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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

Running Title: *Schrage et al.; Primary Prevention ICD Use in HFrEF*

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Abstract

Background: Most randomized trials on implantable cardioverter-defibrillator (ICD) use for primary prevention of sudden cardiac death in heart failure with reduced ejection fraction (HFrEF) enrolled patients >20 years ago. We investigated the association between ICD use and all-cause mortality in a contemporary HFrEF cohort and examined relevant subgroups.
Methods: Patients from the Swedish HF Registry (SwedeHF) 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 1,599 (10%) had an ICD. After matching, 1,305 ICD recipients were compared to 1,305 non-recipients. ICD use was associated with a reduction in all-cause mortality risk within 1 year [hazard ratio (HR): 0.73, 95% confidence interval (CI): 0.60-0.90] and 5 years (HR: 0.88, 95%CI: 0.78-0.99). Results were consistent in all subgroups including patients with vs. without ischemic heart disease, males vs. females, in those aged <75 vs. ≥75 years, in those with earlier vs. later enrollment in SwedeHF and in patients with vs. without cardiac resynchronization therapy.
Conclusions: In a contemporary HFrEF 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: Heart failure; Heart failure with reduced ejection fraction; implantable cardioverter-defibrillator; primary prevention; SwedeHF; registry.

Non-standard Abbreviations and Acronyms
HFrEF: heart failure with reduced ejection fraction
SCD: sudden cardiac death
RCT: randomized controlled trial
ICD: implantable cardioverter-defibrillator
ESC: European society of cardiology
NYHA: New York heart association
DANISH: Danish study to assess the efficacy of ICDs in patients with non-ischemic systolic heart failure on mortality
IHD: ischemic heart disease
SwedeHF: Swedish heart failure registry
CRT-D: cardiac resynchronization therapy – defibrillator
CRT-P: cardiac resynchronization therapy – pacemaker
PS: propensity score
CV: cardiovascular
IQR: interquartile range
HR: hazard ratio
CI: confidence interval
ARR: absolute risk reduction
MADIT: multicenter automatic defibrillator implantation trial
SCD-HeFT: sudden cardiac death in heart failure trial

REVERSE: remodeling in systolic left ventricular dysfunction
CERTITUDE: cause of death analysis of patients with cardiac resynchronization therapy
COMPANION: comparison of medical therapy, pacing, and defibrillation in heart failure
RESET: re-evaluation of optimal re-synchronisation therapy in patients with chronic heart failure
IMPROVE HF: Registry to improve the use of evidence-based heart failure therapies in the outpatient setting
DEFINITE: Defibrillators in non-Ischemic cardiomyopathy treatment evaluation
NT-proBNP: N-terminal pro-B-type natriuretic peptide
BMI: body mass index

Clinical Perspective

What is new?

- In our analysis of the Swedish HF Registry, there was underuse of implantable cardioverter-defibrillator (ICD) for primary prevention of sudden cardiac death in patients with heart failure with reduced ejection fraction (HFrEF)(only 10%).
- Primary prevention ICD use was associated with 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 vs. without ischemic heart disease, in males vs. females, across age strata, and in patients with earlier vs. later registration in SwedeHF, as well as with vs. without cardiac resynchronization therapy.

What are the clinical implications?

- Our findings support the current guidelines recommendation for primary prevention ICD in HFrEF and call for better implementation of ICD in clinical practice.

Introduction

Patients with heart failure with reduced ejection fraction (HFrEF) have increased risk of sudden cardiac death (SCD) due to malignant arrhythmias.[1] Two randomized controlled trials (RCTs) testing implantable cardioverter defibrillator (ICD) use for primary prevention of SCD have shown that the ICD reduces SCD and to 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 HFrEF patients with non-ischemic dilated cardiomyopathy [IB recommendation in European Society of Cardiology (ESC) HF guidelines and IA in American HF guidelines)] or ischemic heart disease at least 40 days after a myocardial infarction, with EF≤35%, New York heart association (NYHA) II-III on optimal medical therapy (at least 3 months according ESC), provided they are expected to survive more than 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 HFrEF patient' risk profile, leading to a 44% reduction in SCD risk over the last two decades.[6-8] Therefore, the beneficial prognostic effects of ICD might be currently different due to the improved risk profile.

