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RESEARCH ARTICLE

Predictors of primary prevention implantable cardioverter-defibrillator use in heart failure with reduced ejection fraction: impact of the predicted risk of sudden cardiac death and all-cause mortality

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Aims Use of implantable cardioverter-defibrillators (ICD) for primary prevention of sudden cardiac death (SCD) in heart failure with reduced ejection fraction (HFrEF) is limited. We aimed to investigate barriers to ICD use in HFrEF while considering the predicted risk of mortality and SCD.

Method and results Patients from the SwedeHF registered in 2011–2018 and with an indication for primary prevention ICD were analysed. The Seattle Proportional Risk and Seattle Heart Failure Models were used to predict the proportional SCD and all-cause mortality risk, respectively. A multivariable logistic regression model was fitted to identify independent predictors of ICD use/non-use; Cox regression models to evaluate the interaction between predicted SCD/mortality risk and ICD use for mortality. Of 13 475 patients, only 15.5% had an ICD. Those with higher predicted proportional SCD risk (>45%) had an ~80% higher likelihood to have an ICD. Other predictors of non-use were follow-up in primary versus specialty care, higher comorbidity burden and lower socioeconomic status. ICD use was associated with lower mortality only in patients with higher predicted SCD and lower mortality risk (34% and 37% relative risk reduction for 3-year all-cause and cardiovascular mortality, respectively). In this subgroup of patients, underuse of ICD was 81.8%.

Conclusion In a contemporary registry, only 15.5% of patients with an indication for primary prevention ICD received the device. While a high predicted proportional SCD risk was appropriately linked to ICD use, the lack of specialized follow-up, higher comorbidity burden, and lower socioeconomic status were major unjustified impediments to implementation. Our findings suggest areas for improving ICD use for primary prevention of SCD in clinical practice.

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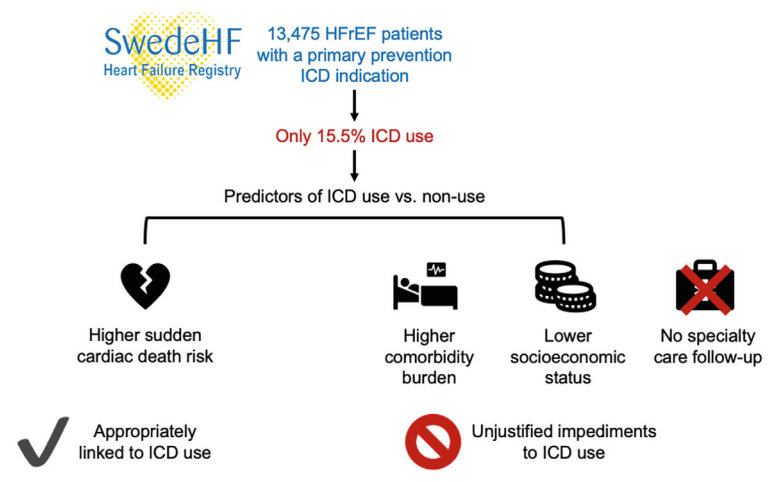
Graphical Abstract



In this study of 13 475 contemporary treated patients with heart failure with reduced ejection fraction (HFrEF) meeting criteria for primary prevention implantable cardioverter-defibrillator (ICD) use, only 15.5% had an ICD. While a high predicted proportional risk of sudden cardiac death was appropriately linked to ICD use, the lack of specialized follow-up, higher comorbidity burden, and lower socioeconomic status were major unjustified impediments to implementation. These findings suggest areas for improving primary prevention ICD use for HFrEF in clinical practice.

Keywords Implantable cardioverter-defibrillator • Primary prevention • Heart failure with reduced ejection fraction • Underuse • Implementation • Guideline recommendation

Introduction

The European Society of Cardiology (ESC) guidelines on heart failure (HF) recommend the use of an implantable cardioverter-defibrillator (ICD) for primary prevention of sudden cardiac death (SCD) in patients with symptomatic HF with an ejection fraction (EF) ≤35% (class of recommendation I, level of evidence A for ischaemic HF; class of recommendation IIa, level of evidence A for non-ischaemic HF).[1] This recommendation is based on the findings of two randomized controlled trials which have shown a survival benefit with primary prevention ICD use in HF with reduced EF (HFrEF), and one randomized controlled trial suggesting lack of benefit in terms of overall survival in non-ischaemic HF.[2–4] Evidence from large meta-analyses and registry-based studies support the use of ICD for primary prevention of SCD in HFrEF regardless of the aetiology.[5–7]

Despite the prognostic benefits, primary prevention ICDs are still underused in daily clinical practice in both Europe[8] and the US.[9] This might be partly explained by a steady improvement in HFrEF medical therapy,[1] which has led to a decline in the risk of all-cause mortality but also SCD.[10] As ICDs only prevent SCD, a shift from SCD to non-SCD risk might have correctly contributed to non-use of ICD in a certain proportion of HFrEF patients. However, it is currently unclear if this is the main driver of ICD underuse or if there are other and potentially inappropriate barriers to the implementation in clinical practice.

Therefore, the aim of this study was to analyse predictors of primary prevention ICD use, while considering the predicted all-cause mortality risk as well as the predicted proportion of SCD, in a large, contemporary, real-world HFrEF cohort.

Methods

Study protocol and setting

The design of the Swedish Heart Failure Registry (SwedeHF, www.SwedeHF.se) has been previously described.[11] Briefly, SwedeHF is an ongoing nationwide quality registry enrolling patients from primary and secondary care clinics as outpatients or at discharge from hospital in Sweden since 11 May 2000. Inclusion criterion to be registered in SwedeHF was clinician-judged HF until April 2017 and thereafter a diagnosis of HF according to the International Classification of Diseases, Tenth Revision (ICD-10) codes I50.0, I50.1, I50.9, I42.0, I42.6, I42.7, I25.5, I11.0, I13.0, I13.2. Approximately 80 variables are recorded at discharge from hospital or after an outpatient visit.

