



Seattle Heart Failure and Proportional Risk Models Predict Benefit From Implantable Cardioverter-Defibrillators

Kenneth C. Bilchick, MD,^a Yongfei Wang, MS,^{b,c} Alan Cheng, MD,^d Jephtha P. Curtis, MD,^{b,c} Kumar Dharmarajan, MD,^{b,c} George J. Stukenborg, PhD,^e Ramin Shadman, MD,^f Inder Anand, MD,^g Lars H. Lund, MD,^h Ulf Dahlström, MD, PhD,ⁱ Ulrik Sartipy, MD, PhD,^{j,k} Aldo Maggioni, MD,^l Karl Swedberg, MD, PhD,^{m,n} Chris O'Connor, MD,^o Wayne C. Levy, MD^p

ABSTRACT

BACKGROUND Recent clinical trials highlight the need for better models to identify patients at higher risk of sudden death.

OBJECTIVES The authors hypothesized that the Seattle Heart Failure Model (SHFM) for overall survival and the Seattle Proportional Risk Model (SPRM) for proportional risk of sudden death, including death from ventricular arrhythmias, would predict the survival benefit with an implantable cardioverter-defibrillator (ICD).

METHODS Patients with primary prevention ICDs from the National Cardiovascular Data Registry (NCDR) were compared with control patients with heart failure (HF) without ICDs with respect to 5-year survival using multivariable Cox proportional hazards regression.

RESULTS Among 98,846 patients with HF (87,914 with ICDs and 10,932 without ICDs), the SHFM was strongly associated with all-cause mortality ($p < 0.0001$). The ICD–SPRM interaction was significant ($p < 0.0001$), such that SPRM quintile 5 patients had approximately twice the reduction in mortality with the ICD versus SPRM quintile 1 patients (adjusted hazard ratios [HR]: 0.602; 95% confidence interval [CI]: 0.537 to 0.675 vs. 0.793; 95% CI: 0.736 to 0.855, respectively). Among patients with SHFM-predicted annual mortality $\leq 5.7\%$, those with a SPRM-predicted risk of sudden death below the median had no reduction in mortality with the ICD (adjusted ICD HR: 0.921; 95% CI: 0.787 to 1.08; $p = 0.31$), whereas those with SPRM above the median derived the greatest benefit (adjusted HR: 0.599; 95% CI: 0.530 to 0.677; $p < 0.0001$).

CONCLUSIONS The SHFM predicted all-cause mortality in a large cohort with and without ICDs, and the SPRM discriminated and calibrated the potential ICD benefit. Together, the models identified patients less likely to derive a survival benefit from primary prevention ICDs. (J Am Coll Cardiol 2017;69:2606–18) © 2017 by the American College of Cardiology Foundation.



Listen to this manuscript's
audio summary by
JACC Editor-in-Chief
Dr. Valentin Fuster.



From the ^aDepartment of Medicine, University of Virginia Health System, Charlottesville, Virginia; ^bCenter for Outcomes Research and Evaluation, Yale-New Haven Hospital, New Haven, Connecticut; ^cDepartment of Internal Medicine, Yale University, New Haven, Connecticut; ^dDepartment of Medicine, Johns Hopkins Medical Institutions, Baltimore, Maryland; ^eDepartment of Public Health Sciences, University of Virginia, Charlottesville, Virginia; ^fSouthern California Permanente Medical Group, Los Angeles, California; ^gUniversity of Minnesota, Minneapolis, Minnesota; ^hDepartment of Medicine/Cardiology, Karolinska University Hospital, Stockholm, Sweden; ⁱDepartment of Cardiology and Department of Medical and Health Sciences, Linköping University, Linköping, Sweden; ^jDepartment of Molecular Medicine and Surgery, Karolinska Institutet, Stockholm, Sweden; ^kSection of Cardiothoracic Surgery, Karolinska University Hospital, Stockholm, Sweden; ^lItalian Association of Hospital Cardiologists Research Center, Florence, Italy; ^mDepartment of Clinical and Molecular Medicine, Sahlgrenska Academy, University of Gothenburg, Sweden; ⁿNational Heart and Lung Institute, Imperial College, London, United Kingdom; ^oInova Healthcare System, Fairfax, Virginia; and the ^pDepartment of Medicine, University of Washington, Seattle, Washington. The University of Washington CoMotion holds the copyrights for the SHFM and SPRM and has received licensing fees from Thoratec (St. Jude Medical), HeartWare (Medtronic), GE Healthcare, and Athena Health. Dr. Bilchick was supported by grant R03 HL135463 from the National Institutes of Health. Drs. Bilchick, Cheng, and Levy were supported by a research grant from the National Cardiovascular Data Registry. Dr. Curtis has equity in Medtronic. Dr. Dharmarajan is supported by grant K23AG048331 from the National Institute on Aging and the American Federation for Aging Research through the Paul B. Beeson Career Development Award Program; is

At least 5 million people in the United States have heart failure (HF) (1); >500,000 are diagnosed each year (2), and 2.5 million are hospitalized for this disease (3). Although randomized trials have shown an overall mortality benefit of prophylactic implantable cardioverter defibrillators (ICDs) in those with severe systolic HF (4-6), studies have questioned the effectiveness of ICDs in certain subgroups of patients (7-9). Moreover, most patients with ICDs implanted for primary prevention do not receive therapeutic shocks, and only 21% of patients in the Sudden Cardiac Death in Heart Failure

SEE PAGE 2619

Trial received appropriate shocks during the trial (4). The DANISH-ICD (Danish Study to Assess the Efficacy of ICDs in Patients with Non-Ischemic Systolic Heart Failure on Mortality) trial recently demonstrated that patients with nonischemic HF had an approximate 50% reduction in sudden death with ICD implantation, but this did not translate into an improvement in survival, possibly due to the low rate of sudden death during follow-up and the low proportion of sudden death relative to all-cause mortality (10). In patients with HF associated with a previous myocardial infarction in the MADIT-II (Multicenter Automatic Defibrillator Implantation Trial II), for which a risk model was validated (11), the ICD-associated reduction in mortality was almost entirely due to a reduction in arrhythmic death (12), highlighting the importance of identifying subgroups of patients with a greater proportional risk of arrhythmic death. Considering the health resources used for ICDs implanted for primary prevention and the potential increase in such implantations if all patients meeting guideline-based criteria receive ICDs, the public health impact of improving risk stratification and prognostication in ICD patients could be considerable.

The Seattle Heart Failure Model (SHFM) (9) and the Seattle Proportional Risk Model (SPRM) (13-15) are innovative models for prediction of mortality and

sudden death. The SHFM is a well-validated scoring system (9) that predicts the risk of all-cause mortality, and the SPRM is designed to predict the mode of death (sudden vs. non-sudden) by identifying the proportional risk of sudden death, including death from ventricular arrhythmia (VA) (14). Application of these models in a large cohort of potential ICD patients could improve our ability to target ICDs to the right patients using precision medicine (15) and could demonstrate the external validity of these models in an important cohort of patients. We hypothesized that the SHFM and SPRM scores would identify HF patients who were more likely and less likely to derive survival benefit from an ICD intended for primary prevention of sudden cardiac death. Our analysis applied both of these models to a large real-world population of National Cardiovascular Data Registry (NCDR) patients and a large control group of patients with HF without ICDs for comparison.