The efficacy of ICD in elderly patients is also debated. Although elderly patients face an increased risk of SCD, competing risk of non-arrhythmic deaths may reduce ICD efficacy.[9] Since ICD trials enrolled populations with a median age of 60-65 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 (Danish Study to Assess the Efficacy of ICDs in Patients with Non-ischemic Systolic Heart Failure on Mortality) trial questioned the efficacy of

primary prevention ICD in patients with non-ischemic cardiomyopathy combined with contemporary treatments.[11]

The aim of the current study was to evaluate the association between primary prevention ICD and all-cause mortality in a large, contemporary cohort of HFrEF patients, examining also prespecified subgroups, such as: (i) patients with vs. without ischemic heart disease (IHD); (ii) males vs. females; (iii) patients aged <75 vs. ≥75 years; (iv) early vs. late enrollment in the Swedish HF registry (SwedeHF); and (v) patients with vs. 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] Briefly, patients with clinician-judged HF have been included in the registry since 11th May 2000. Approximately 80 variables are recorded at discharge from 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 11th May 2000 and 31st December 2016 were included. Inclusion criteria were defined according to the 2016 ESC HF guidelines on ICD for primary prevention of SCD, namely: EF<40% (which is a categorized variable in SwedeHF, i.e. <30%, 30-39%, 40-49%, and ≥50%), HF duration ≥3 months, NYHA class ≥II, follow-up >0 day (i.e. 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 31st December 2016.

Statistical analyses

Missing data for variables of interest were handled by chained equations multiple imputation (R-package *mice;* 10 imputed datasets).[13] The propensity score (PS) for ICD was calculated in each imputed dataset for each patient by a logistic regression model including 31 clinically relevant covariates and then averaged across the imputed datasets.[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 *Table 1*. The ability of the matching to balance baseline characteristics in ICD-recipients vs. non-recipients 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 occurred beyond 1 and 5 years, respectively, were censored. Kaplan-Meier method was used in the PS-matched cohort (i.e. adjusting for selected potential confounders) to estimate survivor functions in ICD recipients vs. non-recipients. As consistency analysis, a Cox proportional hazard model adjusting for PSs was fitted in the unmatched population to account for the reduction in sample size due to the matching procedure. As a negative control outcome analysis, a Cox proportional hazard 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 endpoint was fitted in the matched cohort to investigate the presence of potential residual confounding, since this outcome is not expected to be affected by ICD use (i.e. the exposure). The proportional-hazards assumption for ICD use was assessed based on Schoenfeld residuals and met.

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

Supplementary Table 1 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 (*Supplementary Figure 1)*

Between 11th May 2000 and 31st December 2016, there were 130,420 registrations from 76,506

unique patients in SwedeHF. After applying the inclusion criteria, 16,702 patients were eligible. Of these, 1,599 (10%) patients had an ICD. After PS matching, the analysis was restricted to 2,610 patients, 1,305 (50%) ICD recipients vs. 1,305 (50%) ICD non-recipients.

Baseline characteristics (Table 1)

In the overall cohort, mean age was 73 (±11) years and 73% were male. Most of the baseline characteristics were differently distributed in ICD recipients vs. non-recipients. 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 two study groups.

Outcome analysis

All-cause mortality

In the overall cohort, over a median follow-up of 2.64 [interquartile range (IQR) 0.99–5.00] years, 7,454 deaths (44.6%) occurred. Crude 1-year risk of all-cause mortality in ICD-recipients vs non-recipients was 12.1% [95% confidence interval (CI): 10.4-13.7%] vs. 18.8% (95%CI: 18.2-19.4%; p<0.01), whereas 5-year risk was 45.8% (95%CI: 42.7-48.7%) vs. 54.5% (95%CI: 53.5-55.4%; p<0.01), respectively. Corresponding unadjusted hazard ratios (HR) and 95%CI were 0.61 (0.53-0.71) at 1 year and 0.75 (0.68-0.81) at 5 years (*Supplementary Figure 2)*.

In the matched cohort, 985 deaths (37.7%) occurred over a median follow-up of 2.69 (IQR: 1.07–5.00) years. One-year mortality risk was 12.7% (95%CI: 10.8-14.5%) vs. 16.9% (95%CI: 14.8-19.0%; p<0.01) in ICD recipients vs. non-recipients, with a 4.2% absolute risk reduction (ARR) and HR=0.73 (95%CI: 0.60-0.90)(*Figure 1*). Five-year risk was 47.4%

(95%CI: 43.0-49.5%) vs. 49.5% (95%CI: 46.2-52.6%; p=0.04) in ICD recipients vs. non-recipients, with a 2.1% ARR 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 vs. non-recipients, respectively.

CV mortality

In the overall cohort, 5,146 (30.8%) CV death occurred. Crude 1-year risk of CV death was 9.7% [95%CI: 8.2-11.2%] in ICD recipients vs. 13.9% (95%CI: 13.4-14.5%; p<0.01) in non-recipients, whereas 5-year risk was 36.2% (95%CI: 33.1-39.1%) vs. 41.1% (95%CI: 40.1-42.0%; p<0.01), respectively. Corresponding unadjusted HRs and 95%CI were 0.68 (0.57-0.80) at 1 year and 0.82 (0.74-0.90) at 5 years (Supplementary Figure 2).

