ORIGINAL RESEARCH

Survival Probability and Survival Benefit Associated With Primary Prevention Implantable Cardioverter-Defibrillator Generator Changes

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BACKGROUND: As patients derive variable benefit from generator changes (GCs) of implantable cardioverter-defibrillators (ICDs) with an original primary prevention (PP) indication, better predictors of outcomes are needed.

METHODS AND RESULTS: In the National Cardiovascular Data Registry ICD Registry, patients undergoing GCs of initial non-cardiac resynchronization therapy PP ICDs in 2012 to 2016, predictors of post-GC survival and survival benefit versus control heart failure patients without ICDs were assessed. These included predicted annual mortality based on the Seattle Heart Failure Model, left ventricular ejection fraction (LVEF) >35%, and the probability that a patient's death would be arrhythmic (proportional risk of arrhythmic death [PRAD]). In 40 933 patients undergoing GCs of initial noncardiac resynchronization therapy PP ICDs (age 67.7±12.0 years, 24.5% women, 34.1% with LVEF >35%), Seattle Heart Failure Model–predicted annual mortality had the greatest effect size for decreased post-GC survival (*P*<0.0001). Patients undergoing GCs of initial noncardiac resynchronization therapy PP ICDs with LVEF >35% had a lower Seattle Heart Failure Model–adjusted survival versus 23 472 control heart failure patients without ICDs (model interaction hazard ratio, 1.21 [95% CI, 1.11–1.31]). In patients undergoing GCs of initial noncardiac resynchonization therapy PP ICDs with LVEF ≤35%, the model indicated worse survival versus controls in the 21% of patients with a PRAD <43% and improved survival in the 10% with PRAD >65%. The association of the PRAD with survival benefit or harm was similar in patients with or without pre-GC ICD therapies.

CONCLUSIONS: Patients who received replacement of an ICD originally implanted for primary prevention and had at the time of GC either LVEF >35% alone or both LVEF ≤35% and PRAD <43% had worse survival versus controls without ICDs.

Key Words: generator change ■ heart failure ■ implantable cardioverter-defibrillator ■ left ventricular ejection fraction ■ risk score ■ risk stratification

Current implantable cardioverter-defibrillator (ICD) implant rates are approximately 150 000 per year in the United States.[1,2] Although clinical trials and guidelines support the use of ICDs in heart failure with left ventricular ejection fraction (LVEF) ≤35%,[3–5] the effectiveness of ICDs is heterogeneous across different subgroups of patients,[6] especially in real-world settings.[7,8] As patients age, competing modes of death may alter the degree to which ICDs provide protection against all-cause mortality. As a result, clinical trials demonstrating a survival benefit associated with an initial ICD implanted based on primary prevention criteria do not necessarily imply a survival benefit for the generator change of that ICD at the time of battery depletion.

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CLINICAL PERSPECTIVE

What Is New?

- A novel study is presented to evaluate the survival benefit for replacing an implantable cardioverter-defibrillator (ICD) (for battery depletion) originally implanted for primary prevention of sudden cardiac arrest in patients with heart failure in the National Cardiovascular Data Registry, ICD Registry.
- The Seattle Heart Failure Model had the greatest effect size for prediction of all-cause mortality compared with left ventricular ejection fraction >35%/left ventricular ejection fraction ≤35% and other predictors.
- The proportional risk of arrhythmic death parameter based on the Seattle Proportional Risk Model identified patients expected to have survival benefit or harm with the ICD generator change, and the association between proportional risk of arrhythmic death and survival benefit did not depend on whether there were ICD therapies before the generator change.

What Are the Clinical Implications?

- These results provide clinicians with data that can be used for the purpose of shared decision making with respect to whether a patient should undergo replacement of an ICD at the time of battery depletion.
- Clinicians may be encouraged to use free online calculators available at https://depts.washington.edu/shfm and https://depts.washington.edu/sprm to determine the predicted annual mortality and proportional risk of arrhythmic death after a generator change.
- Better selection of patients for ICD generator changes could result in more efficient allocation of health care resources.

Nonstandard Abbreviations and Acronyms

HF-NO-ICD	heart failure without implantable cardioverter-defibrillator
ICD-GC-HR	hazard ratio associated with the implantable cardioverter-defibrillator generator change
ICD-PP-GC	primary prevention first implantable cardioverter-defibrillator generator change
NCDR	National Cardiovascular Data Registry
PRAD	proportional risk of arrhythmic death
SHFM	Seattle Heart Failure Model
SPRM	Seattle Proportional Risk Model

Despite this, the current clinical practice guidelines still recommend periodic generator changes when the ICD battery is near its end of life.

There has been ongoing interest in better risk stratification for individuals being considered for ICD generator changes,[9] with many still advocating an approach focused on prior therapies or the LVEF.[10] Unfortunately, criteria based on the LVEF only at the time of generator changes have offered limited performance for risk stratification.[11] As a result, there is an unmet need to predict prognosis after replacement ICD insertion to inform decision making and the design of future clinical trials.

Based on these considerations, the purpose of the present study was to address the clinical problem of identifying optimal patients for a generator change of an initial ICD not delivering cardiac resynchronization therapy that was originally implanted for primary prevention of sudden cardiac death. The approach to risk stratification is based on the predicted annual mortality from the Seattle Heart Failure Model (SHFM), the predicted proportional risk of arrhythmic death (PRAD) from the Seattle Proportional Risk Model (SPRM), and the LVEF at the time of generator change. The hypotheses tested are that the predicted annual mortality from the SHFM provides an accurate reflection of overall survival after the generator change, and the PRAD combined with the LVEF at the time of generator change provides effective assessment of survival benefit from the ICD generator change.

