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ORIGINAL RESEARCH ARTICLE

Association Between Use of Primary-Prevention Implantable Cardioverter-Defibrillators and Mortality in Patients With Heart Failure

A Prospective Propensity Score–Matched Analysis From the Swedish Heart Failure Registry

Editorial, see p 1540

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BACKGROUND: Most randomized trials on implantable cardioverter-defibrillator (ICD) use for primary prevention of sudden cardiac death in heart failure with reduced ejection fraction enrolled patients >20 years ago. We investigated the association between ICD use and all-cause mortality in a contemporary heart failure with reduced ejection fraction cohort and examined relevant subgroups.

METHODS: Patients from the Swedish Heart Failure Registry fulfilling the European Society of Cardiology criteria for primary-prevention ICD were included. The association between ICD use and 1-year and 5-year all-cause and cardiovascular (CV) mortality was assessed by Cox regression models in a 1:1 propensity score–matched cohort and in prespecified subgroups.

RESULTS: Of 16 702 eligible patients, only 1599 (10%) had an ICD. After matching, 1305 ICD recipients were compared with 1305 nonrecipients. ICD use was associated with a reduction in all-cause mortality risk within 1 year (hazard ratio, 0.73 [95% CI, 0.60–0.90]) and 5 years (hazard ratio, 0.88 [95% CI, 0.78–0.99]). Results were consistent in all subgroups including patients with versus without ischemic heart disease, men versus women, those aged <75 versus ≥75 years, those with earlier versus later enrollment in the Swedish heart failure registry, and patients with versus without cardiac resynchronization therapy.

CONCLUSIONS: In a contemporary heart failure with reduced ejection fraction population, ICD for primary prevention was underused, although it was associated with reduced short- and long-term all-cause mortality. This association was consistent across all the investigated subgroups. These results call for better implementation of ICD therapy.

Key Words: defibrillators, implantable ■ heart failure ■ primary prevention ■ registries

Sources of Funding, see page 1538

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Clinical Perspective

What Is New?

- In our analysis of SwedeHF (the Swedish Heart Failure Registry), there was underuse of implantable cardioverter-defibrillators (ICDs) for the primary prevention of sudden cardiac death in patients who have heart failure with a reduced ejection fraction (only 10%).
- Primary-prevention ICD use was associated with a reduced risk of 1-year and 5-year all-cause death.
- The association between ICD use and all-cause mortality was consistent in patients with versus without ischemic heart disease, in men versus women, across age strata, and in patients with earlier versus later registration in SwedeHF, and with versus without cardiac resynchronization therapy.

What Are the Clinical Implications?

- Our findings support the current guidelines recommendation for primary-prevention ICDs in heart failure with reduced ejection fraction and call for better implementation of ICDs in clinical practice.

Patients with heart failure with reduced ejection fraction (HFrEF) have an increased risk of sudden cardiac death (SCD) attributable to malignant arrhythmias.[1] Two randomized, controlled trials (RCTs) testing implantable cardioverter defibrillator (ICD) use for primary prevention of SCD have shown that ICD reduces SCD and improves survival in HFrEF.[2,3] Therefore, both American and European guidelines recommend ICD therapy for primary prevention of SCD to reduce mortality in select patients who have HFrEF with nonischemic dilated cardiomyopathy (IB recommendation in the European Society of Cardiology [ESC] heart failure [HF] guidelines and IA in the American HF guidelines) or ischemic heart disease at least 40 days after a myocardial infarction, with ejection fraction (EF)≤35%, New York Heart Association (NYHA) class II to III on optimal medical therapy (at least 3 months according to ESC), provided they are expected to survive >1 year with good functional status.[4,5] However, both trials enrolled patients >20 years ago and might not reflect the characteristics and contemporary management of HFrEF. Recent advances have impacted the risk profile of patients with HFrEF, leading to a 44% reduction in SCD risk over the past 2 decades.[6–8] Therefore, the beneficial prognostic effects of ICDs might currently be different because of the improved risk profile.

The efficacy of ICDs in elderly patients is also debated. Although elderly patients face an increased risk of SCD, competing risk of nonarrhythmic deaths may reduce ICD efficacy.[9] Because ICD trials enrolled populations with a median age of 60 to 65 years, their results may not fully translate to the real-world setting with a median age of ≈75 years in the HFrEF population.[10] Furthermore, the DANISH trial (Danish Study to Assess the Efficacy of ICDs in Patients with Non-ischemic Systolic Heart Failure on Mortality) questioned the efficacy of primary-prevention ICDs in patients with nonischemic cardiomyopathy combined with contemporary treatments.[11]

The aim of the current study was to evaluate the association between primary-prevention ICDs and all-cause mortality in a large, contemporary cohort of patients with HFrEF, examining also prespecified subgroups, such as: (1) patients with versus without ischemic heart disease (IHD); (2) men versus women; (3) patients aged <75 versus ≥75 years; (4) early versus late enrollment in the Swedish Heart Failure Registry (SwedeHF); and (5) patients with versus without cardiac resynchronization therapy (CRT).