For this analysis, SwedeHF was linked to the National Patient Registry, which provided baseline comorbidities; to Statistics Sweden, which provided information on socioeconomic status; and to the Cause of Death Registry, which provided information on all-cause and

cardiovascular mortality. Definitions of variables and initial selection criteria are shown at https://kiheartfailure.github.io/shfdb3/.

SwedeHF, as well as this analysis requiring the linking across the above-mentioned registries, were approved by the Swedish Ethical Review Authority. Individual patient consent was not required, but patients were informed of entry into SwedeHF and allowed to opt out. The study was conducted in accordance with the Declaration of Helsinki.

Patients

Patients registered in SwedeHF between 1 January 2011 and 31 December 2018 were included, as some variables needed for this analysis were only recorded since 2011 onwards (i.e. sodium, diuretic dose). Inclusion criteria were defined according to the 2016 and 2021 ESC HF guidelines[1,12] which were adapted to our variable definitions as follows: EF <40% (EF is collected as a categorized variable in SwedeHF, i.e. <30%, 30%–39%, 40%–49%, and ≥50%, and therefore EF ≤35% could not be assessed), HF duration ≥3 months (as surrogate for 3 months of optimal medical treatment), New York Heart Association (NYHA) class ≥II (also NYHA class IV was considered since patients could have transitioned to NYHA class IV after ICD implantation). Patients with missing data on ICD use and patients who died during the index hospitalization were excluded. If the same patient had multiple eligible registrations, the first registration was selected to allow for longer follow-up. The index date was defined as either the day of the outpatient visit, or the day of hospital discharge.

Statistical analyses

Continuous variables are shown as mean (± standard deviation) and compared by *t*-test if normally distributed, and as median (interquartile range) and compared by Mann–Whitney U test if non-normally distributed. Categorical variables are shown as frequencies (percentages) and compared by chi-square test.

Missing data were handled by chained equations multiple imputation (R-package *mice*; 10 imputed datasets generated).[13] Variables included in the multiple imputation models are shown in *Table 1*.

To assess the independent associations between patient characteristics (independent variables) and use/non-use of ICDs (dependent variable), a multivariable logistic regression model was fitted including the predicted risk of all-cause mortality and proportional SCD risk calculated by the Seattle Heart Failure Model (SHFM) and the Seattle Proportional Risk Model (SPRM), respectively, as well as other potential predictors (clinical and organizational factors, comorbidities, and socioeconomics as shown in *Figure 1*) which are not considered for the calculation of SHFM and SPRM. The SHFM predicts 1-year survival in patients with HFrEF based on readily available clinical variables. Conversely, the SPRM does not predict the actual risk of SCD in a given time frame, but rather the proportional risk of SCD. Fewer clinical variables are needed for the calculation of the SPRM compared with the SHFM, including data on renal function, digoxin use and body mass index, which are not considered for the SHFM. In the original SPRM publication, it has been shown that both scores are inversely correlated, i.e. the proportion of SCD (as assessed by the SPRM) decreases together with an increase in the absolute mortality risk (as assessed by the SHFM).[14] The SHFM and the SPRM were applied to the 10 imputed datasets as reported in online supplementary *Tables S1 and S2* and then averaged.[14,15] High/low risk of all-cause mortality was categorized by the median SHFM score of 0.2052, translating into a 1-year all-cause mortality risk of ∼4.8%; and high/low proportional risk of SCD was categorized by the SPRM score of −0.2073, translating into a proportional SCD risk of 45% and predicted ICD relative risk reduction of 15%, and which has been assumed as an appropriate cut-point for ICD use in a previous analysis.[16] Predicted high/low risk of all-cause mortality/SCD were included in the models as a combined variable, i.e. one variable with four levels – high/high, high/low, low/high and low/low. Additionally, another multivariable logistic regression model was fitted including the individual components of the SHFM and the SPRM, rather than the SHFM and the SPRM, as well as the same other patient characteristics used above, considered as potential predictors, and not represented in the two scores.

To investigate the association between ICD use and outcomes in patients at different levels of predicted all-cause mortality/SCD risk, multivariable Cox regression models were fitted with 3-year all-cause/cardiovascular mortality as outcomes and including an interaction term between ICD use and high/low predicted risk of all-cause mortality/SCD together with other patient characteristics (clinical and organizational factors, comorbidities, socioeconomics as shown in *Figure 1*). Similarly, multivariable Cox regression models were fitted including the SHFM categorized by tertiles rather than medians and adjusted for the SPRM as a continuous variable, and by categorizing the patients into three groups using the SPRM scores of −0.2073 (predicted ICD relative risk reduction of 15%, 45% proportion SCD) and of −0.0869 (predicted ICD relative risk reduction of 20%, 48% proportion SCD), respectively, and adjustments performed by the SHFM as a continuous variable. For the outcome analysis, patients were censored either at 31 December 2018, after 3 years, or when non-cardiovascular death occurred (for the analysis on 3-year cardiovascular death only), or after emigration from Sweden.

The above-described methods were also applied to a sub-cohort of patients with an EF <30% as a sensitivity analysis.

All statistical analyses were performed by R 3.5.3.[17] A p-value <0.05 was considered as statistically significant.