METHODS

GENERAL DESIGN. 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. Data from the NCDR ICD Registry Version 1 was linked to Social Security Death Index records to determine long-term mortality up to 5 years following device implantation. SPRM and SHFM risk scores were determined for all patients in the ICD Registry. In addition, SPRM and SHFM risk scores were also determined for a control cohort of 10,932 subjects (left ventricular ejection fraction [LVEF] $\leq 35\%$) without ICDs from 3 HF registries and 3 clinical trials: the University of Washington Registry (16), the Italian Network on Congestive Heart Failure (17), the Swedish Heart Failure Registry (18), the Carvedilol or Metoprolol European Trial (19), the Valsartan Heart Failure Trial (20), and the Prospective

ABBREVIATIONS AND ACRONYMS

AUC = area under the curve

CI = confidence interval

CPH = Cox proportional hazards

CRT-D = cardiac resynchronization therapy defibrillator

HF = heart failure

HR = hazard ratio

ICD = implantable cardioverter-defibrillator

LVEF = left ventricular ejection fraction

NCDR = National Cardiovascular Data Registry

NYHA = New York Heart Association

SCA = sudden cardiac arrest

SHFM = Seattle Heart Failure Model

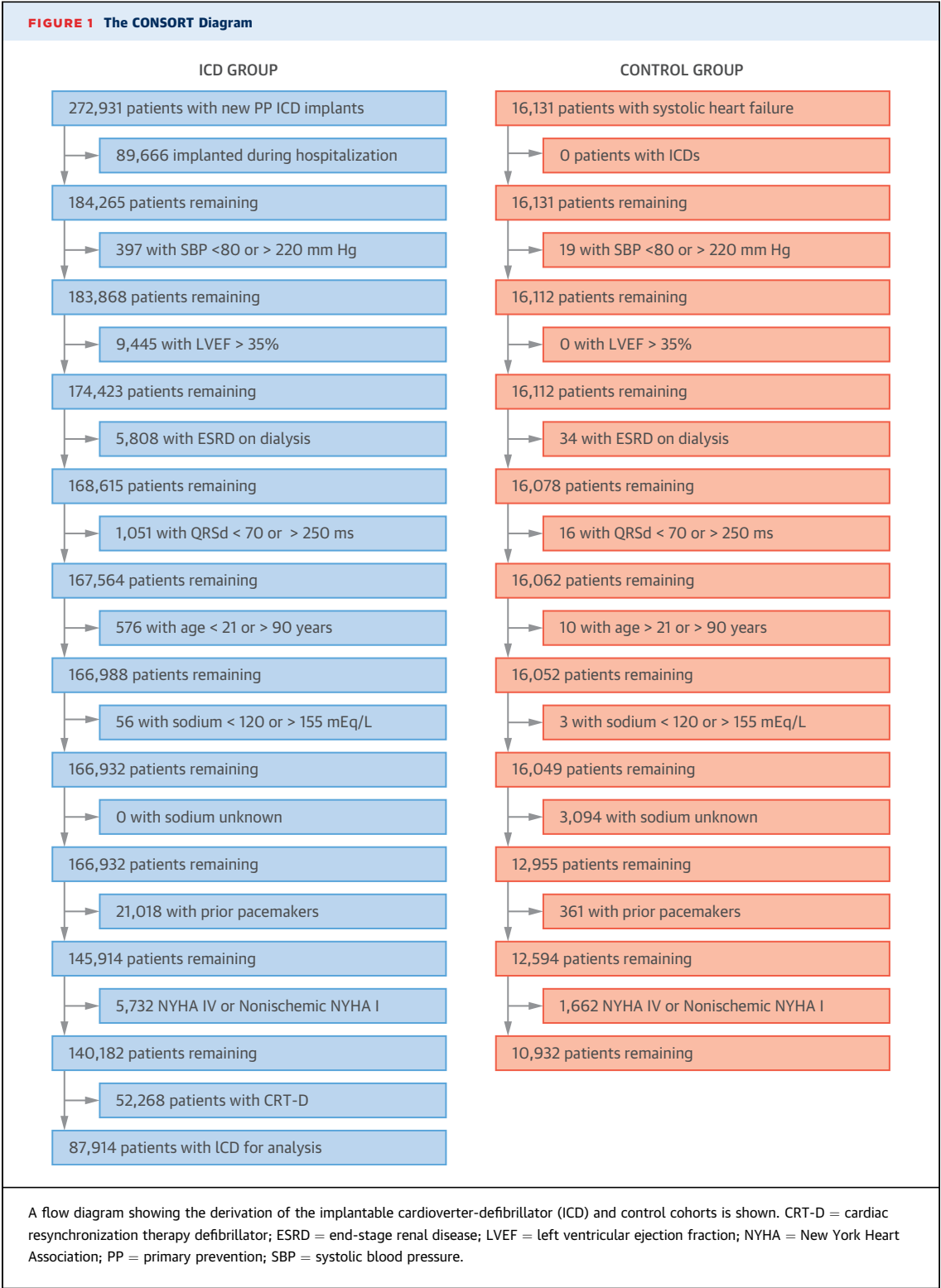
SPRM = Seattle Proportional Risk Model

VA = ventricular arrhythmia

YNT = years needed to treat

also supported by grant P30AG021342 from the Yale Claude D. Pepper Older Americans Independence Center; has received salary support under contract with the Centers for Medicare & Medicaid Services; and serves as a consultant and scientific advisory board member for Clover Health. Dr. Lund has received research grants from Boston Scientific, AstraZeneca, and Novartis; speaker honoraria from St. Jude Medical, AstraZeneca, Novartis, and Merck; and consulting honoraria from AstraZeneca, Novartis, Sanofi, Bayer, Vifor Pharma, Relypsa, Merck, and Heartware. Dr. Dahlstrom has received speaker and consulting honoraria from Novartis; and research grants from AstraZeneca. Dr. Maggioni has received honoraria for serving on study committees for Novartis, Bayer, and Cardiorientis. Dr. Swedberg has received research grants from Servier; and serves as a consultant for Amgen, AstraZeneca, Novartis, Pfizer, Servier, and Vifor Pharma. Dr. Levy is a Clinical Endpoint Committee Member for the CardioMEMS CHAMPION Post Approval Study (Abbott) and RELAX-ASIA (Novartis); is a Steering Committee Member for ADMIRE ICD (GE Healthcare); and has received research grants from Amgen, Resmed, and Novartis. Arthur J. Moss, MD, served as Guest Editor for this paper.

Manuscript received November 23, 2016; revised manuscript received February 27, 2017, accepted March 17, 2017.



Randomized Amlodipine Survival Evaluation 1 trial (21). These studies were chosen for the control group because they provided high-quality and generalizable data on patients who would otherwise be candidates

for primary prevention ICDs but who did not receive them, mainly because these trials enrolled patients before the widespread use of ICDs. Survival data were collected for patients in these studies and registries

throughout follow-up and used for the present analysis. We performed overall survival analysis by calculating the SHFM and SPRM scores in both the ICD Registry and control patients to assess the association of a primary prevention ICD with survival. We further used these scores to identify key subgroups that would potentially derive more and less survival benefit from ICD implantation.