METHODS

Study Protocol and Setting

The data that support the findings of this study are available from the corresponding author, provided that data sharing is permitted by European Union General Data Protection Regulation regulations and appropriate ethics committees.

The design of SwedeHF has been described previously.[12] In brief, patients with clinician-judged HF have been included in the registry since May 11, 2000. Approximately 80 variables are recorded at discharge from the hospital or after an outpatient clinic visit.

The National Patient Registry and the Cause of Death Registry, administered by the Swedish Board of Health and Welfare, provided date of death, additional baseline comorbidities, and the outcome hospitalization for renal failure/dialysis/chronic lower respiratory disease/influenza and pneumonia/liver disease/rheumatoid arthritis.

Establishment of the HF registry and this analysis with linking of the above registries were approved by a multisite ethics committee. Individual patient consent is not required, but patients in Sweden are informed of entry into national registries and allowed to opt out.

Patients

For the current analysis, patients registered as inpatients or outpatients in SwedeHF between May 11, 2000 and December 31, 2016 were included. Inclusion criteria were defined according to the 2016 ESC HF guidelines on ICD use for primary prevention of SCD, namely: EF<40% (which is a categorized variable in SwedeHF, ie, <30%, 30%–39%, 40%–49%, and ≥50%), HF duration ≥3 months, NYHA class ≥II, follow-up >0 day (ie, patients who died during the hospitalization/visit linked to first SwedeHF registration were excluded), and no missing information on ICD use.[4] If the same patient had multiple eligible registrations, the first one was selected. Index date was defined as the day of the outpatient visit or the day of hospital discharge when patients were registered in SwedeHF. End of follow-up was December 31, 2016.

Statistical Analyses

Missing data for variables of interest were handled by multiple imputation with chained equations (R-package *mice*; 10 imputed data sets).[13] The propensity score (PS) for ICD use was calculated in each imputed data set for each patient by a logistic regression model including 31 clinically relevant covariates and then averaged across the imputed data sets.[14] ICD recipients were matched 1:1 to non-ICD recipients by their PSs, using the nearest neighbor method with a caliper of 0.05 and no replacement. Variables included in either the multiple imputation models or considered for PS calculation are shown in the Table. The ability of the matching to balance baseline characteristics in ICD recipients versus nonrecipients was assessed by absolute standard differences, with a value <10% considered as not significant.

Primary outcomes in this analysis were 1-year and 5-year all-cause mortality. Secondary outcomes were 1-year and 5-year cardiovascular (CV) mortality, with censoring for non-CV death. For 1-year and 5-year analyses, events that occurred beyond 1 and 5 years, respectively, were censored. Kaplan–Meier method was used in the PS-matched cohort (ie, adjusting for selected potential confounders) to estimate survivor functions in ICD recipients versus nonrecipients. As consistency analysis, a Cox proportional hazards model adjusting for PSs was fitted in the unmatched population to account for the reduction in sample size attributable to the matching procedure. As a negative control outcome analysis, a Cox proportional hazards model with 1-year and 5-year risk of hospitalization for renal failure/dialysis/chronic lower respiratory disease/influenza and pneumonia/liver disease/rheumatoid arthritis as end point was fitted in the matched cohort to investigate the presence of potential residual confounding, because this outcome is not expected to be affected by ICD use (ie, the exposure). The proportional hazards assumption for ICD use was assessed based on Schoenfeld residuals and met.

Cox proportional hazards models including the interaction between ICD use and the variable representing the prespecified subgroup of interest were fitted in the matched cohort.

Table I in the online-only Data Supplement displays the definition for the variables used in the current analysis.

All statistical analyses were performed by R 3.5.3.[15] A *P* value <0.05 was considered as statistically significant.

RESULTS

Study Cohort

Between May 11, 2000, and December 31, 2016, there were 130 420 registrations from 76 506 unique patients in SwedeHF (Figure I in the online-only Data Supplement). After applying the inclusion criteria, 16 702 patients were eligible. Of these, 1599 (10%) patients had an ICD. After PS matching, the analysis was restricted to 2610 patients, 1305 (50%) ICD recipients versus 1305 (50%) ICD nonrecipients.

Baseline Characteristics

In the overall cohort, mean age was 73 (±11) years and 73% were male. Most of the baseline characteristics (Table) were differently distributed in ICD recipients versus nonrecipients. ICD recipients were younger, more likely to be male and to receive guideline-recommended medical HF therapy, to have history of IHD, lower EF, and longer duration of HF, but less likely to have other comorbidities.

After PS matching, baseline characteristics considered for PS calculation were equally distributed between the 2 study groups.