METHODS

General Design

Because of the sensitive nature of the data collected for this study, requests to access the data set through initiation of a research proposal from qualified researchers trained in human subject confidentiality protocols may be submitted to the NCDR (National Cardiovascular Data Registry). Further information is available at https://cvquality.acc.org/NCDR-Home/research/submit-a-proposal/Steps-for-Submitting-a-Proposal. The analysis was approved by the University of Virginia Human Subjects Institutional Review Board, Yale University's Human Investigation Committee, and a Swedish multisite ethics committee. Informed consent was waived. Two cohorts of patients with heart failure were studied. The first cohort was drawn from NCDR ICD Registry Version 2 patients who received a first generator change after an initial ICD implant for primary prevention of sudden cardiac arrest (primary prevention ICD first generator change group [ICD-PP-GC]) between July 2012 and March 2016. The NCDR ICD Registry is the largest ICD registry in the United States. Although participation in the NCDR ICD Registry is voluntary, participation in this registry by US hospitals is common, and several hundred

thousand ICD procedures are captured on an annual basis.[2] ICD Registry Version 2 patients during this time period who were not undergoing a first generator change were excluded. The second cohort heart failure without implantable cardioverter-defibrillator (HF-NO-ICD) included subjects without ICDs from 3 heart failure registries and 3 clinical trials: the University of Washington Registry,[12] Italian Network on Congestive Heart Failure,[13] SwedeHF Registry (Swedish Heart Failure Registry),[14] Carvedilol or Metoprolol European Trial,[15] the Valsartan Heart Failure Trial,[16] and the Prospective Randomized Amlodipine Survival Evaluation 1 Trial.[17] These studies were chosen as the control group[18] because they provided high-quality and generalizable data on patients who would otherwise be candidates for primary prevention ICDs. Inclusion of both registry and clinical trial patients in the control group is justified by a prior analysis showing that adjustment for SHFM completely accounts for differences in survival probabilities in patients from clinical trials and registries.[19] These patients were designated as the HF-NO-ICD group for the purposes of the present study. Of note, the main reason control group patients were eligible for ICDs but did not receive them was related to geographical considerations. A recent editorial highlighted geographical discrepancy in ICD implantation rates both between different continents (577 implants per 1 million people in the United States compared with 155 per 1 million people in Europe) and countries, and also within the same country.[20] Major differences within European Society of Cardiology regions have also been described.[21] Furthermore, the validity of this comprehensive approach using this control group for analysis of outcomes after an initial primary prevention ICD has previously been validated.[18]

Determination of Survival Outcomes

Patient data from the NCDR ICD Registry Version 2 were linked to the National Death Index maintained by the Centers for Disease Control and Prevention to determine long-term mortality up to 6 years following device implantation in the ICD-PP-GC group. Although cause of death was not available, the mechanism of potentially improved adjusted survival with the ICD generator change was inferred be a reduction in arrhythmic death, because an ICD potentially saves lives by treatment of arrhythmic death. Dates of birth, names, and social security numbers were used to perform the matching between the NCDR database and the National Death Index. Survival for patients in the HF-NO-ICD group was obtained from follow-up in the associated studies and registries used to compose this group.

Inclusion and Exclusion Criteria

The following inclusion and exclusion criteria were applied to the ICD-PP-GC and HF-NO-ICD groups.

Inclusion criteria were: (1) age ≥30 years and (2) QRS <150 milliseconds to restrict the analysis to patients who did not have a class I indication for cardiac resynchronization therapy.[22] This temporal subset of Version 2 of the ICD Registry was chosen to balance the priority of having as contemporary a cohort as possible (in this case, with replacement ICDs implanted within the past 10 years) with the need for approximately 4 years of follow-up after device implantation to facilitate meaningful findings. Exclusion criteria were: (1) creatinine >4 mg/dL, (2) sodium <120 or >155 mEq/L, (3) hemoglobin <7 or >19 g/dL, (4) LVEF >60%, (5) systolic blood pressure <80 mm Hg or >220 mm Hg, and (6) known presence of a genetic syndrome associated with sudden cardiac arrest. Because a history of ICD therapies after the primary prevention initial implant and before the generator change has not been shown to predict a survival benefit from the generator change,[23] patients with and without ICD therapies between the time of initial primary prevention ICD implant and generator change were included in the analysis. The additional exclusion criterion applied to patients in the ICD-PP-GC group was that the device implanted was not one that delivered cardiac resynchronization therapy. The additional exclusion criterion applied to the HF-NO-ICD group was that they did not have a pacemaker implanted for either a bradycardia or cardiac resynchronization therapy indication.

Determination of SHFM and SPRM Scores

The SHFM and SPRM scores were determined as in our prior analyses of these models in the NCDR ICD Registry Version 1.[18,19] The SHFM model was calculated based on age, sex, New York Heart Association class, ischemic cause of cardiomyopathy, LVEF, systolic blood pressure, sodium, creatinine, angiotensin-converting enzyme inhibitor use or angiotensin receptor blocker use, β-blocker use, digoxin use, loop diuretic use, statin use, diabetes, lung disease, and QRS width. The SPRM[18,24,25] was calculated using age, sex, New York Heart Association class, LVEF, systolic blood pressure, sodium, creatinine, digoxin use, and diabetes with the following exception: body mass index was not available in the NCDR cohort, and the next strongest variable, ischemic cause of cardiomyopathy, was added.

Changes in Risk Scores Over Time

To address to impact of changes in the SPRM or SHFM on survival after ICD generator changes, linkage of a subset of the patients in the ICD-PP-GC group from Version 2 of the NCDR ICD Registry to the records for the corresponding initial ICD implant in Version 1 of the NCDR ICD Registry was performed. The SHFM, SPRM, and the change in these parameters between

the initial implant and generator change were then evaluated with respect to their associations with survival.

Statistical Analysis

Analyses were performed for the primary statistical analysis using SAS version 9.4 (SAS Institute, Cary, NC). Baseline continuous variables in the ICD-PP-GC and HF-NO-ICD groups were described using the mean and standard deviation, whereas categorical variables were described based on their frequency and percentage. Differences between groups for continuous variables were assessed using the Student t test, whereas differences between groups for categorical variables were assessed using χ^2 tests.

Survival analysis with determination of log-rank P values was initially used to determine differences in overall survival times in the ICD-PP-GC group with stratification by: (1) quartiles of the SHFM score (equivalent to predicted annual mortality) and (2) LVEF >35%/ LVEF≤35%. For this analysis, censoring was applied if the patient was still alive at the end of the follow-up period. Next, Cox proportional hazards analysis of both cohorts (ICD-PP-GC and HF-NO-ICD) adjusted by the SHFM score (equivalent to predicted annual mortality) was performed to determine if there was overall survival benefit or harm associated with the replacement ICD. Adjustment by the SHFM to account for expected differences in annual mortality of patients in the different cohorts was the prespecified strategy for this analysis based on validation in prior work.[19] Of note, the models were not adjusted by the occurrence of ICD therapies because this covariate was not available in patients without ICDs. The proportional hazards assumption was confirmed by demonstration of proportional separation of the associated Kaplan-Meier curves.