COHORT SELECTION. The cohort included: 1) patients in the ICD Registry who underwent ICD implantation between 2006 and 2009 for primary prevention of sudden cardiac death, with follow-up through 2011, linkage to the Social Security Death Index for determination of dates of death, and complete essential data in the registry; and 2) the control cohort with HF but without ICDs (approximate enrollment 2000 to 2010), as described previously, with the same data fields as those available in the ICD Registry and similar follow-up for death events. The control patients were not part of the ICD Registry, and data were collected separately for these patients. Based on current guidelines for ICD implantation (22), patients in both the ICD and control cohorts were required to have LVEFs of $\leq 35\%$. The following exclusion criteria were also applied to both ICD and control patients (Figure 1): systolic blood pressure < 80 or > 220 mm Hg; New York Heart Association (NYHA) functional class IV; NYHA functional class I with nonischemic cardiomyopathy; advanced chronic kidney disease with creatinine > 4.0 mg/dl or requiring dialysis; age younger than 21 years or older than 90 years; serum sodium < 120 mEq/l, > 155 mEq/l, or missing; and previous pacemaker implantation. ICD Registry patients were excluded if the ICD implantation was performed during an inpatient hospitalization, or if a cardiac resynchronization therapy defibrillator (CRT-D) was implanted, because CRT-D devices modify the HF substrate through biventricular pacing.

LINKAGE AND DETERMINATION OF OUTCOMES. Linkage between the ICD Registry and the Social Security Death Index was performed using deterministic methods by the NCDR Analytic Center to determine vital status during follow-up. In the control cohort, survival data were obtained directly from the associated registries and clinical trials. Of note, time to death was available for all patients. Although the cause of death was not available for this analysis, the magnitude of the ICD-associated improvement in survival relative to control patients was easily determined and used as the primary outcome measure to address the study hypotheses. The rationale for this approach is that the mechanism by which ICDs

	All (N = 98,846)	ICD (n = 87,914)	Control (n = 10,932)	Standardized Difference
Age, yrs	65.4 \pm 12.1	65.6 \pm 12.1	63.8 \pm 11.7	0.151
Female	23,626 (23.9)	21,276 (24.2)	2,350 (21.5)	0.064
NYHA functional class				
I	8,332 (8.4)	8,231 (9.4)	101 (0.9)	0.392
II	58,410 (59.1)	52,557 (59.8)	5,853 (53.5)	0.127
III	32,104 (32.5)	27,126 (30.9)	4,978 (45.5)	-0.304
Ischemic CM	69,221 (70.0)	63,059 (72.2)	5,712 (52.3)	-0.419
Lung disease	18,702 (18.9)	17,792 (20.2)	910 (8.3)	0.345
Diabetes mellitus	34,298 (34.7)	31,587 (35.9)	2,711 (24.8)	0.243
LVEF	25.8 \pm 6.1	25.8 \pm 6.1	25.2 \pm 6.1	0.098
Creatinine, mg/dl	1.19 \pm 0.40	1.18 \pm 0.40	1.25 \pm 0.38	-0.179
Sodium, mEq/l	139.1 \pm 3.1	139.0 \pm 3.1	139.5 \pm 3.3	-0.156
Systolic BP, mm Hg	130.6 \pm 21.7	131.4 \pm 21.8	123.5 \pm 19.1	0.385
QRS, ms	110.6 \pm 23.5	110.3 \pm 24.6	112.9 \pm 11.7	-0.135
Medications				
ACEI or ARB	82,453 (83.4)	71,936 (81.8)	10,517 (96.2)	-0.473
Beta-blocker	84,584 (85.6)	78,162 (88.9)	6,422 (58.7)	0.731
Digoxin	25,971 (26.3)	19,589 (22.3)	6,382 (58.4)	-0.791
Diuretic	64,029 (64.8)	54,473 (62.0)	9,556 (87.4)	-0.611

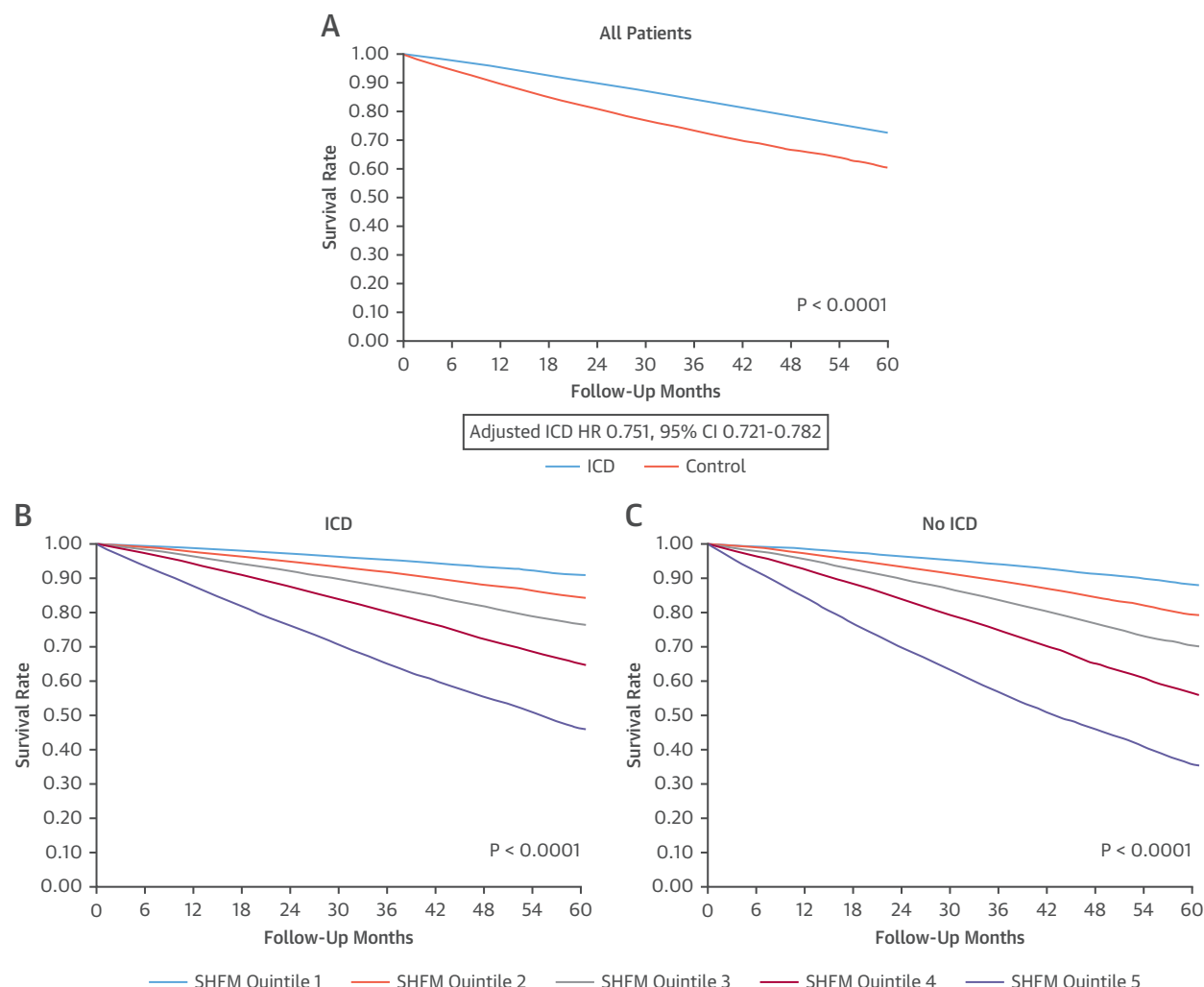
Values in the middle columns are mean \pm standard deviation or n (%). The standardized difference between groups for each parameter is shown in the last column.

ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; BP = blood pressure; CM = cardiomyopathy; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association.

improve survival is through treatment of VA to prevent arrhythmic death (12).