Outcome Analysis

All-Cause Mortality

In the overall cohort, over a median follow-up of 2.64 (interquartile range, 0.99–5.00) years, 7454 deaths (44.6%) occurred. Crude 1-year risk of all-cause mortality in ICD recipients versus nonrecipients was 12.1% (95% CI, 10.4%–13.7%) versus 18.8% (95% CI, 18.2%–19.4%; *P*<0.01), whereas 5-year risk was 45.8% (95% CI, 42.7%–48.7%) versus 54.5% (95% CI, 53.5%–55.4%; *P*<0.01), respectively. Corresponding unadjusted hazard ratios (HRs) and 95% CIs were 0.61 (95% CI, 0.53–0.71) at 1 year and 0.75 (95% CI, 0.68–0.81) at 5 years (Figure II in the online-only Data Supplement).

In the matched cohort, 985 deaths (37.7%) occurred over a median follow-up of 2.69 (interquartile range, 1.07–5.00) years. One-year mortality risk was 12.7% (95% CI, 10.8%–14.5%) versus 16.9% (95% CI, 14.8%–19.0%; *P*<0.01) in ICD recipients versus nonrecipients, with a 4.2% absolute risk reduction and HR=0.73 (95% CI, 0.60–0.90; Figure 1). Five-year risk was 47.4% (95% CI, 43.0%–49.5%) versus 49.5% (95% CI, 46.2%–52.6%; *P*=0.04) in ICD recipients versus nonrecipients, with a 2.1% absolute risk reduction and HR=0.88 (95% CI, 0.78–0.99; Figure 1).

The consistency analysis in the overall cohort adjusted for (rather than matched by) PS showed HR=0.79 (95% CI, 0.66–0.93) for 1-year all-cause mortality and HR=0.87 (95% CI, 0.79–0.96) for 5-year risk in ICD recipients versus nonrecipients, respectively.

CV Mortality

In the overall cohort, 5146 (30.8%) CV deaths occurred. Crude 1-year risk of CV death was 9.7% (95% CI, 8.2%–11.2%) in ICD recipients versus 13.9% (95% CI, 13.4%–14.5%; *P*<0.01) in nonrecipients, whereas 5-year risk was 36.2% (95% CI, 33.1%–39.1%) versus 41.1% (95% CI, 40.1%–42.0%; *P*<0.01), respectively. Corresponding unadjusted HRs and 95% CIs were 0.68 (95% CI, 0.57–0.80) at 1 year and 0.82 (95% CI, 0.74–0.90) at 5 years (Figure II in the online-only Data Supplement).

In the matched cohort, 737 CV deaths (28.2%) occurred. One-year CV mortality risk was 10.1% (95% CI, 8.4%–11.8%) in ICD recipients versus 13.9% (95%

Table. Baseline Characteristics of the Unmatched and the Propensity Score–Matched Cohort