Of note, this approach has been validated in our previous analyses of NCDR outcomes in patients with initial ICD implants to evaluate clinical outcomes in these patients.[18,19] Because the SHFM provides appropriate weighting of risk based on a validated set of covariates, adjustment by the SHFM has been shown to be as effective as individual covariate adjustment to isolate the effect of the device on clinical outcomes.[19] SHFM-adjusted survival curves were generated using the results of the Cox proportional hazards models.

Next, analysis of both cohorts using the SPRM score, equivalent to the predicted probability that a patient's death would be arrhythmic (PRAD, as defined above), was performed. A Cox proportional hazards analysis including covariates of ICD, SHFM, SPRM, and the interaction covariate SPRM*ICD was performed in the entire combined cohort and then in cohorts stratified based on whether or not the LVEF was >35% at the time of generator change. In this analysis, a significant P value for the SPRM*ICD

interaction covariate indicated that the effectiveness of the ICD varied based on the SPRM score. Inclusion of the SHFM in the model provided adjustment for differences in survival based on patient characteristics in order to facilitate identification of patients likely to have potential harm or benefit from the replacement ICD. Based on the framework of the Cox proportional hazards regression model, the 95% confidence bounds for the hazard ratio (HR) associated with the ICD generator change (ICD-GC-HR) as a function of the SPRM or PRAD were calculated. A similar model in the combined cohort was generated using covariates of ICD, SHFM, LVEF >35%, and LVEF >35%*ICD.

The ICD-GC-HR and associated 95% confidence bounds were then plotted versus the PRAD. The PRAD values for which survival was worse with the ICD were defined as those for which the 95% lower confidence bound of the ICD-GC-HR was >1, whereas the PRAD values for which survival was improved with the ICD were defined as those for which the 95% upper confidence bound of the ICD-GC-HR was <1. The ICD-GC-HR was interpreted as suggesting a possible but nonsignificant effect on survival otherwise. The PRAD, which is a function of SPRM, was plotted on the horizontal axis instead of the SPRM in this plot. Because the SPRM is a raw score, and the PRAD provides the scaled proportional risk of arrhythmic death based on an exponential function of the SPRM, the PRAD rather than the SPRM was used in the plot for ease of interpretation.

The SHFM-predicted annual mortality and the PRAD both at the times of initial implant and generator change are displayed with box plots with stratification by those who were alive or dead at last follow-up after the generator change. In addition, the median changes of these parameters for each patient are also displayed using box plots.

RESULTS

Baseline Risk at Generator Change and Other Characteristics of the Combined Cohort

The main cohort consisted of 40 933 patients in the NDCR ICD Registry with generator changes for ICDs implanted for a primary prevention indication during the period from 2012 to 2016 (ICD-PP-GC group). As shown in Table 1, the patient characteristics were typical of other primary prevention ICD trials. At the time of generator change, 65.9% of patients had an LVEF of ≤35%. Compared with the control cohort of 23 472 patients without ICDs (HF-NO-ICD group), ICD-PP-GC patients had a greater prevalence of ischemic cardiomyopathy. Also, a greater proportion of patients in the ICD-PP-GC group were on β-blockers and statins. The

Table 1. Baseline Characteristics

Characteristic	ICD-PP-GC, N=40 933	HF-NO-ICD, N=23 472	*P* value
Demographics			
Age, y, mean (SD)	67.7 (12.0)	66.2 (11.5)	<0.0001
Sex, men, n (%)	30 907 (75.5)	17 880 (76.2)	0.056
History and risk factors, n (%)			
NYHA class			<0.0001
Class I	8036 (19.7)	1318 (5.6)	
Class II	21 758 (53.2)	12 941 (55.1)	
Class III	10 357 (25.3)	8541 (36.4)	
Class IV	508 (1.2)	672 (2.9)	
Ischemic cardiomyopathy	27 498 (67.2)	10 707 (45.6)	<0.0001
Chronic lung disease	8710 (21.3)	2946 (12.6)	<0.0001
Diabetes	15 871 (38.8)	5875 (25.0)	<0.0001
Diagnostics			
LVEF, %, mean (SD)	33.5 (11.8)	30.6 (8.8)	<0.0001
LVEF ≤35%, n (%)	26 963 (65.9)	17 664 (75.3)	<0.0001
QRS duration, ms, mean (SD)	108.6 (17.7)	105.4 (19.8)	<0.0001
Creatinine, mg/dL, mean (SD)	1.2 (0.45)	1.2 (0.39)	<0.0001
Hemoglobin, g/dL, mean (SD)	13.4 (1.8)	13.8 (1.6)	<0.0001
Sodium, mEq/L, mean (SD)	139.1 (3.1)	139.7 (3.3)	<0.0001
Systolic BP, mm Hg, mean (SD)	132.3 (21.1)	125.7 (19.3)	<0.0001
Medications, n (%)			
ACE inhibitor or ARB	30 716 (75.0)	22 217 (94.7)	<0.0001
β-Blocker	37 161 (90.8)	15 265 (65.0)	<0.0001
Digoxin	8177 (20.0)	10 201 (43.5)	<0.0001
Loop diuretic	24 765 (60.5)	19 201 (81.8)	<0.0001
Statin	29 913 (73.1)	9017 (38.4)	<0.0001
Severity scores			
SHFM-predicted annual mortality, %, mean	9.1%	12.0%	<0.0001
SPRM-predicted proportional risk of arrhythmic death, %, mean (SD)	49.9% (12.2%)	48.5% (12.4%)	<0.0001
Follow-up, y, median (Q1, Q3)	4.85 (3.74, 6.06)	2.27 (1.19, 3.94)	<0.0001
Arrhythmia findings, pre-GC, n (%)			
Ventricular tachycardia	15 065 (36.8)	N/A	<0.0001
Cardiac arrest	1096 (2.7)	N/A	<0.0001
ATP/shock therapy	7128 (17.4)	N/A	<0.0001
NSVT on EPS	589 (1.4)	N/A	<0.0001