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 vs. 13.9% (95%CI: 12.0-15.8%; p<0.01) in non-recipients, with a 3.8% ARR and HR=0.71 (95%CI: 0.57-0.90)(Figure 1). Five-year risk was 36.6% (95%CI: 33.2-39.7%) vs. 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 vs. non-recipients, 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%) vs. 5.8% (95%CI: 4.5-7.2%; p=0.90) and 21.9% (95%CI: 18.7-24.9% vs. 22.0% (95%CI: 18.8-

25.1%; p=0.88), respectively, in ICD recipients vs. non-recipients. 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 as well as 5-year risk of all-cause mortality in the prespecified subgroups. There was no significant interaction between ICD use and each of the variables which defined the subgroup of interest (i.e. history of IHD, sex, age, year of enrolment in SwedeHF, CRT, NYHA class, EF).

Discussion

Among patients from SwedeHF fulfilling ESC criteria for primary prevention 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 vs. without IHD, males vs. females, patients aged <75 vs. ≥75 years, those enrolled in 2011 or earlier vs. after 2011 and patients with vs. without CRT.

Primary prevention ICD in contemporary HFrEF patients

Around 20 years ago two 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 last 10 years,[4] with advances in HFrEF evidence-based therapy such as beta-blocker,

mineralocorticoid receptor antagonists, CRT and later sacubitril/valsartan. This led to a steady decrease in SCD, beyond 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 ICD is often questioned.[6]

Our analysis confirms the findings from RCTs on primary prevention 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 vs. 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 similar mortality rates to patients receiving an ICD in the corresponding RCTs.[18] Additionally, 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 and reduced mortality was consistent in patient with and without CRT. In the REVERSE (Remodeling in Systolic Left Ventricular Dysfunction) study, 5-years mortality was reduced by CRT-D vs. CRT-P, which is consistent with our results.[19] In the CeRTiTude (Cause of Death Analysis of Patients With Cardiac Resynchronization Therapy) registry, comparing CRT-D vs. CRT-P implanted based on physicians' judgement, mortality was significantly higher in those receiving CRT-P and was mainly due to non-SCD, stressing the importance of competing mortality risks.[20] Conversely, the COMPANION (Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure) trial demonstrated only a nominal benefit of CRT-D 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-D vs. 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, 23% in SCD-HeFT).[2, 3] However, ICD use was associated with reduced mortality regardless of year of enrollment in SwedeHF, after adjustment for HF treatments. The lower risk reduction in our study as compared with RCTs on one hand, along with today´s reduced device costs and side effects on the other, also calls for a re-evaluation of cost-effectiveness of ICD primary prevention use in a contemporary setting.

Our analysis highlights the underuse of ICD 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 longer than 1 year with good functional status, a criterion that is difficult to verify in SwedeHF. Thus, in a certain portion of patients, non-use of ICD may have been appropriate. Previous analyses report higher use of ICD in other European countries.[25] In the USA, IMPROVE HF (Registry to Improve the Use of Evidence-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 ICD in Sweden may be that a majority of HF patients 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 lower likelihood of receiving an ICD, and use of devices is higher

in centers who do implant CRT/ICD.[23] Additionally, 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 of ICD use implementation. Quality control measures in registries and screening initiatives may significantly contribute to device therapy implementation.

Primary prevention ICD in patients with IHD

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

Primary prevention ICD in patients with vs. without IHD has been debated over the last years. In the SCD-HeFT trial, ICD reduced mortality by 21% in patients with ischemic HF and by 27% in those with non-ischemic HF.[3] In the DEFINITE (Defibrillators in Non-Ischemic Cardiomyopathy Treatment Evaluation) trial enrolling 458 patients with non-ischemic dilated cardiomyopathy, ICD 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 randomized 1,116 patients with non-ischemic cardiomyopathy.[11] Although ICD significantly reduced SCD, no effect on all-cause mortality was observed over a median follow-up of approximately 5 years.[11] Notably, 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 DANISH may have been limited a priori.