Variable	Unmatched Cohort				Matched Cohort		
	No ICD (n=15 103)	ICD (n=1599)	*P* Value	% Missing	No ICD (n=1305)	ICD (n=1305)	SD
Demographics							
Age, y*†	73.4 (±11.2)	67.6 (±10.7)	<0.01	0	68.3 (±12.6)	68.4 (±10.5)	1.0
Age ≥ 75 y	7897 (52.3)	436 (27.3)			479 (36.7)	395 (30.3)	
Sex, male*†	10 878 (72.0)	1338 (83.7)	<0.01	0	1089 (83.4)	1077 (82.5)	2.4
Outpatient*†	9589 (63.5)	1012 (63.4)	0.92	0.5	815 (62.5)	821 (63.0)	1.0
Year of registration*†			<0.01	0			5.4
2000–2011	9184 (60.8	770 (48.2)			694 (53.2)	659 (50.5)	
2012–2016	5919 (39.2)	829 (51.8)			611 (46.8)	646 (49.5)	
Clinical							
Heart failure duration*†			<0.01	0			2.5
<6 mo	2871 (19.0)	117 (7.3)			117 (9.0)	108 (8.3)	
≥6 mo	12 232 (81.0)	1482 (92.7)			1188 (91.0)	1197 (91.7)	
Ejection fraction*†			<0.01	0			3.1
<30%	7703 (51.0)	1076 (67.3)			861 (66.0)	842 (64.5)	
30%–39%	7400 (49.0)	523 (32.7)			444 (34.0)	463 (35.5)	
NYHA class*†			0.12	0			2.7
NYHA II	7088 (46.9)	712 (44.5)			572 (43.8)	589 (45.1)	
NYHA III	7231 (47.9)	809 (50.6)			670 (51.4)	653 (50.1)	
NYHA IV	784 (5.2)	78 (4.9)			63 (4.8)	63 (4.8)	
Heart rate, bpm*†	72.7 (±14.8)	70.3 (±12.3)	<0.01	4.8	71.2 (±13.0)	70.6 (±12.7)	4.8
MAP, mm Hg*†	88.7 (±12.7)	85.7 (±11.9)	<0.01	1.3	86.0 (±12.7)	86.0 (±12.1)	0.5
Hemoglobin, g/L	132.9 (±17.0)	134.4 (±16.5)	<0.01	2.0	134.8 (±17.2)	134.1 (±16.5)	4.1
NT-proBNP (≥2510 pg/L)	3532 (53.9)	355 (44.7)	<0.01	56.0	331 (52.4)	284 (44.4)	15.9
Body mass index, kg/m^2	26.9 (±5.3)	27.7 (±4.9)	<0.01	42.0	27.3 (±5.4)	27.7 (±4.9)	7.5
eGFR, mL·min^{-1}·1.73 m^{-2}*†	58.2 (±22.6)	61.4 (±22.6)	<0.01	0.8	60.6 (±24.2)	61.0 (±22.4)	1.8
Treatments							
CRT*†	607 (4.0)	740 (46.3)	<0.01	0	427 (32.7)	449 (34.4)	3.6
β-Blocker*†	13 809 (91.6)	1548 (97.1)	<0.01	0.2	1254 (96.2)	1257 (96.6)	2.4
RASI*†	13 590 (99.6)	1518 (99.9)	0.14	0.4	1209 (99.8)	1236 (99.8)	1.9
MRA*†	6155 (41.0)	892 (56.1)	<0.01	0.5	699 (53.7)	703 (54.2)	1.1
Diuretic*†	12 717 (84.2)	1312 (82.1)	0.03	0	1089 (83.4)	1077 (82.5)	2.4
Digoxin*†	2630 (17.5)	250 (15.7)	0.08	0.4	212 (16.3)	213 (16.4)	0.4
Oral anticoagulant*†	6963 (46.3)	907 (56.9)	<0.01	0.3	734 (56.3)	717 (55.1)	2.5
Platelet inhibitor*†	7133 (47.6)	692 (44.0)	<0.01	0.9	584 (45.1)	580 (45.1)	0.1
Nitrate*†	2741 (18.2)	230 (14.4)	<0.01	0.4	196 (15.0)	199 (15.3)	0.8
Statin*†	7865 (52.2)	1069 (67.0)	<0.01	0.3	852 (65.3)	857 (65.8)	1.0
Comorbidities							
Dilated cardiomyopathy*†	3419 (22.6)	764 (47.8)	<0.01	0	563 (43.1)	559 (42.8)	0.6
Ischemic heart disease*†	9800 (64.9)	1218 (76.2)	<0.01	0	1007 (77.2)	997 (76.4)	1.8
Prior coronary revascularization*†	5905 (39.1)	908 (56.8)	<0.01	0	751 (57.5)	746 (57.2)	0.8
Smoking*†			<0.01	21.5			1.7
Current	1537 (13.0)	120 (9.5)			109 (10.5)	103 (10.0)	
Former	5621 (47.4)	689 (54.8)			563 (54.2)	558 (54.3)	
Never	4697 (39.6)	449 (35.7)			366 (35.3)	367 (35.7)	

(*Continued*)

Table. Continued

Variable	Unmatched Cohort				Matched Cohort		
	No ICD (n=15 103)	ICD (n=1599)	*P* Value	% Missing	No ICD (n=1305)	ICD (n=1305)	SD
Atrial fibrillation*†	8839 (58.5)	915 (57.2)	0.33	0	770 (59.0)	758 (58.1)	1.9
Anemia*†	5196 (35.0)	506 (32.9)	0.11	4.1	438 (34.4)	420 (33.5)	1.8
Diabetes mellitus*†	4847 (32.1)	506 (31.6)	0.74	0	426 (32.6)	423 (32.4)	0.5
Hypertension*†	9635 (63.8)	906 (56.7)	<0.01	0	760 (58.2)	757 (58.0)	0.5
Valvular heart disease*†	4741 (31.4)	407 (25.5)	<0.01	0	345 (26.4)	349 (26.7)	0.7
Peripheral vascular disease*	1927 (12.8)	194 (12.1)	0.50	0	198 (15.2)	168 (12.9)	6.6
Lung disease*†	3465 (22.9)	307 (19.2)	<0.01	0	267 (20.5)	258 (19.8)	1.7
Cancer within the last 3 y*†	1677 (11.1)	123 (7.7)	<0.01	0	113 (8.7)	112 (8.6)	0.3
History of bleeding*	2928 (19.4)	310 (19.4)	1.00	0	278 (21.3)	256 (19.6)	4.2
Stroke/transient ischemic attack*	2389 (15.8)	240 (15.0)	0.42	0	208 (15.9)	185 (14.2)	4.9

Continuous variables are presented as mean (±standard deviation), categorical as frequency (%). The *t* test was used to compare ICD recipients vs nonrecipients for continuous variables; the Fisher exact test was used for categorical variables. Standardized differences (SD) are defined as the difference in means, proportions, or ranks divided by the mutual standard deviation. In multiple imputation models and for propensity scores calculation, NYHA class was classified as II versus III/IV. CRT indicates cardiac resynchronization therapy; eGFR, estimated glomerular filtration rate (calculated by Chronic Kidney Disease Epidemiology Collaboration formula); ICD, implantable cardioverter-defibrillator; MAP, mean arterial pressure; MRA, mineralocorticoid receptor antagonist; NYHA, New York Heart Association; NT-proBNP, N-terminal pro-B-type natriuretic peptide; and RASI, renin-angiotensin-system inhibitor.