DETERMINATION OF SHFM AND SPRM SCORES FROM ICD REGISTRY. Because some variables for the SHFM model were missing in the NCDR registry (weight, carvedilol use, and diuretic daily dose) and could not be used in the SHFM model, the following variables were used to create a slightly revised version of the SHFM with comparable statistical power that could be prospectively applied to both NCDR registry patients and control subjects: age; sex; NYHA functional class; ischemic etiology; LVEF; systolic blood pressure; sodium; creatinine; angiotensin-converting enzyme inhibitor use or angiotensin receptor blocker use; beta-blocker use; digoxin use; diuretic use; statin use; and the new variables of diabetes mellitus, lung disease, and QRS width. The SPRM in this cohort was calculated as previously described using age, sex, NYHA functional class, LVEF, systolic blood pressure, sodium, creatinine, digoxin use, diabetes mellitus, and the substitution of ischemic etiology of cardiomyopathy for body mass index (not available in this NCDR cohort), because both ischemic etiology of cardiomyopathy and body mass index had similar statistical power. Both models were derived in the control group and prospectively applied in the NCDR registry. For simplicity, we refer to these slightly revised models as SHFM and SPRM in the present analysis.

FIGURE 2 Overall Survival by SHFM Score in Control and ICD Cohorts



Kaplan-Meier curves demonstrate survival by Seattle Heart Failure Model (SHFM) in **(A)** the entire cohort, **(B)** the ICD cohort, and the **(C)** control cohort. In both groups, an increase in the SHFM quintile was associated with decreased survival over 5 years. CI = confidence interval; HR = hazard ratio; SPRM = Seattle Proportional Risk Model; ICD = implantable cardioverter-defibrillator.

STATISTICAL ANALYSIS. Analyses were performed for the primary statistical analysis using SAS version 9.4 (SAS Institute, Cary, North Carolina). Baseline continuous variables in the control and ICD cohorts were described using the mean \pm SD if normality criteria were satisfied with the Shapiro-Wilk test or with the median and interquartile range, whereas categorical variables were described based on the associated frequencies and percentages. Differences between continuous variables between groups were assessed using Student's *t* tests if normality criteria were satisfied or the Wilcoxon rank sum test if not,

whereas differences between categorical variables were assessed using chi-square tests.

A Cox proportional hazards (CPH) analysis was performed based on the combined cohort with and without ICDs with adjustment by the SHFM score, which has been previously shown to account for the contribution of baseline variables to overall mortality in the setting of HF (9). We used CPH regression to determine how overall survival varied depending on the SHFM score, and then we tested the interaction term of SHFM*ICD in SHFM-adjusted CPH models. We evaluated the extent to which increased survival

TABLE 2 SHFM-Adjusted HRs (95% CIs) for the Effect of the ICD on Mortality Versus Controls by Quintile of SHFM and SPRM

	SPRM Q1: PPAD 6.97%-40.15%	SPRM Q2: PPAD 40.16%-47.55%	SPRM Q3: PPAD 47.56%-53.96%	SPRM Q4: PPAD 53.97%-61.16%	SPRM Q5: PPAD 61.17%-89.41%
SHFM Q1: PIYM 0.58%-3.18%	—*	1.00 (0.25-4.09)	0.73 (0.37-1.42)	0.53 (0.36-0.79)	0.81 (0.61-1.07)
SHFM Q2: PIYM 3.19%-4.75%	—*	1.00 (0.58-1.70)	1.11 (0.74-1.67)	0.90 (0.67-1.22)	0.52† (0.43-0.64)
SHFM Q3: PIYM 4.76%-6.78%	0.87 (0.59-1.27)	1.16 (0.85-1.57)	0.80† (0.63-1.00)	0.58‡ (0.48-0.71)	0.58‡ (0.46-0.73)
SHFM Q4: PIYM 6.79%-10.39%	0.89 (0.72-1.10)	0.82† (0.69-0.98)	0.71‡ (0.61-0.84)	0.62‡ (0.52-0.74)	0.63‡ (0.48-0.82)
SHFM Q5: PIYM ≥10.40%	0.78‡ (0.72-0.85)	0.75‡ (0.67-0.85)	0.65‡ (0.56-0.76)	0.59‡ (0.48-0.73)	0.59† (0.37-0.93)

The p values correspond to hazard ratios (HRs) for implantable cardioverter-defibrillator (ICD) vs. no ICD in Seattle Heart Failure Model (SHFM) and Seattle Proportional Risk Model (SPRM) subgroups. *Not enough data to determine a meaningful HR. †p < 0.05. ‡p < 0.001.
CI = confidence interval; PIYM = predicted 1-yr mortality; PPAD = predicted proportion with arrhythmic deaths.

associated with ICD implantation varied as a function of the SPRM score by testing an interaction term of SPRM*ICD in the adjusted model. We performed a multivariable CPH model to assess the effect of the ICD on survival based on the SPRM after adjustment for the SHFM score. We determined the association of the ICD with survival in key subgroups by grouping patients relative to the median SHFM value, and then further subdividing each SHFM group based on the SPRM median. Associations between ICD use and survival were also assessed in quintiles of SHFM and quintiles of SPRM. Multivariable logistic regression and receiver-operating characteristic analysis were also performed to determine the association of the SHFM with 3-year survival in the NCDR cohort.

The number of life years gained and years needed to treat (YNT) to save a life were determined as previously described (23). The additional years of life gained for each year of therapy were calculated as: (total survival with ICD – total survival without ICD)/total survival with ICD. The inverse of this value was defined as the YNT value. YNT was calculated based on the scenario that all patients would continue in their treatment assignment until death.