Results

ICD use in the study cohort

In 2011–2018 there were 100 905 SwedeHF registrations. After applying the inclusion criteria, 13 475 patients were eligible (online supplementary *Figure S1*) for this analysis and therefore had an indication for primary prevention ICD, but only 2093 (15.5%) patients had received an ICD. In the overall study cohort, mean age was 72 (±11) years and 26.4% were female. As many as 6927 patients had an EF <30% (51.4% of the study cohort), with 1311 (18.9%) having an ICD.

Figure 2 shows ICD use stratified by the predicted mortality and SCD risk. There was higher use of ICDs among patients with a high SCD risk as compared to patients with a low SCD risk (18.2% for low mortality and high SCD risk and 19.8% for high mortality and high SCD risk vs. 11.5% for low mortality and low SCD risk and 13.5% for high mortality and low SCD risk). Similar observations were made in the sensitivity analysis of patients with an EF <30% (online supplementary *Figure S2*).

Baseline characteristics according to ICD use/non-use

Patients with an ICD were younger and male, had lower EF and N-terminal pro-B-type natriuretic peptide levels, but a higher

Table 1 Baseline characteristics of the overall study cohort

Variable	Overall study cohort (n = 13 475)	% missing	Patients with ICD (n = 2093)	Patients without ICD (n = 11 382)	p-value
Demographics					
Age, years	72.14 (11.32)	0	67.91 (10.36)	72.92 (11.31)	<0.001
Age >75 years[a]	5785 (42.9)		498 (23.8)	5287 (46.5)	<0.001
Female sex[a]	3563 (26.4)	0	379 (18.1)	3184 (28.0)	<0.001
Registration after DANISH[a]	4229 (31.4)	0	807 (38.6)	3422 (30.1)	<0.001
Clinical factors					
Ejection fraction <30%[a]	6927 (51.4)	0	1311 (62.6)	5616 (49.3)	<0.001
Outpatient[a]	10 790 (80.1)	0	1683 (80.4)	9107 (80.0)	0.697
Duration of HF, days	1093.00 [266.00–3003.00]	0	2268.00 [784.00–4110.00]	916.50 [232.00–2742.25]	<0.001
Duration of HF >6 months[a]	11 151 (82.8)		1973 (94.3)	9178 (80.6)	<0.001
NYHA class[a]		0			0.002
II	7097 (52.7)		1028 (49.1)	6069 (53.3)	
III	5917 (43.9)		988 (47.2)	4929 (43.3)	
IV	461 (3.4)		77 (3.7)	384 (3.4)	
Weight[a], kg	82.43 (18.74)	8.8	85.77 (18.17)	81.82 (18.78)	<0.001
Height[a], cm	173.11 (9.36)	35.9	174.85 (8.63)	172.77 (9.46)	<0.001
Body mass index, kg/m^2	27.33 (5.33)	39.0	27.91 (5.03)	27.22 (5.38)	<0.001
Body mass index ≥30 kg/m^2	2184 (26.6)		394 (29.7)	1790 (26.0)	0.006
Systolic blood pressure[a], mmHg	122.11 (19.60)	1.7	116.58 (18.55)	123.12 (19.62)	<0.001
Diastolic blood pressure[a], mmHg	71.75 (11.48)	1.6	70.69 (11.01)	71.94 (11.56)	<0.001
Mean blood pressure, mmHg	88.52 (12.66)	1.7	85.97 (12.22)	88.99 (12.69)	<0.001
Heart rate, bpm	70.00 [62.00–80.00]	2.4	70.00 [61.00–76.00]	70.00 [62.00–80.00]	<0.001
Heart rate ≥70 bpm[a]	7132 (54.2)		1014 (50.2)	6118 (55.0)	<0.001
Haemoglobin[a], g/L	133.40 (16.91)	9.0	135.06 (16.47)	133.10 (16.98)	<0.001
Sodium[a], mmol/L	139.67 (3.22)	15.5	139.48 (3.04)	139.70 (3.25)	0.008
Sodium <135 or >145 mmol/L	895 (7.9)		115 (6.6)	780 (8.1)	0.038
Creatinine[a], μmol/L	100.00 [82.00–126.00]	2.3	102.00 [84.00–128.00]	99.00 [82.00–125.00]	0.001
eGFR (CKD-EPI), ml/min/1.73 m^2	61.27 (22.37)	2.3	62.93 (22.93)	60.97 (22.26)	<0.001
eGFR <30 ml/min/1.73 m^2	960 (7.3)		133 (6.6)	827 (7.4)	0.206
NT-proBNP, pg/ml	2245.00 [899.00–5190.00]	34.7	1799.00 [696.50–3948.50]	2310.00 [947.50–5430.00]	<0.001
NT-proBNP <2245 pg/ml[a]	4401 (50.0)		623 (43.5)	3778 (51.3)	<0.001
Treatments					
Loop diuretics use[a]	10 549 (78.5)	0.3	1595 (76.5)	8954 (78.9)	0.013
Furosemide equivalent dose[a], mg	45.85 (66.75)	0.4	46.74 (67.52)	45.69 (66.60)	0.508
Renin–angiotensin system inhibitors[a]	12 464 (93.0)	0.5	1985 (95.5)	10 479 (92.5)	<0.001
Angiotensin-converting enzyme inhibitors	7299 (54.3)	0.2	1008 (48.3)	6291 (55.4)	<0.001
Angiotensin receptor blockers	4557 (34.0)	0.4	719 (34.5)	3838 (33.8)	0.570
Angiotensin receptor–neprilysin inhibitor	892 (17.0)	61.1	334 (33.8)	558 (13.1)	<0.001
Beta-blocker[a]	12 714 (94.5)	0.1	2045 (97.8)	10 669 (93.8)	<0.001
Mineralocorticoid receptor antagonist[a]	6581 (49.0)	0.3	1349 (64.6)	5232 (46.1)	<0.001
Digoxin[a]	1772 (13.2)	0.2	271 (13.0)	1501 (13.2)	0.794
Antiplatelets[a]	5372 (40.0)	0.3	794 (38.0)	4578 (40.3)	0.052
Anticoagulants[a]	7034 (52.3)	0.2	1194 (57.1)	5840 (51.4)	<0.001
Statins[a]	7756 (57.6)	0.2	1418 (67.8)	6338 (55.8)	<0.001
Nitrates[a]	1700 (12.6)	0.2	239 (11.4)	1461 (12.9)	0.078
Cardiac resynchronization therapy[a]	1619 (12.0)	0.0	1079 (51.6)	540 (4.7)	<0.001
Follow-up in nurse-led heart failure clinic[a]	3311 (25.3)	2.8	401 (19.7)	2910 (26.3)	<0.001
Follow-up in primary care vs. specialized care[a]	10 476 (78.9)	1.5	1939 (93.4)	8537 (76.2)	<0.001