*Variables were included in the multiple imputation models together with the outcomes all-cause death and ICD use.

†Variables were used for the calculation of propensity scores.

CI, 12.0%–15.8%; *P*<0.01) in nonrecipients, with a 3.8% absolute risk reduction and HR=0.71 (95% CI, 0.57–0.90; Figure 1). Five-year risk was 36.6% (95% CI, 33.2%–39.7%) versus 39.5% (95% CI, 36.1%–42.7%; *P*=0.1), respectively, leading to HR=0.88 (95% CI, 0.77–1.02; Figure 1).

The consistency analysis in the overall cohort adjusted for (rather than matched by) PS showed HR=0.81 (95% CI, 0.67–0.98) for 1-year CV mortality and HR=0.91 (95% CI, 0.81–1.02) for 5-year risk in ICD recipients versus nonrecipients, respectively.

Negative Control Analysis

One-year and 5-year risk of hospitalization for renal failure/dialysis/chronic lower respiratory disease/influenza and pneumonia/liver disease/rheumatoid arthritis was 5.7% (95% CI, 4.4%–7.1%) versus 5.8% (95% CI, 4.5%–7.2%; *P* =0.90) and 21.9% (95% CI, 18.7%–24.9% versus 22.0% (95% CI, 18.8%–25.1%;*P*=0.88), respectively, in ICD recipients versus nonrecipients. There was no difference in risk of the negative control outcome between the study arms (1-year HR=0.98 [95% CI, 0.70–1.38]; 5-year HR=0.98 [95% CI, 0.80–1.21]).

Subgroup Analysis

Figure 2 reports the association between ICD use and 1-year and 5-year risk of all-cause mortality mortality in the prespecified subgroups. There was no significant interaction between ICD use and each of the variables that defined the subgroup of interest (ie, history of IHD, sex, age, year of enrollment in SwedeHF, CRT, New York Heart Association class, and EF).

DISCUSSION

Among patients from SwedeHF fulfilling ESC criteria for primary-prevention use of ICD, only 10% had the device. ICD use was associated with a 27% 1-year and 12% 5-year reduction in all-cause mortality, and with a 29% reduction in 1-year risk of CV death, but no significant reduction at 5 years. The observed reduced all-cause mortality associated with ICD use was consistent across several subgroups including patients with versus without IHD, men versus women, patients aged <75 versus ≥75 years, those enrolled in 2011 or earlier versus after 2011, and patients with versus without CRT.

Primary-Prevention ICDs in Contemporary Patients With HFrEF

Approximately 20 years ago, 2 RCTs, the MADIT II (Multicenter Automatic Defibrillator Implantation Trial II) and SCD-HeFT (Sudden Cardiac Death in Heart Failure Trial), investigated the effect of primary-prevention ICD on survival in HFrEF, showing a reduction in all-cause mortality by 31% and 23%, respectively.[2,3] These findings were later confirmed by a meta-analysis pooling data from 8 RCTs.[16] However, HF care has substantially changed over the past 10 years,[4] with advances in HFrEF evidence-based therapy such as β-blockers, mineralocorticoid receptor antagonists, CRT, and later sacubitril/valsartan. This led to a steady decrease in SCD, beyond