RESULTS

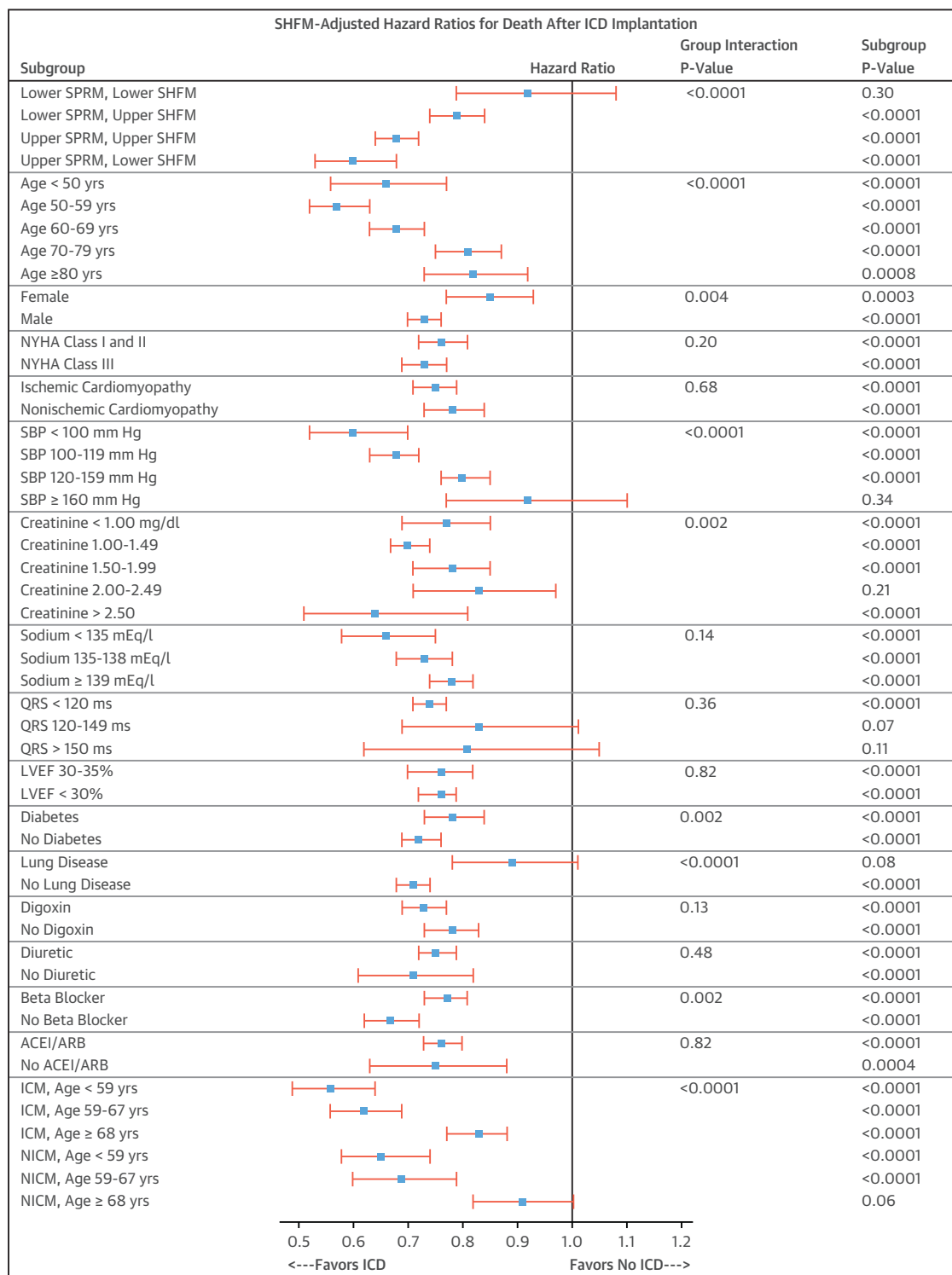
CHARACTERISTICS OF COHORT. The final analysis (n = 98,946) was based on 87,914 NCDR patients with primary prevention non-CRT ICD implants between 2006 and 2009, and 10,932 patients with systolic HF, derived from registries and clinical trials, who were enrolled between approximately 2000 and 2010 (Figure 1). Characteristics of these 2 groups are described in Table 1, which includes the standardized differences for all parameters. We accounted for parameter differences between groups through adjustment in the Cox proportional hazards models.

OVERALL EFFECT OF THE ICD ON SURVIVAL. Among the 98,946 patients in the cohort, patients who underwent ICD implantation had a 25% lower risk of death after adjustment for the SHFM (hazard ratio [HR]: 0.751; 95% confidence interval [CI]: 0.721 to 0.782) during follow-up over 5 years (mean 3.2 ± 1.4 years) compared with control patients. Kaplan-Meier curves for patients with and without ICDs are shown in Figures 2A to 2C.

SHFM SCORE AND OVERALL MORTALITY. An increase in the SHFM quintile was associated with increased mortality in both patients with and without ICDs (Figures 2B and 2C). Table 2 demonstrates the robust prediction of overall survival with the ICD based on SHFM quintiles. In multivariable logistic regression models, SHFM was essentially as good as all the covariates combined for prediction of 3-year mortality (area under the curve for SHFM and all other covariates: 0.730; p < 0.0001; area under the curve with SHFM only: 0.723; p < 0.0001). The ICD HRs are shown in specific subgroups of interest based on the model covariates in Figure 3. The findings in Figure 3 with respect to the subgroups based on ischemic versus nonischemic etiology of cardiomyopathy stratified by age groups of younger than 59 years of age, 59 to 67 years of age, and 68 years of age or older, showed a decreased benefit in patients with nonischemic cardiomyopathy and age 68 years or older, which was consistent with the results of the recent DANISH ICD trial (10). Although both women and men had statistically significant HRs that favored the ICD, the ICD was favored even more strongly in men than in women (HR: 0.73 vs. HR: 0.85, respectively; interaction p = 0.004).

SPRM AND OVERALL MORTALITY. While the SHFM score was strongly associated with all-cause mortality even with the ICD, the SPRM score

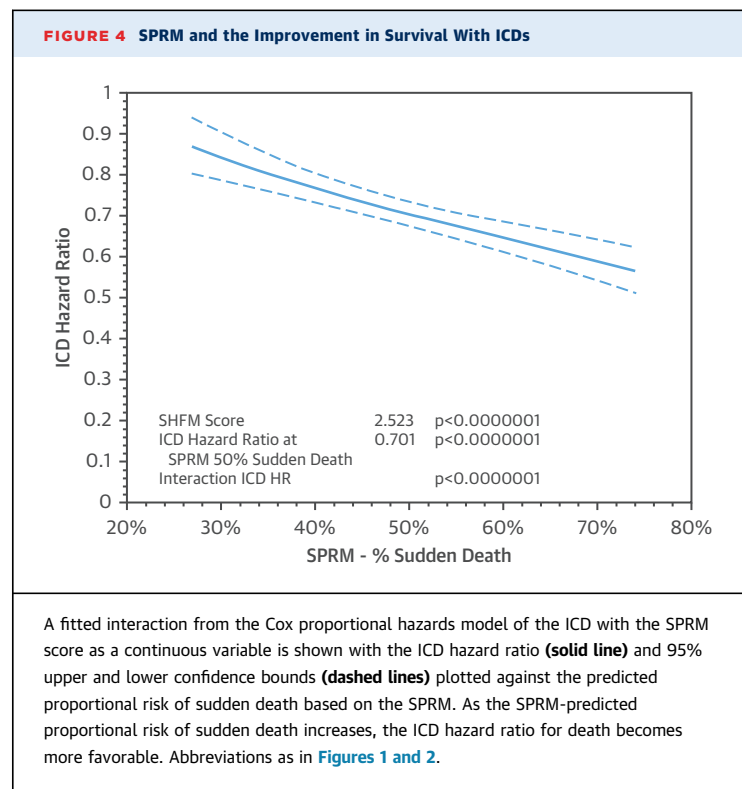
FIGURE 3 Forest Plot for the Effect of the ICD on Survival in Subgroups of Interest



The hazard ratios for death with ICD implantation in subgroups of interests based on covariates of interest are plotted in the figure. Group interaction p-values are shown in addition to the p-values for ICD benefit in each subgroup of interest. ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; ICM = ischemic cardiomyopathy; NICM = nonischemic cardiomyopathy; other abbreviations as in [Figures 1 and 2](#).

was strongly associated with the magnitude of benefit from the ICD, even after adjustment for the SHFM score. **Figure 4** demonstrates how an increasing SPRM score was associated with the effect of the ICD on survival based on the fitted line of the SPRM ICD interaction in the CPH model. For example, patients in SPRM quintiles 1 and 2 had a 19% to 21% reduction in mortality with the ICD, whereas patients in SPRM quintiles 4 and 5 had a 38% to 40% adjusted reduction in mortality with the ICD ($p < 0.0001$ for improvement in survival with the ICD in these groups). In a multivariable model for survival, the covariates of ICD ($p < 0.0001$), SPRM ($p = 0.015$), SHFM ($p < 0.0001$), and the interaction terms SPRM*ICD ($p < 0.0001$) and SHFM*ICD ($p = 0.0006$) were all significant. The high level of significance for the SPRM*ICD interaction term (HR: 0.811; 95% CI: 0.751 to 0.875; chi-square statistic = 29.2) demonstrated that the benefit of ICD implantation clearly increased as the SPRM-estimated proportion of sudden death increased. Of note, the SPRM*ICD interaction term favored the ICD more strongly when the cohort was limited to patients with ischemic cardiomyopathy (HR: 0.776; 95% CI: 0.703 to 0.856) versus those with nonischemic cardiomyopathy (HR: 0.871; 95% CI: 0.770 to 0.985).

