/390 (71.0)	0.006
Non-Hispanic Black	26/223 (11.7)	49/446 (11.0)	0.021	41/195 (21.0)	88/390 (22.6)	0.037
Hispanic	13/223 (5.8)	19/446 (4.3)	0.074	9/195 (4.6)	16/390 (4.1)	0.025
Other	7/223 (3.1)	20/446 (4.5)	0.068	6/195 (3.1)	9/390 (2.3)	0.049
Educational level						
< High school	73/221 (33.0)	186/445 (41.8)	0.18	72/195 (36.9)	134/390 (34.4)	0.054
High school graduate or some college	109/221 (49.3)	196/445 (44.0)	0.106	95/195 (48.7)	191/390 (49.0)	0.005
College graduate or postgraduate	39/221 (17.6)	63/445 (14.2)	0.097	28/195 (14.4)	65/390 (16.7)	0.063
Body measurement and vital statistics						
Height, cm	172.4 ± 8.9	172.2 ± 9.2	0.023	172.9 ± 9.5	172.9 ± 9.2	0.002
Weight, kg	86.5 ± 16.5	86.1 ± 18.7	0.022	89.0 ± 21.5	89.5 ± 23.0	0.022
Body mass index mean	29.1 ± 5.2	29.0 ± 5.7	0.016	29.7 ± 7.2	29.7 ± 6.8	0
Body mass index distribution						
<25	50/222 (22.5)	111/445 (24.9)	0.057	52/193 (26.9)	103/387 (26.6)	0.007
25–30	88/222 (39.6)	176/445 (39.6)	0.002	57/193 (29.5)	120/387 (31.0)	0.032
>30	84/222 (37.8)	158/445 (35.5)	0.049	84/193 (43.5)	164/387 (42.4)	0.023
Systolic BP, mmHg	119.1 ± 19.3	120.9 ± 16.6	0.102	119.9 ± 18.6	121.7 ± 18.0	0.094
Pulse, beats/min	69.6 ± 10.1	70.3 ± 11.3	0.064	71.5 ± 11.3	71.4 ± 12.2	0.005
Co-morbidities						
Hypertension	141/216 (65.3)	274/427 (64.2)	0.023	107/187 (57.2)	217/374 (58.0)	0.016
Diabetes mellitus	92/223 (41.3)	178/446 (39.9)	0.027	50/195 (25.6)	96/390 (24.6)	0.024
Atrial fibrillation	13/223 (5.8)	20/446 (4.5)	0.062	17/195 (8.7)	24/390 (6.2)	0.1
Peripheral vascular disease	42/223 (18.8)	70/446 (15.7)	0.084	14/195 (7.2)	33/390 (8.5)	0.047
Prior stroke or TIA	29/223 (13.0)	69/446 (15.5)	0.07	19/195 (9.7)	43/389 (11.1)	0.043
Alcohol and smoking						
Smoking status						
Current smoker	35/222 (15.8)	76/445 (17.1)	0.035	38/195 (19.5)	73/390 (18.7)	0.02
Former smoker	148/222 (66.7)	281/445 (63.1)	0.073	92/195 (47.2)	177/390 (45.4)	0.036
Never smoked	39/222 (17.6)	88/445 (19.8)	0.056	65/195 (33.3)	140/390 (35.9)	0.054
Alcohol consumption						
Current consumption, >2 oz/day	65/223 (29.1)	130/446 (29.1)	0	48/195 (24.6)	107/390 (27.4)	0.064
Previous consumption, >2 oz/day	71/223 (31.8)	118/446 (26.5)	0.12	45/195 (23.1)	89/390 (22.8)	0.006
Never consumed alcohol	87/223 (39.0)	198/446 (44.4)	0.109	102/195 (52.3)	194/390 (49.7)	0.051

(Continues)

Table 2 (continued)