ACE indicates angiotensin-converting enzyme; ARB, angiotensin receptor blocker; ATP, anti-tachycardia pacing; BP, blood pressure; EPS, electrophysiology study; GC, generator change; HF-NO-ICD, heart failure group without implantable cardioverter-defibrillator; ICD-PP-GC, primary prevention first implantable cardioverter-defibrillator generator change group; LVEF, left ventricular ejection fraction; NSVT, nonsustained ventricular tachycardia; NYHA, New York Heart Association; Q1, Q3, quartile 1, quartile 3; SHFM, Seattle Heart Failure Model; and SPRM, Seattle Proportional Risk Model.

median follow-up time for the combined cohort was 4.14 years (interquartile range [IQR], 2.02–5.44 years), and the follow-up times by group are given in Table 1.

Adjustment for differences in patient characteristics was effectively performed using the SHFM score, which was a significant predictor of overall survival after ICD generator change (Figure 1). Compared with unadjusted survival curves stratified by LVEF >35% (Figure 1A), there is greater separation of the survival curves stratified by the quartile of the SHFM score (Figure 1B). The best survival was observed in SHFM quartile 1, and increasingly worsening survival was observed in SHFM quartiles 2 through 4.

With respect to delivery of ATP/shock therapies before the ICD generator change, pre–generator change ICD therapies were noted to have a more unfavorable SHFM-adjusted prognosis in patients in the ICD-PP-GC group (HR, 1.08 [95% CI, 1.03–1.13];
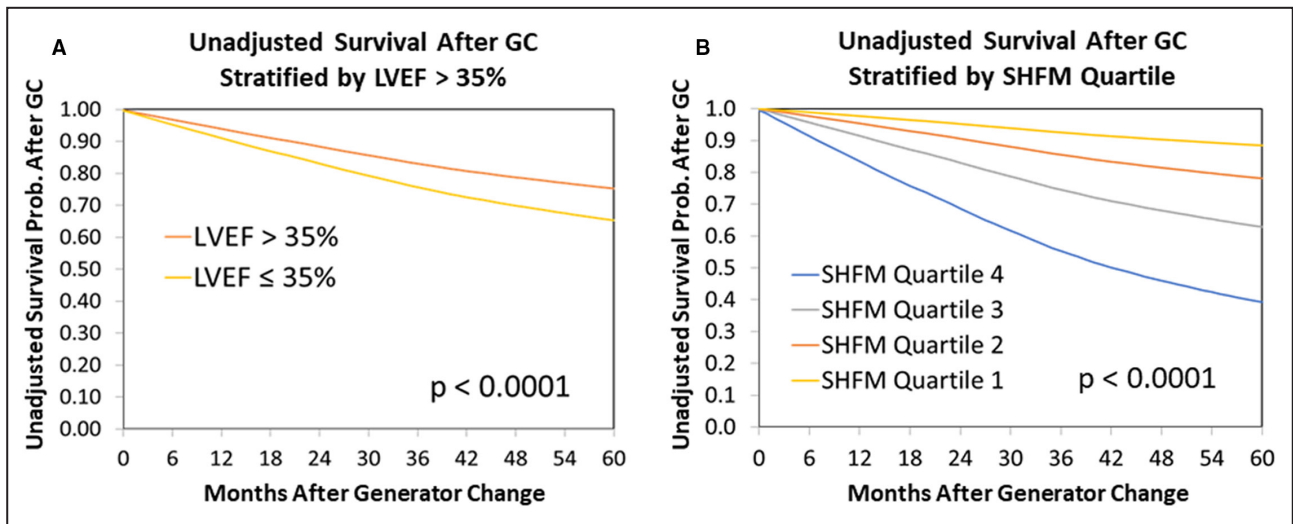
Figure 1. Unadjusted survival after implantable cardioverter-defibrillator (ICD) generator change (GC).
Among patients with ICD GCs, survival after the GC is shown to vary significantly based on whether the LVEF is >35% or ≤35% (**A**) and the quartile of the Seattle Heart Failure Model (SHFM) (**B**). The separation of the survival curves is greater in (**B**). Prob. indicates probability.

P=0.0006); however, this covariate did not apply to the control group and thus could not be used in the analysis of factors evaluated with respect to whether they identified patients expected to have a survival benefit from the generator change.

LVEF, Survival, and Survival Benefit After ICD Generator Change

Although patients in the ICD-PP-GC group with LVEF >35% had improved unadjusted survival after

Table 2. Cox Proportional Hazards Models

Covariate in model	β coefficient	SE β coefficient	Hazard ratio*	95% CI hazard ratio*	P value
Model 1: all ICD-PP-GC and HF-NO-ICD patients					
SHFM	0.952	0.0090	2.59	2.54–2.64	<0.0001
LVEF >35%	−0.0037	0.035	0.996	0.93–1.07	0.16
ICD-PP-GC	0.0227	0.019	1.02	0.99–1.06	<0.0001
ICD-PP-GC*LVEF>35%	0.1880	0.040	1.21	1.12–1.31	<0.0001
Model 2: all ICD-PP-GC and HF-NO-ICD patients					
SHFM	0.859	0.010	2.36	2.31–2.41	<0.0001
ICD-PP-GC	0.025	0.018	1.03	0.99–1.06	0.16
SPRM	−0.122	0.027	0.88	0.84–0.93	<0.0001
SPRM*ICD-PP-GC	−0.143	0.030	0.87	0.82–0.92	<0.0001
Model 3: LVEF ≤35% stratification group					
SHFM	0.870	0.013	2.39	2.33–2.45	<0.0001
ICD-PP-GC	0.009	0.020	1.01	0.97–1.05	0.66
SPRM	−0.070	0.032	0.93	0.88–0.99	0.03
SPRM*ICD-PP-GC	−0.113	0.035	0.89	0.83–0.96	0.001
Model 4: LVEF >35% stratification group					
SHFM	0.862	0.024	2.37	2.26–2.48	<0.0001
ICD-PP-GC	0.154	0.050	1.17	1.06–1.29	0.002
SPRM	−0.334	0.060	0.72	0.64–0.81	<0.0001
SPRM*ICD-PP-GC	−0.083	0.065	0.92	0.81–1.04	0.201