Table 1 (Continued)

Variable	Overall study cohort (*n* = 13 475)	% missing	Patients with ICD (*n* = 2093)	Patients without ICD (*n* = 11 382)	*p*-value
Comorbidities					
Current smoking[a]	1337 (11.8)	15.8	179 (10.4)	1158 (12.0)	0.067
Diabetes[a]	4074 (30.2)	0.0	648 (31.0)	3426 (30.1)	0.446
Arterial hypertension[a]	8873 (65.8)	0.0	1214 (58.0)	7659 (67.3)	<0.001
Atrial fibrillation[a]	7605 (56.4)	0.0	1139 (54.4)	6466 (56.8)	0.045
Anaemia	4116 (33.6)	9.0	573 (30.4)	3543 (34.1)	0.002
Chronic obstructive pulmonary disease[a]	1868 (13.9)	0.0	248 (11.8)	1620 (14.2)	0.004
Cancer diagnosis within the past 3 years[a]	1876 (13.9)	0.0	220 (10.5)	1656 (14.5)	<0.001
Ischemic heart disease[a]	8361 (62.0)	0.0	1519 (72.6)	6842 (60.1)	<0.001
Valvular heart disease[a]	3555 (26.4)	0.0	468 (22.4)	3087 (27.1)	<0.001
Prior revascularization[a]	5684 (42.2)	0.0	1155 (55.2)	4529 (39.8)	<0.001
Peripheral artery disease[a]	1371 (10.2)	0.0	208 (9.9)	1163 (10.2)	0.726
Liver disease[a]	330 (2.4)	0.0	47 (2.2)	283 (2.5)	0.563
Neurologic/psychiatric disease[a]	1098 (8.1)	0.0	127 (6.1)	971 (8.5)	<0.001
Stroke/transient ischaemic attack[a]	2541 (18.9)	0.0	391 (18.7)	2150 (18.9)	0.847
Socioeconomics					
Living alone vs. cohabitating[a]	6038 (44.9)	0.2	811 (38.8)	5227 (46.0)	<0.001
Highest degree[a]		1.7			<0.001
University	2287 (17.3)		436 (21.1)	1851 (16.6)	
Secondary school	5575 (42.1)		934 (45.1)	4641 (41.5)	
Compulsory school	5379 (40.6)		701 (33.8)	4678 (41.9)	
Disposable income <median[a]	4582 (34.1)	0.2	564 (27.0)	4018 (35.4)	<0.001
Risk scores					
Seattle Proportional Risk Model score	−0.26 (0.56)	0.0	−0.15 (0.52)	−0.28 (0.56)	<0.001
Predicted ICD hazard ratio	0.88 [0.72–1.05]		0.83 [0.69–0.98]	0.89 [0.73–1,07]	<0.001
Proportion of SCD, %	44 (13)		47 (12)	43 (13)	<0.001
Seattle Heart Failure Model score	0.26 (0.65)	0.0	0.23 (0.61)	0.27 (0.66)	0.009
Predicted 1-year mortality risk, %	6.2 (5.17)		5.9 (4.4)	6.3 (5.3)	0.001

Values are mean ± standard deviation, *n* (%), or median [interquartile range].
CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; eGFR, estimated glomerular filtration rate; ICD, implantable cardioverter-defibrillator; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; SCD, sudden cardiac death.
[a]Variables used for the multiple imputation together with ICD use and the outcome of 3-year all-cause mortality.

NYHA class, and were less frequently treated with diuretics. Additionally, in patients with an ICD, use of guideline-recommended HFrEF treatments and follow-up in specialty care was more likely, although a follow-up in nurse-led HF clinics was less used. Except for ischaemic heart disease, which was more prevalent in patients with an ICD, the overall comorbidity burden was higher in patients without an ICD. Patients with an ICD were more likely to have higher income, cohabitate (rather than living alone) and had higher education level.

The overall SPRM score was −0.26, translating into a proportional SCD risk of 44% and predicted a relative risk reduction with ICD of 12%; and mean SHFM score was 0.26, translating into a mean predicted risk of 1-year all-cause mortality of 6.2%. As in the original publication, the SPRM was inversely correlated to the SHFM in this data set ($\beta = -0.73$, $p < 0.01$). Patients treated versus not treated with an ICD had a higher SPRM-predicted SCD risk (47 vs. 43%, $p < 0.001$) and a lower SHFM-predicted 1-year mortality risk (5.9 vs. 6.3%, $p = 0.001$).

Results were consistent in the sensitivity analysis, which considered only patients with an EF <30% (online supplementary *Table S3*).