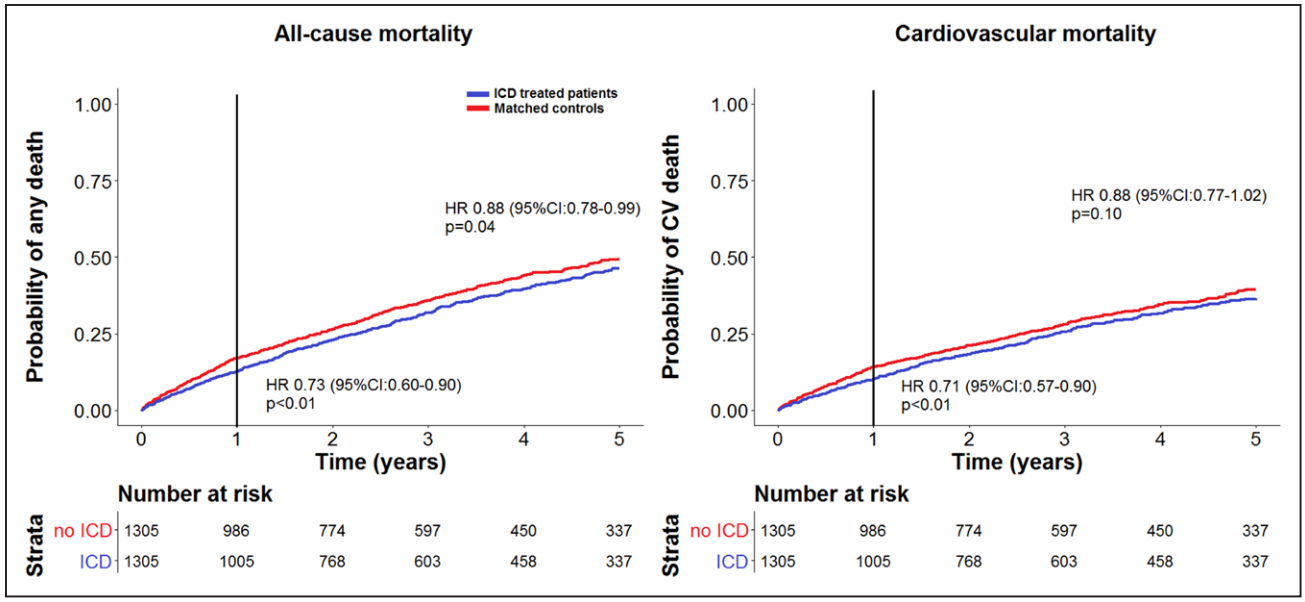

Figure 1. Kaplan–Meier curves for all-cause and cardiovascular mortality in implantable cardioverter-defibrillator recipients versus nonrecipients in the propensity score–matched population.
CV indicates cardiovascular; HR, hazard ratio; and ICD, implantable cardioverter-defibrillator.

the expected reduction in HF and all-cause mortality risk. Although SCD still contributes to a relevant proportion of deaths in this population, the benefit-risk ratio of primary-prevention ICDs is often questioned.[6]

Our analysis confirms the findings from RCTs on primary-prevention use of ICD in a real-world HFrEF population receiving contemporary care. In patients fulfilling the ESC criteria for ICD primary-prevention use, ICD use was associated with a significant reduction in 1-year and 5-year all-cause mortality. Consistently with previous registry analyses, mortality rates were higher than in RCTs.[17] This finding may reflect the greater burden of comorbidities and more severe HF in our and other registry cohorts versus trial populations. Indeed, in an analysis of the American National CV Data Registry ICD Registry, patients receiving an ICD and meeting MADIT-II and SCD-HeFT selection criteria had mortality rates similar to patients receiving an ICD in the corresponding RCTs.[18] In addition, we also showed an association between ICD use and reduced 1-year but not 5-year risk of CV death, which may be explained by competing risk.

In our subgroup analysis, the association between ICD use and reduced mortality was consistent in patients with and without CRT. In the REVERSE study (Remodeling in Systolic Left Ventricular Dysfunction), 5-year mortality was reduced by CRT-defibrillator versus CRT-pacemaker (CRT-P), which is consistent with our results.[19] In the CERTITUDE registry (Cause of Death Analysis of Patients With Cardiac Resynchronization Therapy), comparing CRT-defibrillator versus CRT-P implanted based on physicians' judgment, mortality was significantly higher in those receiving CRT-P and was mainly attributable to non-SCD, stressing the importance of competing mortality risks.[20] Conversely, the COMPANION trial (Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure) demonstrated only a nominal benefit of CRT-defibrillator over CRT-P,[21] and a Bayesian network meta-analysis of randomized trials could not show significantly reduced risk of mortality in patients with CRT-defibrillator versus ICD or CRT-P alone.[22] The RESET CRT trial (Re-evaluation of Optimal Re-synchronisation Therapy in Patients With Chronic Heart Failure; ClinicalTrial.gov NCT03494933), which is currently ongoing, will further address this question.

The high use of HF treatments, including CRT, and the greater comorbidity burden in our cohort might explain the lower risk reduction in mortality than in RCTs (12% in SwedeHF, 31% in MADIT II, and 23% in SCD-HeFT).[2,3] However, ICD use was associated with reduced mortality regardless of the year of enrollment in SwedeHF, after adjustment for HF treatments. The lower risk reduction in our study in comparison with RCTs on the one hand, along with today´s reduced device costs and side effects on the other, also calls for a reevaluation of the cost-effectiveness of ICD primary-prevention use in a contemporary setting.