HF-NO-ICD indicates heart failure group without implantable cardioverter-defibrillator; ICD-PP-GC, primary prevention first implantable cardioverter-defibrillator generator change group; LVEF, left ventricular ejection fraction; SHFM, Seattle Heart Failure Model; and SPRM, Seattle Proportional Risk Model.
*Hazard ratio is based on a unit increase of the parameter.

implantation of a replacement ICD (unadjusted HR, 0.67 [95% CI, 0.65–0.70]) relative to those with LVEF ≤35% (Figure 1A), the Cox proportional hazards Model 1 in Table 2 indicates worse SHFM-adjusted survival in patients with LVEF >35% having generator changes relative to control group patients with LVEF >35% based on the HR of 1.21 (95% CI, 1.11–1.31) for the interaction between the replacement ICD and LVEF >35%. This model also indicates no significant difference in survival times overall for LVEF ≤35% with or without a replacement ICD. This can be seen by setting the LVEF >35% covariate to 0 and then noting a nonsignificant HR for the ICD.

Enhancement of LVEF Model for Survival Benefit/Harm With SPRM/PRAD

As shown in Figure 2, SHFM-adjusted survival was greatest in patients in the PP-ICD-GC group with SPRM/PRAD in the highest quartile and decreased with decreasing quartiles of SPRM/PRAD. A survival benefit for the generator change was mostly observed with SPRM above the median (quartiles 3 and 4). There was no evidence of benefit with the ICD generator change in patients in the lowest SPRM/PRAD quartile.
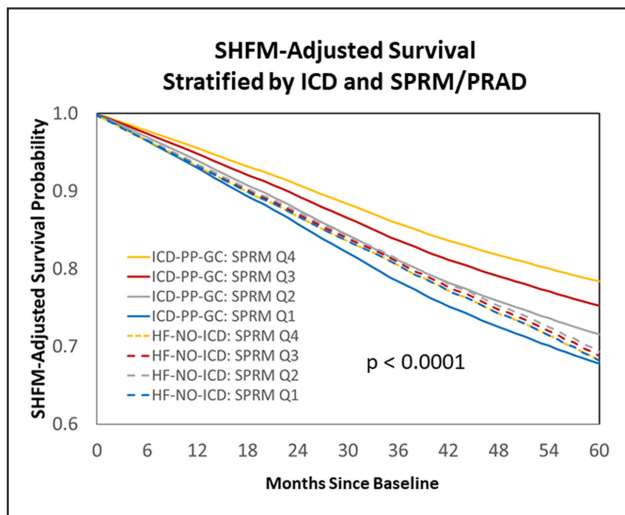

Figure 2. Seattle Heart Failure Model (SHFM)-adjusted survival stratified by proportional risk of arrhythmic death (PRAD)/Seattle Proportional Risk Model (SPRM) and implantable cardioverter-defibrillator (ICD) generator change status.
SHFM-adjusted survival curves with stratification by PRAD/SPRM quartiles and cohort (ICD-PP-GC vs HF-NO-ICD) are shown. The potential survival benefit for patients with generator changes versus control patients appears to be limited to SPRM quartile (Q) 3 and Q4 (SPRM above the median) based on the separation of ICD-PP-GC and HF-NO-ICD survival curves in these quartiles. HF-NO-ICD indicates heart failure group without implantable cardioverter-defibrillator; and ICD-PP-GC, primary prevention first implantable cardioverter-defibrillator–generator change group.
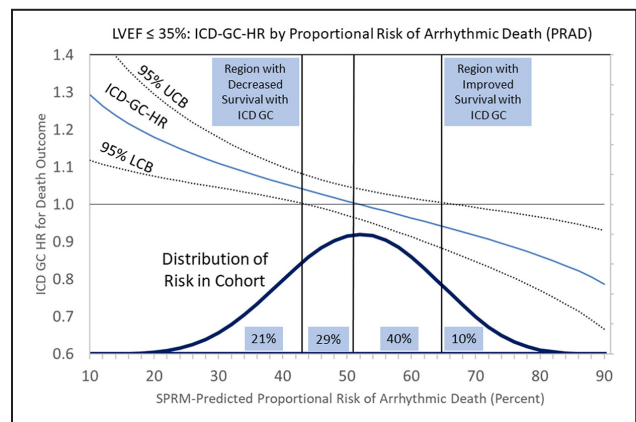

Figure 3. Implantable cardioverter-defibrillator (ICD) generator change (GC) hazard ratio versus Seattle Proportional Risk Model (SPRM)-predicted proportional risk of sudden death (PRAD).
The ICD-GC-HR as a function of the PRAD at the time of GC is plotted with 95% confidence bounds for patients with left ventricular ejection fraction (LVEF) ≤35%. This hazard ratio is defined as the time-dependent hazard associated with the ICD-GC divided by the corresponding hazard for similar patients (based on Seattle Heart Failure Model adjustment) in the control group without an ICD GC. The strongest indication of benefit or harm corresponds to PRAD values for which the 95% confidence bounds for this hazard ratio does not include 1. ICD-GC-HR indicates hazard ratio associated with ICD generator change; LCB, lower confidence bound; and UCB, upper confidence bound.

Based on a Cox proportional hazards model adjusted for the SHFM with covariates of SHFM, SPRM, ICD, and ICD*SPRM, the survival benefit from the ICD generator change depended strongly on the SPRM score, with *P*<0.0001 for the SPRM*ICD interaction term. In Table 2, 3 additional models (Models 2–4) are shown: the model for the entire combined cohort (Model 2), the model for the combined cohort the LVEF ≤35% (Model 3), and the model for the combined cohort with LVEF >35% (Model 4). In the overall cohort and patients with LVEF ≤35%, the SPRM*ICD interaction term was highly significant in the survival model, demonstrating the usefulness of the SPRM/PRAD for prediction of survival benefit after the generator change.