Independent predictors of ICD use/non-use

Differences in characteristics between patients with versus without ICD reported in *Table 1* are unadjusted. Therefore, we performed a multivariable logistic regression analysis to investigate the independent associations between patient characteristics and the likelihood of ICD use/non-use (*Figure 1*).

Overall, higher SCD risk was among the strongest independent predictors of ICD use. ICD use was approximately twofold more likely in patients at higher SCD risk regardless of the concomitant risk of all-cause death, as compared with those at lower SCD risk (high mortality and SCD risk: odds ratio [OR] 1.88, 95% confidence interval [CI] 1.49–2.36; low mortality and high SCD risk: OR 1.79, 95% CI 1.48–2.16). Although the magnitude of the association was

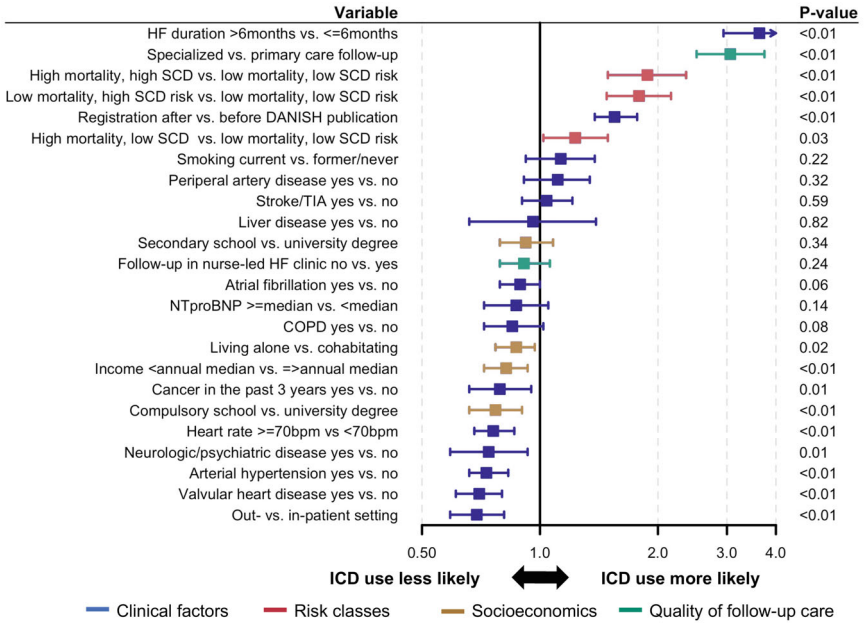


Figure 1 Independent predictors of implantable cardioverter-defibrillator (ICD) use. The underlying logistic regression model was adjusted for all variables shown in the forest plot. Additionally, it was also adjusted for cardiac resynchronization therapy use, which was strongly associated with ICD use (odds ratio 20.09, 95% confidence interval 17.64–22.87), but which was omitted from the forest plot since its association was out of proportion as compared to the other variables. COPD, chronic obstructive pulmonary disease; HF, heart failure; NTproBNP, N-terminal pro-B-type natriuretic peptide; SCD, sudden cardiac death; TIA, transient ischaemic attack.

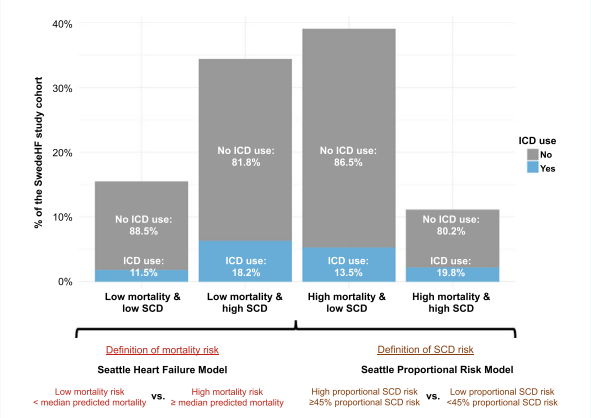


Figure 2 Implantable cardioverter-defibrillator (ICD) use in the study cohort per proportional risk of sudden cardiac death (SCD) and all-cause mortality risk.

smaller (OR 1.23, 95% CI 1.02–1.49), ICD use was also more likely in patients at high mortality risk but at low SCD risk, as compared with those at low risk of mortality and SCD.

Other major patient characteristics independently associated with ICD use were duration of HF, concomitant cardiac resynchronization therapy (CRT) use and follow-up in specialty care. In particular, concomitant CRT use was the strongest predictor of ICD use (OR 20.09, 95% CI 17.64–22.87), which reflects the higher use of CRT with defibrillator (CRT-D) versus CRT with pacemakers (CRT-P) in this study cohort. Additionally, being registered in SwedeHF after the publication of the DANISH trial[4] was also associated with higher likelihood of ICD use.

Lower socioeconomic status (i.e. lower income, education level and living alone), and higher comorbidity burden (i.e. history of cancer, hypertension, and valvular disease) were associated with ICD non-use.

Fitting in the multivariable model the individual components of the SHFM/SPRM rather than the predicted risk of all-cause mortality/SCD provided further information on specific factors driving patient selection for ICD. Additional independent predictors of ICD use were beta-blocker use, ischaemic heart disease and higher NYHA class; whereas loop diuretic use, higher blood pressure, female sex and older age were relevant predictors of non-use (online supplementary *Figure S3*).

These results were largely consistent with the sensitivity analysis which only considered patients with an EF <30%, except for high mortality/low SCD risk being no longer associated with more likely ICD use (online supplementary *Figures S4* and *S5*).