Our analysis highlights the underuse of ICDs in Sweden, which has been previously investigated.[23,24] Only 10% of patients with a primary-prevention indication received the device. However, primary-prevention ICD is only indicated in patients who are expected to survive >1 year with good functional status, a criterion that is difficult to verify in SwedeHF. Thus, in a certain portion of patients, the nonuse of ICDs may have been appropriate. Previous analyses report higher use of ICDs in other European countries.[25] In the United States, IMPROVE HF (Registry to Improve the Use of Evidence-

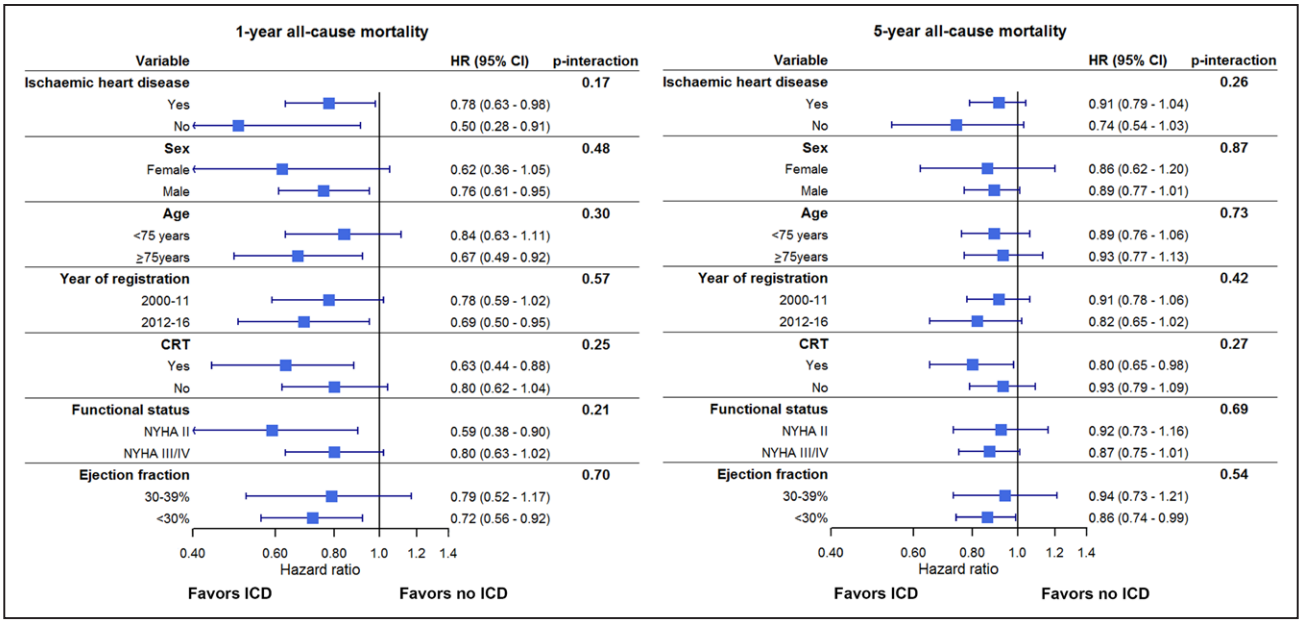

Figure 2. Association between implantable cardioverter-defibrillator use and 1-year and 5-year all-cause mortality risk in prespecified subgroups. 2012 was chosen as the cutoff for defining more versus less contemporary care based on the publication of the European Society of Cardiology heart failure guidelines in 2012, which are the most recent European guidelines that can be captured in the time period explored in our analysis. CRT indicates cardiac resynchronization therapy; HR, hazard ratio; ICD, implantable cardioverter-defibrillator; and NYHA, New York Heart Association.

Based Heart Failure Therapies in the Outpatient Setting) showed ≈60% of patients with an indication received an ICD.[17] A potential explanation for the poor use of ICDs in Sweden may be that a majority of patients with HF are seen by primary care physicians and geriatricians who may have less knowledge and acceptance of device therapy but a higher perception of contraindications. Indeed, previous analyses show that patients not seen by cardiologists have a lower likelihood of receiving an ICD, and the use of devices is higher in centers that do implant CRTs/ICDs.[23] In addition, nurse-based clinics, which are well established in Sweden, are more likely to identify those patients who need pharmacological therapy uptitration, rather than those in need of a device.[26] Our data emphasize the need for ICD use implementation. Quality-control measures in registries and screening initiatives may significantly contribute to device therapy implementation.

Primary-Prevention ICDs in Patients With IHD

A previous meta-analysis showed that primary-prevention ICD use reduced mortality by 24% in both patients with and without IHD.[27] In our real-world HFrEF cohort, we consistently observed no interaction between ICD use and history of IHD for mortality.

Primary-prevention ICD in patients with versus without IHD has been debated over the past years. In the SCD-HeFT trial, ICD reduced mortality by 21% in patients with ischemic HF and by 27% in those with nonischemic HF.[3] In the DEFINITE trial (Defibrillators in Non-Ischemic Cardiomyopathy Treatment Evaluation), enrolling 458 patients with nonischemic dilated cardiomyopathy, ICDs significantly reduced the risk of SCD, but the reduction in all-cause mortality only approximated statistical significance.[28]

Recently, these findings have been challenged by the DANISH trial, which randomly assigned 1116 patients with nonischemic cardiomyopathy.[11] Although ICD significantly reduced SCD, no effect on all-cause mortality was observed over a median follow-up of ≈5 years.[11] It is notable that the DANISH trial enrolled a large proportion of patients with CRT (58%), which may have lowered the overall mortality by disease modification.[8] Therefore, the chance of observing any effect of ICD on top of CRT in the DANISH trial may have been limited a priori.