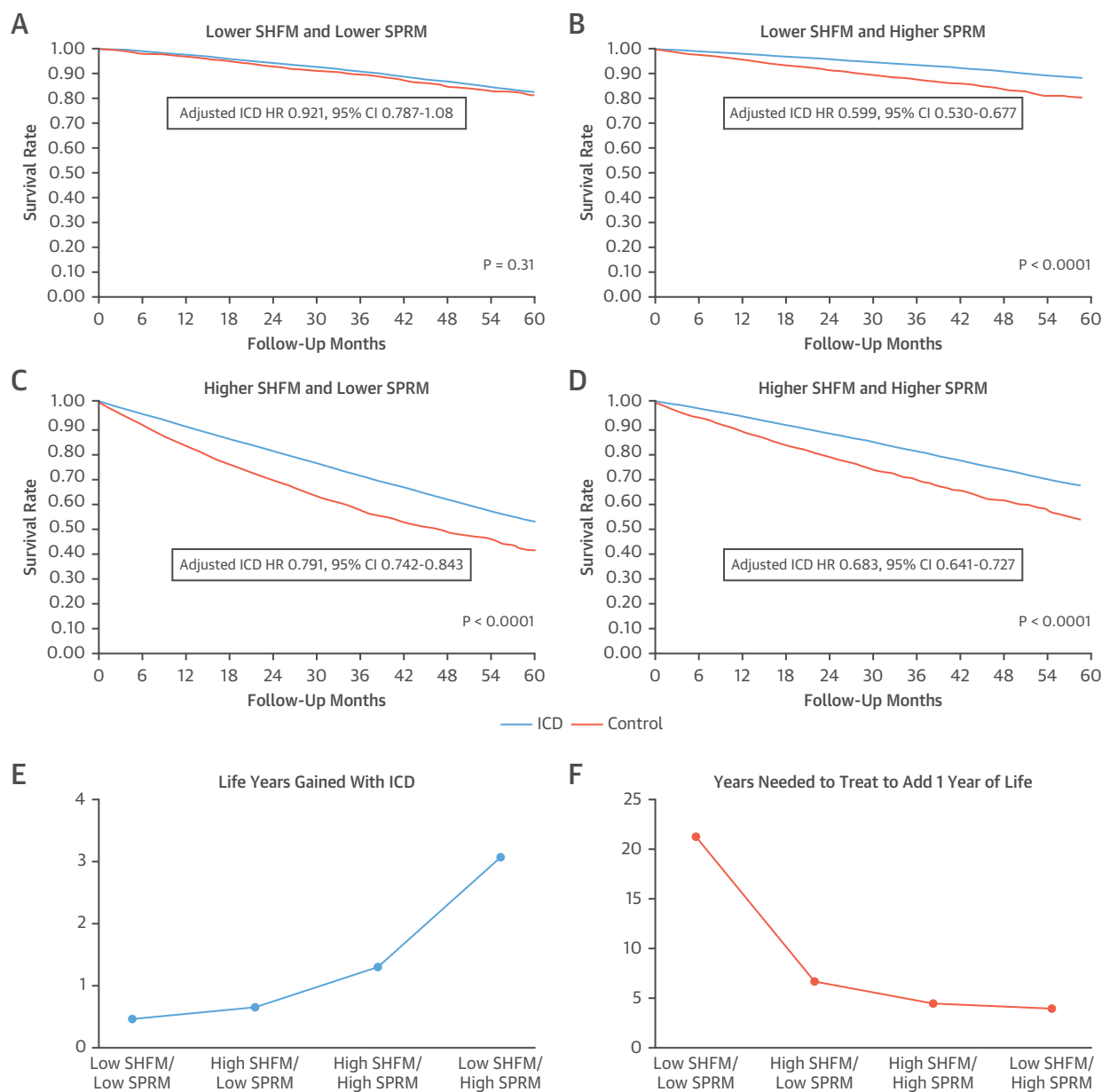
COMBINED ASSESSMENT OF OVERALL SURVIVAL AND EFFECT OF ICD ON SURVIVAL WITH SHFM AND SPRM. The combined use of the SHFM score and the SPRM score for comprehensive risk stratification in ICD candidates was of particular interest. To create 4 groups of equal size based on SHFM and SPRM (lower SHFM/lower SPRM, lower SHFM/higher SPRM, higher SHFM/lower SPRM, and higher SHFM, higher SPRM), we used threshold values based on the median SPRM-predicted proportional rate of arrhythmic death and the median SHFM-predicted 1-year mortality rate (5.7%). Characteristics of the patients in these 4 groups can be found in the [Online Table 1](#). Kaplan-Meier survival curves for patients in these 4 groups with and without an ICD are shown in [Figures 5A to 5D](#). The ICD had a clear benefit (adjusted ICD HR: 0.599; 95% CI: 0.530 to 0.677; $p < 0.0001$) in patients with both an SHFM-predicted 1-year mortality of $\leq 5.7\%$ and a SPRM-predicted proportional risk of sudden death above the median, but not in patients with an SHFM-predicted 1-year mortality of $\leq 5.7\%$ and a SPRM-predicted proportional risk of sudden death below the median (adjusted HR: 0.921; 95% CI: 0.787 to 1.08; $p = 0.31$). Among patients with an SHFM-predicted 1-year mortality rate $> 5.7\%$, patients with a higher SPRM-predicted proportional risk of sudden death above the median ($> 44.3\%$) had a greater adjusted



improvement in survival over 5 years with the ICD (adjusted ICD HR: 0.683; 95% CI: 0.641 to 0.727; $p < 0.0001$) compared with patients who had a SPRM-predicted proportional risk of sudden death of $\leq 44.3\%$ (adjusted ICD HR: 0.791; 95% CI: 0.742 to 0.843; $p < 0.0001$). HRs for the ICD patients versus control patients are shown in more granular fashion in [Table 2](#) in a 5×5 matrix form for specific SPRM and SHFM quintiles. The SHFM-adjusted mortality rates at 1 and 5 years by quintile of SPRM score and quintile of SHFM score are shown in [Figure 6](#).

As shown in [Table 3](#) and in [Figures 5E and 5F](#), patients with a lower predicted overall mortality (lower SHFM) and a lower SPRM-predicted proportional risk of sudden death (the group without a statistically significant improvement in survival during follow-up with ICDs) would be projected to have minimal improvement in life expectancy with the ICD (0.5 years) during their lifetime, such that these patients would need to be treated 22.5 years with an ICD to add 1 year of life. In contrast, patients with a lower predicted overall mortality (lower SHFM) and a higher SPRM-predicted proportional risk of sudden death (the group with the greatest survival improvement with the ICD) would be projected to have a life expectancy improvement of 3.3 years resulting from the ICD, and these patients would only need to be treated for 4.2 years to add 1 year of life.