Association between ICD use and 3-year all-cause mortality according to the predicted risk of all-cause mortality and sudden cardiac death

Over a median follow-up of 2.06 (interquartile range 0.85–3.00) years, 3450 (25.6%) all-cause deaths occurred, corresponding to

an event rate of 135 (95% CI 131–140) per 1000 patient-years for 3-year all-cause death.

Figure 3 shows the independent associations between ICD use and 3-year all-cause mortality for the predicted mortality/SCD risk. The lowest HR (greatest risk reduction) for the association between ICD use and all-cause mortality was observed in patients with high predicted SCD risk and low predicted mortality risk (HR 0.66, 95% CI 0.48–0.90), whereas the highest HR (lowest or absent risk reduction) was observed in patients with low predicted SCD and low predicted mortality risk (HR 1.11, 95% CI 0.81–1.51). However, the interaction between predicted risk of SCD/mortality, ICD use and 3-year all-cause mortality did not reach statistical significance (*p*-value for interaction 0.06). The observation of a lower HR associated with ICD use with lower predicted mortality risk and higher predicted SCD risk was consistent when the SHFM predicted all-cause mortality risk was analysed in tertiles and adjusted for SCD risk, and vice versa (*Figure 3*). These results were consistent in the sensitivity analysis considering only patients with an EF <30% (online supplementary *Figure S6*).

Association between ICD use and 3-year cardiovascular mortality according to the predicted risk of all-cause mortality and sudden cardiac death

Over a median follow-up of 2.06 (interquartile range 0.85–3.00) years, 2344 (17.4%) cardiovascular deaths occurred, corresponding to an event rate of 92 (95% CI 88–96) per 1000 patient-years for 3-year cardiovascular death.

When considering the risk of 3-year cardiovascular death, consistent with the above-reported analyses on all-cause mortality, the lowest HR was observed in patients with high predicted SCD but low predicted mortality risk (HR 0.63, 95% CI 0.43–0.93), and the highest HR in patients with low predicted SCD and low predicted mortality risk (HR 1.26, 95%CI 0.87–1.82). The interaction between the predicted risk of SCD/mortality, ICD use and 3-year cardiovascular mortality was statistically significant (*p*-value for interaction 0.03). A similar finding was observed when the SHFM predicted mortality risk was analysed in tertiles and adjusted for SCD risk, and vice versa (*Figure 3*). These results were consistent in the sensitivity analysis considering only patients with EF <30% (online supplementary *Figure S6*).

Discussion

In this analysis of SwedeHF, a nationwide registry enrolling a contemporary cohort of patients with HFrEF, only 15.5% of the patients with an indication for primary prevention ICD per the most recent guidelines received the device, demonstrating considerable underuse. Higher SCD risk was a strong predictor of ICD use, suggesting that ICD decisions are in part appropriate. However, despite extensive adjustments, lower socioeconomic status, female sex, older age, lack of referral to specialty care follow-up and higher comorbidity burden also predicted ICD underuse, which is not justified (*Graphical Abstract*). Finally, the risk for 3-year cardiovascular mortality with versus without an ICD was lowest in patients with high predicted SCD and low predicted all-cause mortality risk, which might suggest a specific role for ICD in this phenotype. If only this specific phenotype was considered as eligible for an ICD, underuse would still be unreasonably high, i.e. 81.8%.

Use of ICDs in contemporary HFrEF

In a previous SwedeHF study enrolling patients in 2000–2016, only 10% of eligible patients had an ICD.[6] In the present analysis of the same data source, covering the years 2011–2018, crude use has increased to 15.5%. Although these findings highlight that ICD use in Sweden has somehow improved over time,[18] it is still significantly low. Notably, even in the subgroup of patients with high SCD/low mortality risk who are those who might be more likely to benefit from an ICD, underuse was still unreasonably high, i.e. 81.8%.

In the ESC HF Long-Term (ESC-HF-LT) registry enrolling patients in 2011–2013 from specialized centres, ~75% of HFrEF patients with an indication had the device.[8] In the US, ICD use among patients with an indication was 40% in the Get With The Guidelines-HF registry (GWTG-HF) considering patients enrolled in 2005–2009,[19] whereas it was 41% in 2015–2017 in the CHAMP-HF registry considering patients with HFrEF (EF ≤40%) receiving at least one guideline-recommended treatment, and therefore this estimate considers as denominator both patients with and without an indication for ICD.[20] In the Asian-HF registry, ICD use was 12% in 2010–2015, although large disparities existed across different countries (e.g. >50% ICD use in Japan, <5% in Indonesia).[21]

Overall, these data highlight great geographical variations in ICD use, which might be explained by different attitudes toward device therapy, different healthcare systems with different reimbursement mechanisms and performance metrics, but could also reflect the different selection criteria, and therefore the different generalizability, of the above-mentioned data sources and analyses (e.g. this study utilized SwedeHF, an unselected cohort of HFrEF patients, whereas GWTG-HF enrolled patients discharged after an HF hospitalization, CHAMP-HF considered patients receiving at least one recommended HFrEF medication, and the ESC-HF-LT registry enrolled patients in more specialized care).

Nevertheless, the existing data on ICD use in HFrEF highlights that underuse remains considerable and therefore the present detailed investigation of barriers to the implementation of this life-saving treatment is needed.

Patient characteristics appropriately driving ICD use and non-use

According to the 2016 and 2021 ESC HF guidelines, ICD use should be considered in patients who are likely to survive longer than 1 year with good functional status.[1,12] Consistent with these recommendations, our study showed that patients with more comorbidities (e.g. valvular heart disease, recent cancer diagnosis), which might negatively affect functional status and non-modifiable survival, were less likely to have ICD treatment.