As shown in Figure 3, based on the 65.9% of patients in the ICD-PP-GC group with LVEF ≤35%, increased survival relative to controls after generator change was more likely in the 10% of patients with PRAD >65%, whereas decreased survival with the ICD-PP-GC group was more likely in the 21% of patients with PRAD <43%. In patients with LVEF >35%, the ICD-GC-HR was >1 for nearly the entire range of PRAD (PRAD <88%), with wider CIs compared with those observed in the model for patients with LVEF ≤35%.

In a sensitivity analysis of ICD patients with ICD therapies before the generator change versus control patients, and ICD patients without ICD therapies

before the generator change versus control patients, similar prognostication was achieved with the SPRM. In Cox proportional hazards regression models with covariates of SHFM, SPRM, ICD, and the SPRM*ICD interaction term, the HR for the SPRM*ICD interaction term was statistically significant and <1 in both groups (patients with ICD generator change with and without therapies before the generator change), indicating that the SPRM identifies patients expected to have a survival benefit from the generator change regardless of whether they had pre–generator change ICD therapies (no prior therapies: interaction HR, 0.85 [95% CI, 0.80–0.91]; *P*<0.0001; prior therapies: interaction HR, 0.90 [95% CI, 0.82–0.988]; *P*=0.027).

Changes in Predicted Overall and Arrhythmic Risk From the Time of Initial Implant to the Time of Generator Change

For the purpose of evaluating changes in the SHFM and patient risk from the time of initial ICD implant to the time of ICD generator change, outcomes were evaluated after matching 6593 patients with ICD generator changes in Version 2 of the ICD registry with 6593 corresponding entries for the initial implant of the primary prevention ICD in Version 1 of the ICD Registry (Table 3). From the time of the initial primary prevention ICD implant to the time of the generator change, the LVEF increased from 28.2% to 33.3%, angiotensin-converting enzyme inhibitor use increased from 69.9% to 75.9%, β-blocker use increased from 88.0% to 92.1%, and diuretic use was stable at between 61% and 62%.

The box plots in Figure 4 show the median and interquartile ranges for predicted annual mortality at the time of initial ICD implant (Figure 4A), at the time of generator change (Figure 4B), and the change per patient in predicted annual mortality between these 2 time points (Figure 4C). At the time of the initial implant, the predicted annual mortality was just slightly increased in nonsurvivors after generator change (6.9% [IQR, 3.9%–12.4%]) versus survivors after generator change (6.3% [IQR, 3.5%–11.9%]) (*P*=0.04). In contrast, at the time of the generator change, the predicted annual mortality was markedly lower in survivors after generator change (4.10% [IQR, 2.5%–6.8%]) than in nonsurvivors after generator change (8.4% [IQR, 4.9%–13.6%]) (*P*<0.0001). As shown in Figure 4C, there was also a greater increase in predicted annual mortality from initial implant to generator change for patients who died after the replacement ICD versus those who were alive at the last follow-up (*P*<0.0001).

An analogous set of box plots is shown in Figure 4D through 4F for the proportional risk of sudden death. At the time of initial implant (Figure 4D), the proportional risk of sudden death was similar in survivors

Table 3. Baseline Characteristics of Linked National Cardiovascular Data Registry Patients at the Time of Generator Change

Characteristic	Summary
Demographics	
Age, y, mean (SD)	66.6 (12.5)
Sex, men, n (%)	9731 (73.8)
History and risk factors, n (%)	
NYHA class	
Class I	2215 (16.8)
Class II	5866 (44.5)
Class III	4808 (36.5)
Class IV	297 (2.3)
Ischemic disease	8350 (63.3)
Chronic lung disease	2783 (21.1)
Diabetes	5152 (39.1)
Diagnostics, mean (SD)	
LVEF, %	30.8 (11.6)
QRS duration, ms	115.7 (27.2)
Creatinine level, mg/dL	1.2 (0.8)
Sodium, mEq/L	138.8 (3.2)
Systolic BP, mm Hg	131.6 (22.3)
Medications, n (%)	
ACE inhibitor or ARB	9617 (72.9)
β-Blocker	11 874 (90.1)
Digoxin	2615 (19.8)
Loop diuretic	8122 (61.6)
Statin	9130 (69.2)

ACE indicates angiotensin-converting enzyme; ARB, angiotensin receptor blocker; BP, blood pressure; LVEF, left ventricular ejection fraction; and NYHA, New York Heart Association.

after generator change (46.1% [IQR, 35.8%–55.9%]) and nonsurvivors after generator change (45.3% [IQR, 35.2%–54.9%]) (*P*=0.14). In contrast, at the time of generator change (Figure 4E), patients alive at the last follow-up after the generator change had a greater proportional risk of sudden death (52.8% [IQR, 44.6%–60.4%]) than those who had died after the replacement ICD (43.5% [IQR, 34.7%–52.0%]) (*P*<0.0001). As shown in (Figure 4F), there was also a greater increase in the proportional risk of sudden death from initial implant to generator change in survivors after the replacement ICD versus those who had died after the generator change (*P*<0.0001).