FIGURE 5 Survival in ICD and Control Cohorts Stratified by SHFM and SPRM



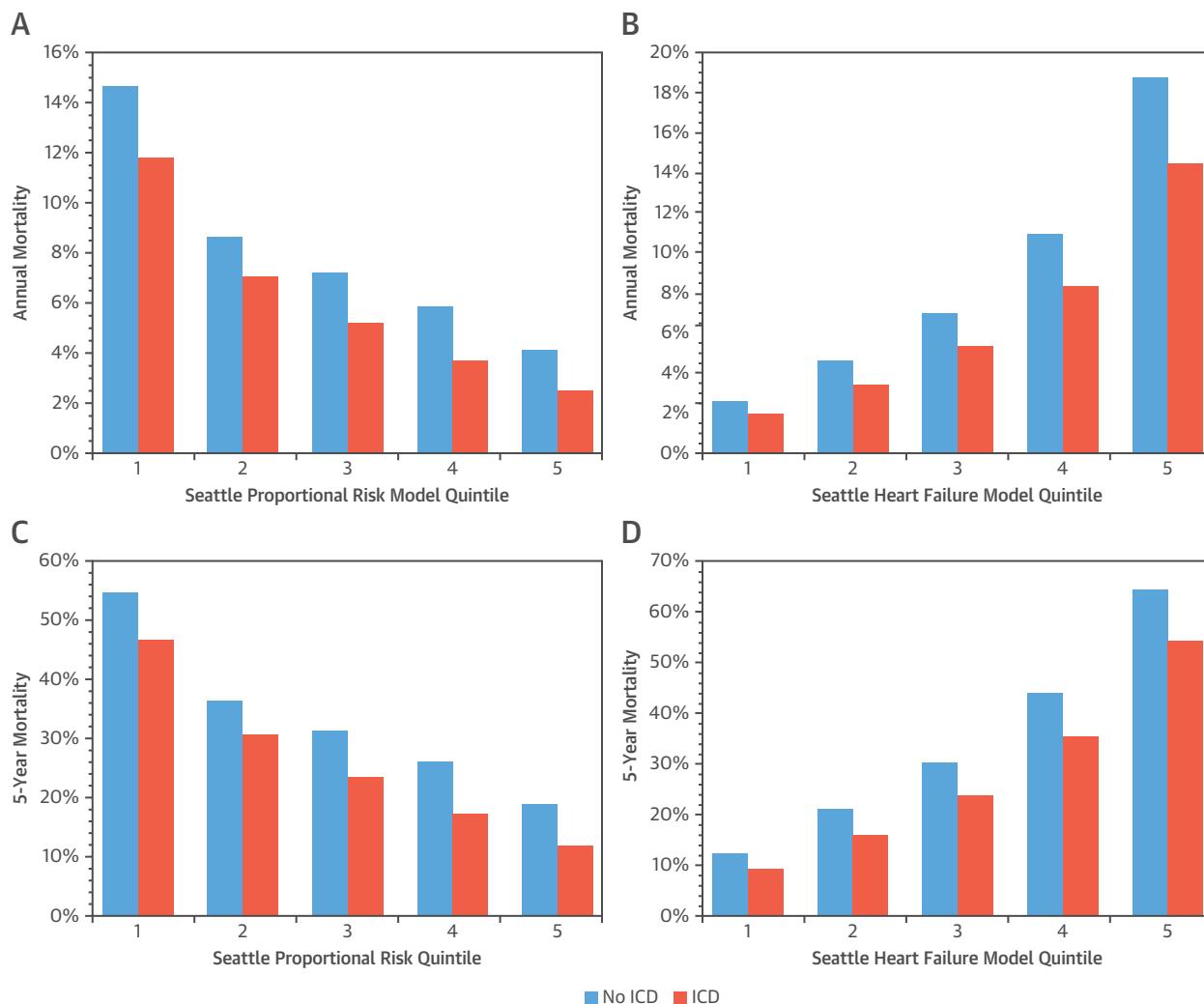
(A to D) Adjusted survival is shown in 4 groups based on whether SHFM and SPRM are above and below the median. (E) Differences in life-years gained with the ICD in these 4 groups and (F) the years needed to treat to add 1 year of life in the 4 groups are also shown. Abbreviations as in [Figures 1 and 2](#).

DISCUSSION

We found that the SPRM and SHFM together provide a useful assessment of overall mortality and expected ICD effectiveness. The SHFM provides a powerful measure of overall survival, whereas the SPRM provides an effective assessment of how overall survival with the SHFM is modified by ICD implantation

([Central Illustration](#)). Overall, the ICD was associated with an approximately 25% improvement in adjusted survival in the cohort of approximately 100,000 patients, consistent with results from clinical trials. We also identified a subgroup consisting of one-quarter of the NCDR cohort who did not have a significant survival benefit with an ICD. These patients would be expected to have minimal expected

FIGURE 6 Adjusted Survival at 1 Year and 5 Years by Quintile of SPRM and SHFM



Adjusted 1-year survival with and without ICD implantation is shown for (A) the SPRM and (B) the SHFM. Adjusted survival after 5 years of follow-up with and without ICD implantation is also provided for (C) the SPRM and (D) the SHFM. Abbreviations as in Figures 1 and 2.

improvement in life expectancy with an ICD, such that they would have to be treated for 22.5 years to add a year of life. In contrast, another group with a high predicted proportion of arrhythmic deaths and a good predicted overall survival rate, consisting of one-quarter of the NCDR cohort, had a 40% reduction in mortality with the ICD during follow-up. These patients would need to be treated for only 4.2 years to add a year of life. The remaining one-half of the NCDR cohort with increased HF severity had an intermediate survival benefit with an ICD.

There were several strengths of this study. These included the use of high-quality registry data, linkage

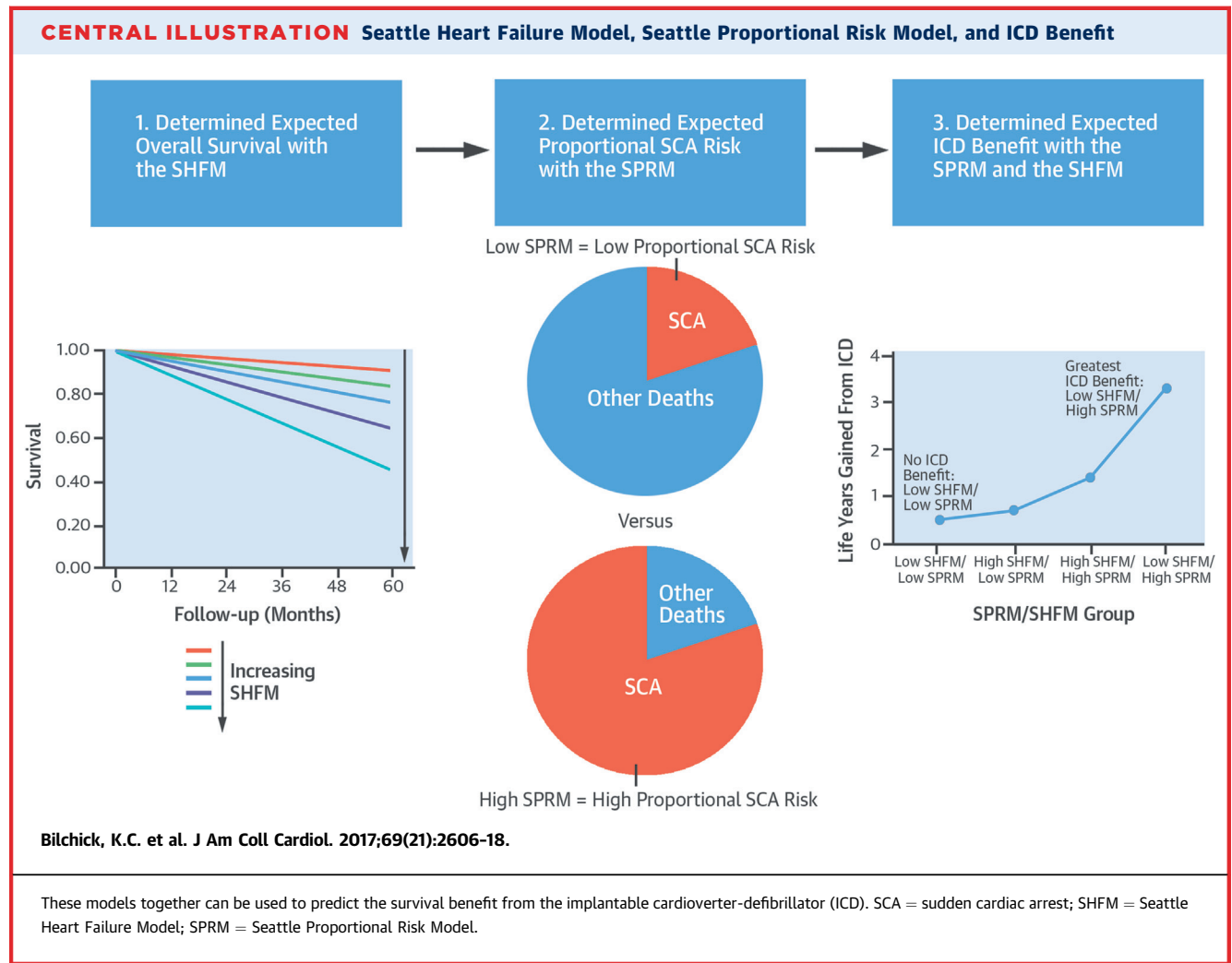
to a reliable death index, the use of a high-quality and generalizable control group from multiple sources, and adjustment for many covariates. The use of a control group has been overlooked in some previous registry studies that evaluated ICD prognosis (24), but it did provide important insights into the magnitude of the effect of the ICD on survival in addition to the overall expected survival with the ICD in this study. Use of the contemporary control group in this case facilitated an analysis of the modulation of the ICD effect on survival based on the SPRM after adjustment for the overall expected survival based on HF parameters, as determined by the SHFM.