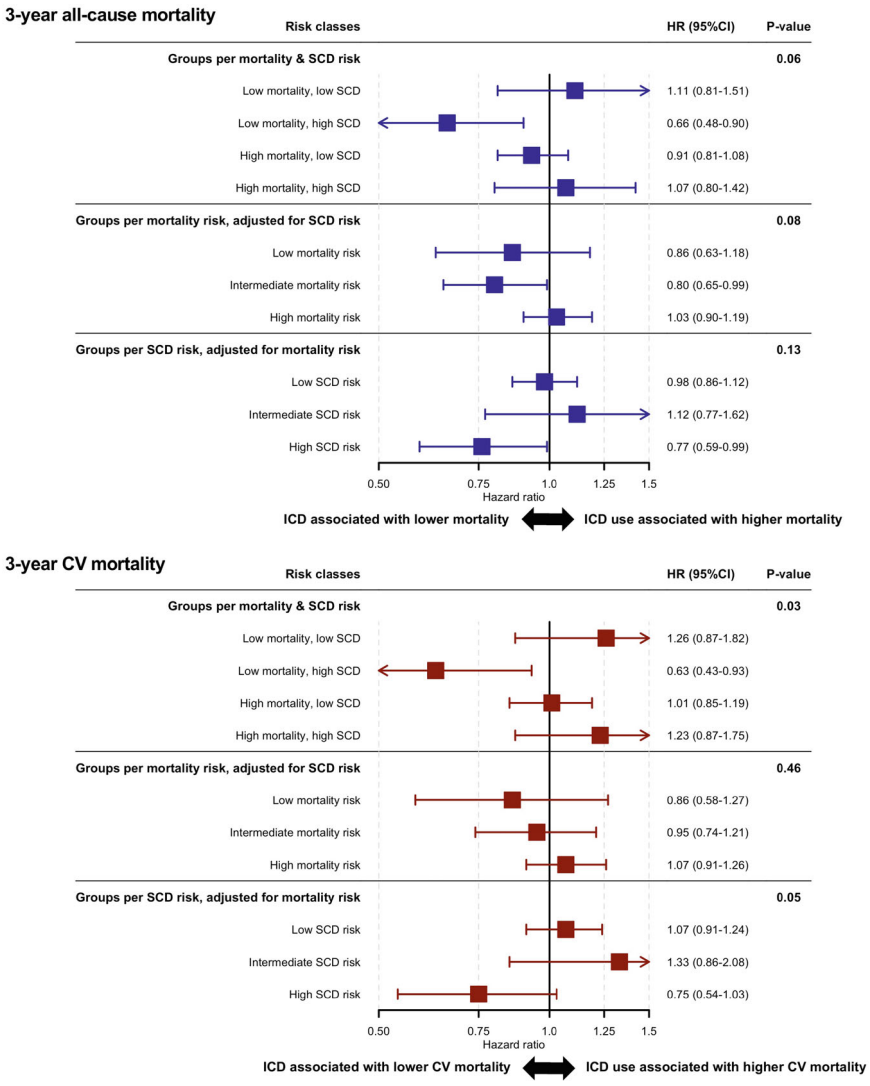


Figure 3 Association between implantable cardioverter-defibrillator (ICD) use and 3-year all-cause and cardiovascular (CV) mortality across different strata of predicted risk of sudden cardiac death (SCD) and all-cause mortality. The underlying Cox regression model was adjusted for all variables shown in *Figure 1*. CI, confidence interval; HR, hazard ratio.

Guidelines also require the optimization of HF treatments before ICD implantation.[1] In our analysis, ICD use was more likely in those treated with beta-blockers and mineralocorticoid receptor antagonists but also in those treated with CRT, reflecting optimized HF treatment. Also, patients with longer HF duration and inpatients were more likely to have an ICD. This may reflect the attempt of up-titrating HF medications in the outpatient setting, followed by an elective hospital admission for ICD implantation, but it might also be explained by the fact that patients with longer life expectancy, and therefore who had had HF for longer time, also had a device.

Another strong predictor of ICD use in this study was ischaemic heart disease, consistent with the findings of the DANISH trial showing ICD use reducing SCD but not all-cause death in non-ischaemic HF,[4] and with guidelines providing a somewhat weaker recommendation for non-ischaemic cardiomyopathy compared to ischaemic cardiomyopathy.[1] In our population, use of ICD increased after the DANISH trial publication, which might be explained by renewed confidence in (or in non-specialist settings, even renewed awareness of) ICD use, at least in younger patients with ischaemic HF, provided by more contemporary evidence.[4]

Overall, the above-mentioned factors seem to adequately drive the selection of patients for ICD implantation, in line with guideline recommendations.

Inappropriate barriers to the implementation of ICD use

In the current study, we identified several patient characteristics not appropriately predicting ICD non-use.

Females were significantly less likely to receive an ICD. It has been previously shown that ICD implantation rates in Europe are consistently lower in females (e.g. 8%–28% of ICD recipients were female in the EU-CERT ICD study depending on the specific participating countries), who are also less represented in all randomized trials in the field.[2–4,22] Although these trials have shown no significant sex-based differences in ICD efficacy, a large meta-analysis reported lower risk of appropriate shocks and deaths in females versus males, but similar risk of inappropriate shocks,[23] which might lead physicians to question ICD implantation in females.[1,12] Similar to what reported for other device-based interventions, females may also be less likely to accept ICD therapy, when offered.[24]

Another important finding was that older age was independently associated with ICD non-use, even after adjustment for HF severity and comorbidities. Age might be a risk factor for non-SCD mortality (e.g. non-modifiable risk of death due to worsening HF or non-cardiovascular comorbidities),[25] but some randomized trials and observational studies did not suggest any difference in benefit with ICD based on age, whereas DANISH found a strong interaction with ICD benefit in age <70 versus no benefit in age >70.[2,3,6,7,26] Therefore, age should not be considered an absolute argument against ICD implantation, but might be considered in the overall clinical context including comorbidities.