The best (unadjusted) survival after generator change was seen in the patients with the most favorable changes in the SHFM from the time of initial implant to generator change. SHFM score change quartile 4 patients (greatest increase in predicted annual mortality) had the worst survival, SHFM score change quartile 1 patients (greatest decrease in predicted annual mortality) had the best survival, and intermediate survival
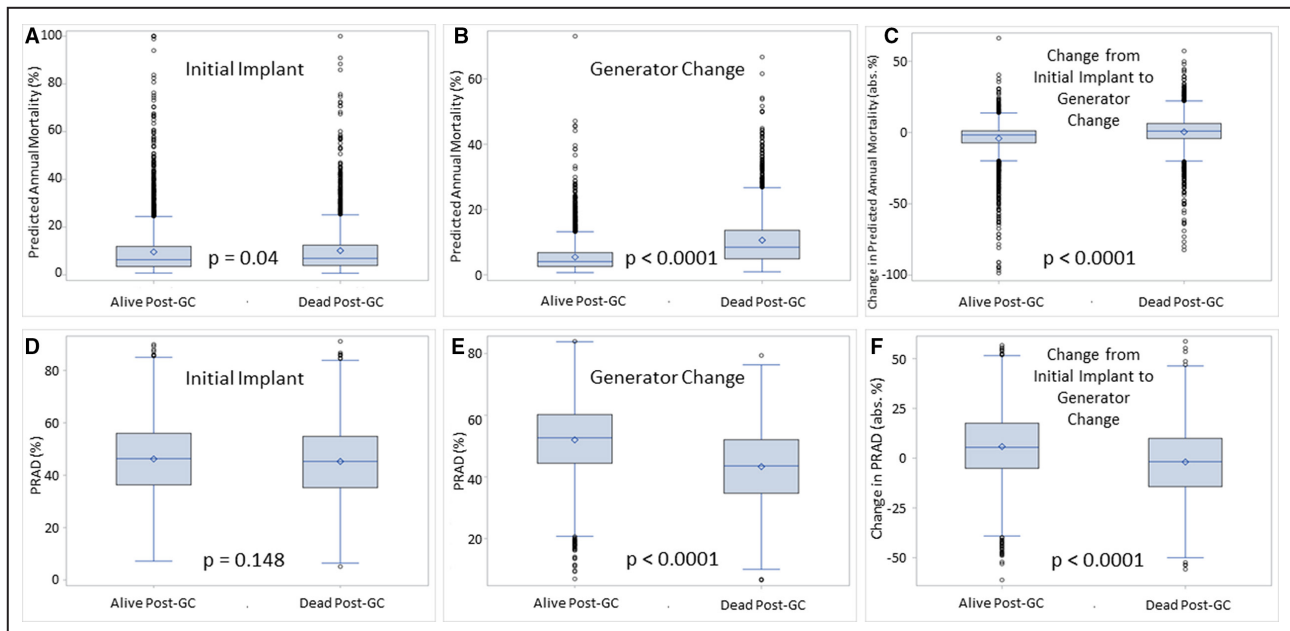
Figure 4. Dynamic nature of risk scores from the time of initial implant to the time of implantable cardioverter-defibrillator (ICD) generator change (GC).
Based on linked records in Versions 1 and 2 of the ICD Registry, box plots are shown with the median and interquartile ranges for Seattle Heart Failure Model–predicted annual mortality at the time of the initial implant (**A**) and the time of the generator change (**B**) grouped by whether the patient was alive or dead at the time of last follow-up after the replacement ICD. The change in this parameter for each patient stratified by those who survived or died following the replacement ICD is shown in (**C**). A similar analysis is shown based on the Seattle Proportional Risk Model–predicted proportional risk of sudden death at the time of the initial ICD implant (**D**) and the time of the generator change (**E**) based on patient records linked across registries. Again, a comparison of this parameter based on the change for each patient stratified by those who survived or died following the replacement ICD is shown in (**F**). abs. indicates absolute; and PRAD, proportional risk of arrhythmic death.

was observed in the middle quartiles (Figure 5). Similar findings were observed with respect to the change in the change in the SPRM score from the time of initial implant to generator change. The 5-year mortality in SHFM quartile 4 and in the remaining 3 quartiles combined was 48.1% and 26.2%, respectively. In this way, both the SHFM-predicted annual mortality and associated temporal change in the SHFM were strongly associated with overall survival. These findings were consistent with the predictive value of SHFM parameters for overall survival, which may be contrasted with the predictive value of the SPRM/PRAD for survival benefit.

With respect to LVEF assessments at the times of the initial implant and generator change, respectively, the LVEF from the time of initial ICD to generator change remained within 10 percentage points in 44.1%, increased by >10 percentage points in 39.7%, and decreased by >10 percentage points in 16.1%. After SHFM adjustment, an increase in the LVEF >10 percentage points was associated with modestly decreased mortality during follow-up (HR, 0.84 [95% CI, 0.77–0.93]; $P=0.006$), whereas a decrease in LVEF >10 percentage points was associated with somewhat increased mortality during follow-up (HR, 1.18 [95% CI, 1.05–1.32]; $P=0.006$).

DISCUSSION

The main findings of this investigation were that in a large, real-world database of over 60 000 patients with heart failure with or without an ICD, many patients do not appear to have a survival benefit from a generator change of an ICD not delivering cardiac resynchronization therapy originally implanted for a primary prevention indication, and the PRAD and LVEF >35% at the time of generator change were effective for identifying patient groups for whom the replacement ICD was associated with survival benefit, harm, or no effect on survival. In this cohort, approximately one-third of patients undergoing these generator changes had a LVEF >35%. These patients had better survival than patients with a persistently reduced LVEF at the time of generator change; however, the control group patients without the ICD and LVEF >35% had comparable or even better adjusted survival, such that there was not a survival benefit and potentially harm associated with the generator change throughout the range of the PRAD parameter with LVEF >35% at the time of generator change. In contrast, in the approximately two-thirds of patients with a persistently reduced LVEF ≤35% at the time of implantation of the replacement ICD, the calculated HR for the ICD indicated a worse
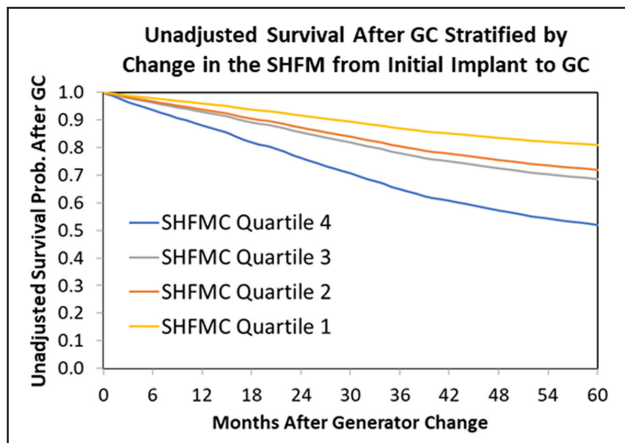
Figure 5. Unadjusted survival after implantable cardioverter-defibrillator (ICD) generator change (GC) based on Seattle Heart Failure Model score change (SHFMC) from initial implant to GC.