Recent meta-analyses, pooling data from all RCTs testing primary-prevention ICD over the past 2 decades, and thus also including the DANISH trial, have confirmed a significant reduction of all-cause mortality associated with ICD use in patients with nonischemic cardiomyopathy.[11,27,29] This may suggest that the DANISH trial was not sufficiently powered to test its primary end point over an extended follow-up period, which might have led to a late alignment of the Kaplan–Meier curves.[11] Despite the inclusion of the DANISH trial, the above-mentioned meta-analyses mainly included trials performed >10 years ago and thus mainly reflect older HFrEF regiments.[11,27,29] The strength of our study is that patients were largely receiving optimal medical HF therapy which generalizes RCT results to the contemporary treated real-world HFrEF.

Primary-Prevention ICD in Younger Versus Older Patients and Women Versus Men

Older age is known to be associated with a higher risk of non-CV events, including non-SCD.[30] A post hoc analysis of the DANISH trial showed an interaction between age and ICD efficacy in terms of the reduction of all-cause death. Indeed, there was an association between ICD and all-cause mortality in patients aged ≤70 years but not in those >70 years of age.[31]

Our analysis did not show any interaction between age and ICD use for 1-year and 5-year mortality. It is notable that a higher age cutoff was used in the present study to represent the higher average age of real-world HFrEF populations. In general, it is speculated that older patients do not benefit from primary-prevention ICDs because of the competing risk of nonarrhythmic events.[9,32] However, among patients selected for ICD after clinical assessment, higher age per se may not be a reliable risk marker for increased mortality risk and thus a limitation for potential ICD-induced benefits.

Another interesting finding from our subgroup analysis was that ICD use was associated with a reduced risk of mortality in both women and men. The effect of ICD in women has been questioned, with some studies showing no survival benefit in women, others reporting improved survival regardless of sex, and others showing better outcome in women versus men.[33–35] However, female participation in ICD trials and real-life registries, including our analysis, is low, and thus prone to type II statistical error.

Limitations

Although SwedeHF collects many variables and allowed us to perform adjustments by PS matching, residual and unmeasured confounding cannot be ruled out. Although our PS models were fitted based on several variables to foster adequate adjustments, we did not consider potential interactions among the covariates. In addition, for PS calculation, we did not consider N-terminal pro-B-type natriuretic peptide levels and body mass index because of the high proportion of missing data, but several patient characteristics that are proxies of N-terminal pro-B-type natriuretic peptide and body mass index (eg, diuretic use, NYHA class, and comorbidity burden) were included. SwedeHF coverage is 54%, with previous studies showing that enrolled patients are less sick and better treated than the overall HF population.[36] This might affect the generalizability of our results.

ICD use was considered at baseline, according to an intention-to-treat protocol in RCTs, and therefore it is possible that non-ICD patients were implanted with a device later during follow-up. It is important to note that crossover is expected to dilute the positive association between ICD use and the outcome that we showed. Furthermore, patients with EF=36% to 40%, who do not have a recommendation for ICD use, were included in the analysis because EF is categorized as <30%, 30% to 39%, 40% to 49%, and ≥50% in SwedeHF. However, in the subgroup analysis, we observed consistent results in patients with EF <30% who had a recommendation for ICD. In addition, we had limited data on HF etiology that could not be considered in the present analysis, and thus we can only speculate about the ischemic/nonischemic cause of HFrEF. Furthermore, our definition of IHD may have prevented the identification of patients with IHD but without a history of myocardial infarction or coronary revascularization. Data on antiarrhythmic drugs were not available. We also missed data on SCD, which would have been an outcome of interest, so we can only speculate that the observed differences in any mortality and CV mortality may be attributable to SCD. Furthermore, we cannot exclude that some of the patients included in our analyses were implanted with an ICD for secondary prevention. Finally, the limited sample size of our PS-matched cohort might have prevented us from observing significant differences in the association between ICD use and outcomes across subgroups.

Conclusions

We identified underuse of ICD for primary-prevention purposes in a large and contemporary real-world cohort of patients with HFrEF. Primary-prevention ICD was associated with reduced short-term and long-term all-cause mortality, which was consistent in patients with versus without IHD, in men versus women, across age strata, and in patients with earlier versus later registration in SwedeHF, and with versus without CRT, as well. Our findings support the current guidelines recommendation for primary-prevention ICD in HFrEF and call for better implementation of ICD in clinical practice.

ARTICLE INFORMATION

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Disclosures

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