Recent meta-analyses, pooling data from all RCTs testing primary prevention ICD over the last two decades, and thus also including the DANISH trial, have confirmed a significant

reduction of all-cause mortality associated with ICD in patients with non-ischemic cardiomyopathy.[11, 27, 29] This may suggest that the DANISH trial was not sufficiently powered to test its primary endpoint 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 more than 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 vs. older patients and females vs. males

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 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. Notably, a higher age cut-off was used in the present study to represent the higher average age of real-world HFrEF populations. It is generally speculated that older patients do not benefit from primary prevention ICD due to competing risk of non-arrhythmic 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 reduced risk of mortality in both females and males. The effect of ICD in females has been questioned, with some studies showing no survival benefit in females, others reporting improved

survival regardless of sex, and others showing better outcome in females vs. males.[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 in order to foster adequate adjustments, we did not consider potential interactions among the covariates. Additionally, for PS calculation we did not consider N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels and body mass index (BMI) due to the high proportion of missing data, but several patient characteristics which are proxies of NT-proBNP and BMI (e.g. diuretic use, NYHA class, 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 generalizability of our results.

ICD use was considered at baseline, as 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. Importantly, crossover is expected to dilute the positive association between ICD use and the outcome which we showed. Furthermore, patients with EF=36-40%, who do not have recommendation for ICD use, were included in the analysis since EF is categorized as <30%, 30-39%, 40-49%, and ≥50% in SwedeHF. However, in the subgroup analysis we observed consistent results in patients with EF <30% who had recommendation for ICD. Additionally, we had limited data on HF etiology which could not be considered in the present analysis, and thus we can only speculate about the ischemic/non-ischemic cause of HFrEF.

Furthermore, our definition of IHD may have prevented the identification of patients with IHD but without history of myocardial infarction or coronary revascularization. Data on antiarrhythmic drugs were not available. We also missed data on SCD, which would have been outcome of interest, so we can only speculate that the observed differences in any mortality and CV mortality may be due 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 HFrEF patients. Primary prevention ICD was associated with reduced short-term and long-term all-cause mortality, which was consistent in patients with vs. without IHD, in males vs. females, across age strata, and in patients with earlier vs. later registration in SwedeHF, as well as with vs. without CRT. Our findings support the current guidelines recommendation for primary prevention ICD in HFrEF and call for better implementation of ICD in clinical practice.

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Table 1. Baseline characteristics of the unmatched and the propensity score matched cohort.

	Unmatched cohort				Matched cohort		
Variable	**No ICD (N=15103)**	**ICD (N=1599)**	**p-value**	**% missing**	**No ICD (N=1305)**	**ICD (N=1305)**	**SD**
Demographics							
Age (years)[*,+]	73.4 (±11.2)	67.6 (±10.7)	<0.01	0	68.3 (±12.6)	68.4 (±10.5)	1.0
Age >= 75 years	7897 (52.3%)	436 (27.3%)			479 (36.7%)	395 (30.3%)	
Sex (male)[*,+]	10878 (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 months	2871 (19.0%)	117 (7.3%)			117 (9.0%)	108 (8.3%)	
≥ 6 months	12232 (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 (mmHg) [*,+]	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/1.73m^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
Beta-blocker [*,+]	13809 (91.6%)	1548 (97.1%)	<0.01	0.2	1254 (96.2%)	1257 (96.6%)	2.4
RASI [*,+]	13590 (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 [*,+]	12717 (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%)	
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 years [*,+]	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 (percentage). T-test was used to compare ICD recipients vs non-recipients for continuous variables, Fisher´s exact test for categorical variables. Standardized differences (SD) are defined as the difference in means, proportions or ranks divided by the mutual standard deviation.

([*]) variables were included in the multiple imputation models together with the outcome all-cause death and ICD use;

In multiple imputation models and for propensity scores calculation, NYHA class was classified as II vs. III/IV.

([+]) variables were used for the calculation of propensity scores.

Abbreviations: ICD: implantable cardioverter-defibrillator; MAP: mean arterial pressure; eGFR: estimated glomerular filtration rate (calculated by Chronic Kidney Disease Epidemiology Collaboration formula); RASI: renin-angiotensin-system inhibitor; CRT: cardiac resynchronization therapy; MRA: mineralocorticoid receptor antagonist. NYHA: New York Heart Association. NT-proBNP: N-terminal pro-B-type natriuretic peptide.

Figure Legends

Figure 1. Kaplan-Meier curves for all-cause and cardiovascular mortality in implantable cardioverter-defibrillator recipients vs. non-recipients in the propensity score matched population. Abbreviations: ICD: implantable cardioverter-defibrillator; CI: confidence intervals.

Figure 2. Association between implantable cardioverter-defibrillator use, 1-year and 5-year all-cause mortality risk in prespecified subgroups. 2012 was chosen as cut-off for defying more vs 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. Abbreviations: CI: confidence interval; CRT: cardiac resynchronization therapy; NYHA: New York heart association.