Variable	Ischaemic			Non-ischaemic		
	ICD (n = 223)	No ICD (n = 446)	Standardized bias	ICD (n = 195)	No ICD (n = 390)	Standardized bias
Status of heart failure						
NYHA classification						
Class I	26/223 (11.7)	64/445 (14.4)	0.08	27/193 (14.0)	56/389 (14.4)	0.012
Class II	123/223 (55.2)	229/445 (51.5)	0.074	116/193 (60.1)	235/389 (60.4)	0.006
Class III	73/223 (32.7)	149/445 (33.5)	0.016	48/193 (24.9)	93/389 (23.9)	0.022
Class IV	1/223 (0.4)	3/445 (0.7)	0.029	2/193 (1.0)	5/389 (1.3)	0.023
LVEF, %	23.3 ± 6.8	24.2 ± 7.6	0.117	24.5 ± 7.3	24.3 ± 7.2	0.031
LVEF ≤ 20%	76/223 (34.1)	139/446 (31.2)	0.062	55/194 (28.4)	111/390 (28.5)	0.002
Distance covered on a 6 min walk, m	353.0 ± 126.6	359.3 ± 151.4	0.044	377.6 ± 124.4	377.7 ± 155.4	0.001
Baseline MMSE score	28.5 ± 2.0	28.4 ± 2.0	0.019	28.5 ± 2.0	28.6 ± 2.1	0.029
Baseline MLWHF score	37.5 ± 24.3	34.2 ± 22.7	0.144	32.9 ± 22.7	32.1 ± 24.7	0.033
Medications						
Aspirin or other antiplatelet agents	136/190 (71.6)	248/344 (72.1)	0.011	104/141 (73.8)	196/273 (71.8)	0.044
Warfarin or other oral anticoagulants	24/223 (10.8)	37/446 (8.3)	0.086	14/195 (7.2)	34/390 (8.7)	0.056
ACE-Inhibitor	165/222 (74.3)	354/446 (79.4)	0.121	165/194 (85.1)	319/390 (81.8)	0.086
ARB	57/221 (25.8)	91/446 (20.4)	0.13	32/193 (16.6)	71/390 (18.2)	0.043
Beta-blocker	209/223 (93.7)	410/446 (91.9)	0.068	181/194 (93.3)	369/390 (94.6)	0.056
Aldosterone blocker	85/146 (58.2)	157/276 (56.9)	0.027	80/130 (61.5)	129/229 (56.3)	0.106
Diuretic	185/223 (83.0)	370/446 (83.0)	0	168/194 (86.6)	339/390 (86.9)	0.01
Statin	185/196 (94.4)	319/352 (90.6)	0.138	118/150 (78.7)	187/256 (73.0)	0.13
Lab data						
Creatinine, mg/dL	1.2 ± 0.3	1.2 ± 0.3	0.124	1.2 ± 0.3	1.2 ± 0.4	0.003
eGFR	64.5 ± 19.6	66.4 ± 19.9	0.094	69.2 ± 20.7	69.7 ± 20.4	0.023
Haemoglobin, g/dL	14.0 ± 1.8	14.0 ± 1.6	0.024	14.1 ± 1.5	14.1 ± 1.5	0.041
Sodium, mEq/L	138.2 ± 3.2	139.2 ± 3.2	0.161	139.6 ± 3.4	139.5 ± 3.3	0.014
WBC count, ×10^9/L	7.7 ± 2.0	7.7 ± 2.1	0.033	7.5 ± 2.4	7.5 ± 2.2	0.019

ACE-Inhibitor, angiotensin-converting enzyme inhibitor; ARB, Angiotensin II receptor blocker; BP, blood pressure; eGFR, estimated glomerular filtration rate; ICD, implantable cardio-defibrillator; LVEF, left ventricular ejection fraction; MLWHF, Minnesota Living with Heart Failure questionnaire; MMSE, Mini-Mental Scale Examination; NYHA, New York Heart Association; TIA, transient ischaemic attack; WBC, white blood cell.
Values are mean ± SD or n (%).

Figure 2 Kaplan–Meier curves showing the survival of those with and without an implantable cardioverter-defibrillator: (A) patients with non-ischaemic heart failure and (B) patients with ischaemic heart failure.

patients younger than 70 years of age.[27] Compared with the DANISH trial in which the median age was 63 years old, NICM patients in the WARCEF trial were considerably younger, with a median age of 58 years old. It is therefore unclear if age or other clinical risk predictors might be helpful in guiding decision for ICD implantation in patients with NICM. Furthermore, statistical power remains a concern for both the DANISH trial and our analysis, as recent meta-analyses continue to suggest a survival benefit for ICD implantation among patients with NICM[7–11] even after the inclusion of the DANISH trial. Nonetheless, differences in patient clinical characteristics and contemporary background medical therapy may affect the validity of these findings, and thereby, future studies with carefully defined patient selection criteria will be needed to clarify whether ICD implantation can be beneficial in subgroups of patients with NICM.[28]