Survival curves are stratified by quartiles of the change in the Seattle Heart Failure Model (SHFM) score from the time of the initial ICD implant to the time of the ICD GC in the cohort of patients with linkage between the initial implant in Version 1 and the first ICD GC in Version 2 of the ICD Registry. Markedly worse survival was observed in the quartile of patients with the most unfavorable change in SHFM (greatest increase in predicted annual mortality) from the time of the initial ICD implant to the time of the first generator change. Prob. indicates probability.

survival associated with the generator change with PRAD <43% and a survival benefit in patients with a PRAD >65%.

Controversy still exists about decision making surrounding these generator changes at the time of battery depletion, particularly in patients who have recovered some degree of left ventricular function.[26] ICDs may be associated with complications, such as hematomas, infections, erosions, and inappropriate shocks, and the benefit of primary prevention ICDs in patients with a low proportional risk of arrhythmic death may be outweighed by the negative consequence of having an ICD. The finding that the proportional risk of arrhythmic death predicts survival benefit makes sense physiologically from the standpoint that patients with a greater proportional risk of arrhythmic death should be more likely to have improved survival with a device designed to treat an arrhythmic cause of death. The reason that the patients with LVEF improved to over 35% at the time of generator change had an aggregate lack of survival benefit or potentially harm across a range of PRAD values also appears related to the fact that the PRAD values were lower in these patients.

With respect to the clinical approach to the patient, these findings suggest that determination of the PRAD and LVEF could be used together to help with shared decision making when patients having primary prevention, non-cardiac resynchronization therapy ICDs with little remaining battery longevity are being evaluated

for the generator change procedure. For example, the third of patients with LVEF >35% could be advised that there is no evidence for an aggregate survival benefit with the generator change. For the two-thirds of patients with LVEF ≤35%, the PRAD could be calculated and used to guide the dicussion. The study design did not allow incorporation of prior ICD therapies or pacing needs into the survival benefit model, because these parameters could not be determined in control patients. As a result, these factors could also be included separately in the discussions between providers and patients on whether to replace the ICD generator.

A particular challenging scenario is the patient with ICD battery depletion, prior ICD therapies, and a low PRAD. In this regard, there is a prevalent misconception that ICD therapies are equivalent to ICD survival benefit in all patients. This was refuted in a study of 617 patients, which found that although ATP or shock therapies before generator replacement predicted ICD therapies after generator replacement, ATP, or shock therapies before generator replacement were not associated with a survival benefit from the generator replacement, and the HR was actually in the direction of harm (HR for mortality after generator replacement, 1.15 [95% CI, 0.63–2.07]; P=0.65).[23] In support of the fact that the PRAD can predict which patients will have a survival benefit from ICD therapies, patients with an initial primary prevention ICD implant in the SCD-HeFT (Sudden Cardiac Death in Heart Failure Trial) had 18% mortality after the first ICD shock when the SPRM/PRAD was below the median versus 2% mortality when the SPRM/PRAD was above the median (P=0.0002).[27] Other studies also support potential harm to patients receiving both appropriate shocks[28,29] and inappropriate shocks.[30] Because the present findings in the NCDR registry confirm these results, patients with a low PRAD should understand that they are less likely to have a survival benefit from the shocks. Although generator replacement is still reasonable in this situation, the findings from this study will provide patients who have a low PRAD with a more realistic understanding of their prognosis.

In addition to these findings with respect to survival benefit, this study also demonstrated that a different established risk model (SHFM) accurately predicted annual estimated mortality after the generator change. Notably, a patient's expected annual mortality from the time of initial primary prevention ICD implantation to generator change may increase, decrease, or stay the same, and this finding is also predictive of actual mortality after the replacement ICD. Although the ICD benefit is tied to the proportional and absolute risks of sudden death,[24,31,32] it has not been previously understood how a patient's proportional risk of sudden death changes from the time of the initial ICD implant to the time of referral for ICD generator change. In this

study, favorable changes were more likely in patients who survived, whereas unfavorable changes were more likely in patients who died.

Of note, the present study did not compare patients who had their devices turned off with those who received replacement ICDs, because such a cohort was not available. Instead, key factors that could influence the survival benefit associated with the replacement ICD were evaluated. Our findings could have an important impact on decision making among patients and providers, as well as future clinical trial designs by highlighting key factors associated with prognosis and survival benefit with replacement ICDs. In addition, these findings also provide key data that could be the basis for a randomized clinical trial to evaluate the effectiveness of a risk model–based intervention to determine the best candidates for replacement ICDs.

Limitations

Several limitations should be considered when applying the findings of this analysis to the broader population. First, this was a retrospective analysis that relied heavily on the accuracy of the data captured in these administrative-based registries. Second, death events rather than the cause of death were available and used for the analysis. Third, in the analysis of changes in the risk scores over time, not all patients were matched between the 2 versions of the NCDR registry. Lastly, the overall analysis focused on individuals with systolic dysfunction as the primary indication for a primary prevention ICD. Caution should be exercised when applying these results to individuals with channelopathies or another genetic predisposition to increased sudden death risk. Although sacubitril/valsartan and sodium-glucose cotransporter-2 inhibitors are now increasingly used in patients with heart failure, the results of this study are expected to be generalizable to these patients because guideline-directed medical therapy did not change the proportional sudden death risk during derivation of the SPRM, and available evidence suggests that guideline-directed medical therapy does not change the proportion of sudden versus nonsudden death, which is the focus of the present study and predicted by the SPRM. For example, the use of an angiotensin-neprilysin inhibitor (sacubitril/valsartan) did not change the proportion of sudden death in the PARADIGM-HF (Prospective Comparison of ARNI With ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure) trial (35.2% versus 37.2%), in which the cause-specific sudden death was decreased by 18% and nonsudden death was decreased by 21%.[33,34] In addition, sodium-glucose cotransporter-2 inhibitors in heart failure with reduced ejection fraction did not change the proportion of sudden death in the DAPA-HF (Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure) trial (33.3% versus 34.3%),[35] and there was not a statistically significant effect on the cause-specific sudden death outcome.

Conclusions

Patients who received replacement of an ICD originally implanted for primary prevention and had at the time of generator change either LVEF >35% alone or both LVEF ≤35% and PRAD <43% had worse survival versus controls without ICDs. The association of the PRAD with survival benefit or harm was similar in patients with or without ICD therapies before generator change.

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