Patients with lower socioeconomic status were less likely to be treated with an ICD, regardless of the underlying SCD risk. As the present study was conducted within a tax-financed healthcare system, it is unlikely that financial affordability explains this observation. However, lower socioeconomic status, e.g. lower education level and lower income, is often linked with worse health literacy and a less engagement in preventive measures.[27,28] Additionally, patients living alone might receive less support in taking care of their follow-up appointments and might be overall less motivated to be compliant to the HF treatment.

One more important finding is that patients who were not referred to specialized follow-up care were also less likely to be treated with an ICD. Specialized follow-up care has been described as a key component for appropriate HF treatment, as it allows the optimization of drug therapy and the screening of patients for potential device treatment.[29,30] As HFrEF therapy has become increasingly complex in the past decades, with the addition of new effective drugs, devices and interventions,[1] treatment optimization, including ICD and CRT counseling, might be unreasonable to expect in a primary care setting. Additionally, follow-up in primary care might be less strict than in specialty care, which could delay the screening for an ICD. Therefore, ICD counseling might be offered too late, e.g. when a patient is considered too old for the device.

Predicted risk of all-cause mortality and sudden cardiac death as predictors of ICD use

In the present study, patients with a higher proportional risk of SCD were more likely to receive an ICD, which is in line with the overall rationale for ICD use. Surprisingly, ICDs were also more likely implanted in patients with an overall higher risk of all-cause death, i.e. irrespective of the underlying proportional risk of SCD. This is counterintuitive, as ICDs may only prevent SCD-related deaths. Furthermore, in our analysis the HR for the association between ICD use and cardiovascular mortality was lowest in patients with higher predicted SCD risk/lower predicted risk of all-cause death, which might suggest that ICD use is associated with better survival only in patients with high SCD risk and low competing risk. However, a significant interaction between ICD use, predicted risk of mortality/SCD and outcomes was observed only for the endpoint of 3-year cardiovascular mortality, but not for 3-year all-cause mortality.

Guidelines use a low EF as main criterion for recommending the implantation of an ICD for primary prevention of SCD in patients with HF. However, SCDs also occur in patients with higher EF, highlighting that more factors other than a low EF might be used to identify patients at high SCD risk. In this regard, the interaction between individual comorbidities and age deserves attention. As an example, among patients with an EF >35% and a recent myocardial infarction, impaired kidney function and diabetes were shown to be associated with a higher SCD risk but also with a higher non-SCD risk. However, in younger patients aged <55 years, the SCD risk seemed to outweigh the non-SCD risk, so that these patients might be candidates for an ICD.[31] However, this finding is not reflected in our study, which showed instead that patients with diabetes were actually less likely to be treated with an ICD.

Although several scores have been developed to summarize different SCD risk factors and to identify the patient phenotype more likely to benefit of an ICD (including but not limited to the SPRM and the SHFM),[14,15,32] none of these is currently recommended by the guidelines or has been used for determining eligibility for ICD in clinical trials. However, these scores can be very valuable to provide more granular information about the proportional SCD risk of a patient as well as the competing non-SCD risk, and might therefore help to guide ICD use towards those most likely to benefit. Furthermore, their predictive value might even be enhanced by novel imaging modalities, e.g. magnetic resonance imaging-based scar detection, which could help to identifying patients at higher/lower risk of malignant arrhythmias.[33,34]

Limitations

The main limitation of this study is its observational design, which cannot rule out the impact of residual or unmeasured confounding. Additionally, due to the recording of EF as a categorical variable in SwedeHF, an EF cut-off of <40%, and not of ≤35% as suggested by the guidelines, was used to assess whether there was an indication for ICD, and thus ICD underuse might have been overestimated. However, the results were consistent in a sensitivity analysis of patients with an EF <30%, where there is an indication for ICD. Use of ICDs was only considered at one time point (e.g. prevalent ICD use), and although patients were required to have had HF for at least 3 months (and 83% of the patients actually had HF for >6 months), we cannot exclude that an ICD might have been implanted during follow-up. Data needed as to fulfil our selection criteria, especially NYHA class and EF, were not available

in all SwedeHF patients, which might have impacted somehow on our results. Risk of all-cause mortality and SCD was defined based on two commonly used scores, but other scores might yield different results. Additionally, the used scores (SHFM and SPRM) were adapted to the available data, which might have partially influenced their performance. Also, the limited sample size might have prevented the observation of statistically significant differences in our outcome analysis, i.e. preventing the observation of a statistically significant different association between ICD use and outcomes based on SHFM/SPRM strata. Finally, this study is based on a Swedish cohort, and therefore generalizability to other countries or healthcare systems might be limited.

Conclusion

In a large, nationwide, contemporary and unselected cohort of HFrEF patients, there was underuse of ICD for primary prevention of SCD, with only 15.5% of the patients with an indication receiving the device. A high proportional risk of SCD was appropriately predicting ICD use. ICD use was associated with lower cardiovascular mortality risk only in patients with high SCD/low mortality risk; however, underuse was unreasonably high even when considering only this subgroup of patients as potential candidate for an ICD (81.8% underuse). Patients referred to follow-up in specialty care were also more likely to receive an ICD, whereas those with higher comorbidity burden, lower socioeconomic status, older age and female sex were significantly less likely to receive it.

Our findings highlight the need to overcome inappropriate barriers to ICD implementation, by ameliorating healthcare inequalities, improving quality of follow-up care, and resolving sex and age disparities.

Supplementary Information

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

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