Limitations

First, our study was retrospective and therefore necessarily hypothesis generating. ICD status was not randomly assigned, which raised the potential for indication bias. To address this, we used a propensity-matching approach, which can address confounding from known baseline covariates. However, residual confounding may still be present, because the decision to place an ICD is often nuanced and incorporates additional unmeasured patient clinical and psychosocial characteristics. Second, past medical history of cardiac arrest was not recorded at baseline, and it is possible that a small number of patients received ICDs for secondary prevention. However, these patients are more likely to benefit from ICDs,[29] which therefore would not affect our null finding for patients with NICM. Third, we did not collect detailed information on CRT status at baseline, or whether patients received ICD and/or CRT during follow-up. We also did not collect electrocardiogram data such as QRS duration or presence of left bundle branch block. We therefore were not able to control for these potential confounders. Fourth, WARCEF was limited to patients in sinus rhythm at baseline, which may limit the external validity of our analysis. Fifth, our propensity matching led to exclusion of more than half of the patients with NICM from the current analysis, and our findings therefore must be interpreted cautiously.

in WARCEF was not blinded to defibrillator status, and the number of sudden death events was small. In addition, the DANISH trial[6] has shown that in the populations with NICM in which ICDs did not reduce overall mortality, ICDs may nonetheless have an apparent effect on sudden death (HR: 0.50; 95% CI: 0.31 to 0.82; P = 0.005).

Despite our findings, there remains uncertainty regarding the current recommendation for ICD implantation in patients with NICM. Subsequent analysis of the DANISH trial has shown that ICD implantation may be beneficial in NICM

Table 3 Hazard ratio to assess the effect of ICD status on mortality for those with ICM and with NICM based on the matched sample

	Patients with ICM		Patients with NICM		Interaction
	Hazard ratio (95% CI)	*P* value	Hazard ratio (95% CI)	*P* value	*P* value
All-cause death	0.640 (0.448–0.915)	0.015	0.984 (0.641–1.509)	0.941	0.131
Cardiovascular death	0.713 (0.473–1.075)	0.107	0.967 (0.578–1.618)	0.898	0.365
Sudden death	0.673 (0.385–1.176)	0.164	0.246 (0.077–0.781)	0.017	0.124

CI, confidence intervals; ICD, implantable cardioverter-defibrillator; ICM, ischaemic cardiomyopathy; NICM, non-ischaemic cardiomyopathy.

Conclusions

In this propensity-matched, retrospective analysis of data from the WARCEF trial, we found that the presence of ICD at baseline conveyed a survival benefit in those with ICM but not in those with NICM. Our results are consistent with previous literature demonstrating that ICDs are beneficial in patients with ICM and corroborated the results of the DAN-ISH trial, which suggested that beneficial effects of ICDs are attenuated in patients with NICM.

Conflict of interest

S.D.A. reports being a consultant for Bayer, Boehringer Ingelheim, Novartis, Stealth Peptides, Servier, Vifor, and Janssen (all for trial/registry steering committee work), and he has received research grants from Abbott Vascular and Vifor. S.H. reports being a consultant for St. Jude Medical, Daiichi Sankyo, Bristol-Myers Squibb, and Pfizer. A. J.L. has received a research grant from Bristol-Myers Squibb/Pfizer for the AREST trial. G.Y.H.L. has served as a consultant for Bayer/Janssen, BMS/Pfizer, Biotronik, Medtronic, Boehringer Ingelheim, Novartis, Verseon, and Daiichi Sankyo and speaker for Bayer, BMS/Pfizer, Medtronic, Boehringer Ingelheim, and Daiichi Sankyo. No fees are directly received personally. R.L.S. has received research grants from NINDS, NCATS, AHA, Evelyn McKnight Brain Foundation, and Boehringer Ingelheim. J.R.T. has received consulting fees/research grants from Actelion, Amgen, Bayer, Cytokinetics, Medtronic, Novartis, St. Jude Medical, and Trevena. The other authors have no conflicts of interest to report.

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Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Appendix S1. Supporting information.

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