SHFM	SPRM	5-Yr Mortality ICD	5-Yr Mortality No ICD	1-Yr Mortality ICD	1-Yr Mortality No ICD	Life Span ICD*	Life Span No ICD*	Life Yrs Gained	Yrs Needed to Treat
Low (P1YM ≤5.7%)	Low (PPAD ≤57.2%)	16.7%	18.0%	3.6%	3.9%	10.7	10.2	0.5	22.5
High (P1YM >5.7%)	Low (PPAD ≤44.3%)	47.1%	55.3%	12.0%	14.9%	5.1	4.4	0.7	7.1
High (P1YM >5.7%)	High (PPAD>44.3%)	33.3%	44.8%	7.8%	11.2%	6.7	5.3	1.4	4.7
Low (P1YM ≤5.7%)	High (PPAD>57.2%)	10.8%	17.3%	2.3%	3.7%	13.7	10.5	3.3	4.2

The cohort was first divided into lower and higher SHFM risk groups using the median P1YM of 5.7% based on the SHFM score. To create 4 groups of equal size, the median PPAD based on the SPRM score was determined for both the lower SHFM risk group (57.2%) and the higher SHFM risk group (44.3%). As a result, the SPRM cutoff is different for the higher and lower SHFM risk groups.

Abbreviations as in [Table 2](#).

Both women and men derived a significant benefit from standard (non-CRT) ICDs in our study, but the more favorable HR for the ICD in men versus women is consistent with previous data from our group that showed that women had a lower proportion of sudden death and a higher proportion of pump failure death for any given SHFM score (25). A network clinical trial meta-analysis also showed that men had a greater survival benefit than women with ICD therapy for the primary prevention indication (26). In contrast, the higher proportion of pump failure death in women might explain why women had a greater benefit with CRT-D in the MADIT-CRT (Multicenter Automatic Defibrillator Implantation Trial with Cardiac Resynchronization Therapy) trial (27).



This analysis provides much needed data to support the use of the SPRM and SHFM in the general population of patients with implanted ICDs for primary prevention of sudden cardiac death from VA, while providing the tools to improve and individualize the clinical care of patients with HF according to the principles of precision medicine in several ways. First, these results provide evidence from a very large registry of ICD implantations that the SHFM score provides an effective assessment of overall survival, which promises to be useful for discussions between providers and patients regarding prognosis. Second, these results provide evidence for the use of the novel SPRM to characterize the proportional risk of sudden death, which was shown to translate into the magnitude of survival improvement with the ICD in the present study. This promises to be useful in clinical decision making. Third, the combined use of the SPRM and SHFM identified a low-risk cohort that included as many as one-quarter of patients with ICDs in the NCDR registry who had an overall survival during 5 years of follow-up of 83% that was not modified by the ICD. This is particularly relevant with the finding from the DANISH-ICD trial that ICDs reduced sudden death in a cohort of patients with nonischemic HF, but not overall survival, because of the smaller proportion of patients with sudden death (10).

The combined use of the SPRM and SHFM in the present study could be particularly useful in identifying patients unlikely to need ICDs because they have a low proportional risk of sudden death. The potential impact on the health care system, if further confirmatory studies showed that up to one-quarter of all patients receiving ICDs would do well without them, would be enormous. Considering that current ICD indications are broad and include low-risk patients unlikely to have improved survival as a result of the ICD (22), we believe a randomized clinical trial of ICDs in low-risk patients characterized by low SHFM and SPRM risk is appropriate. Application of these models at the time of ICD generator replacement might be useful because many patients have ICDs replaced even if they have not received appropriate therapy and no longer meet criteria for primary prevention ICDs.

STUDY LIMITATIONS. One limitation of our analysis was that it was not a randomized clinical trial and used patient data from data sets from previous clinical trials and registries as the control group. Although we accounted for differences between groups with statistical adjustment, there might be unmeasured factors that differed between the groups.

This is an inherent limitation of analyses of large databases and registries; however, this limitation was offset to a significant degree by the opportunity afforded by study designs such as this to evaluate risk models and other interventions in real-world patients. This was particularly important, considering the differences in patient selection and treatment between clinical trials and registries. In addition, although the time during which patients in the control group were enrolled in registries and clinical studies was similar to that of the patients in the NCDR group, the patients in the ICD and control cohorts were not enrolled at the same time in the same way, which could have introduced bias. The reasons that control patients did not receive ICDs were likely related to differences among clinical practice settings and the lower prevalence of ICD use before 2005, when ICDs were not as widely used for primary prevention of sudden cardiac death, especially in patients with nonischemic HF. Even so, available medical therapy for HF was similar for patients in the control group, and analyses were adjusted for differences in the use of these medications, which are included in the SHFM. Of note, we did use slightly adapted versions of the SHFM and SPRM based on available data fields, but the models used had similar statistical performance compared with the original models, and the same re-derived models were used in both ICD and control groups.

CONCLUSIONS

Our analysis showed how the SHFM and SPRM could be used to predict both overall survival and ICD benefit in a large cohort of approximately 100,000 patients. In particular, the SHFM provided a highly effective measure of HF outcomes, whereas the SPRM provided a powerful measure of the proportional risk of sudden death. Considering the large amount of time and expense presently allocated to patients with ICDs for implantation, post-operative care, and subsequent generator changes, application of these models could more effectively allocate these health care resources and personalize device therapy for the benefit of patients and society.

ACKNOWLEDGEMENTS The authors thank the staff of the NCDR Analytic Center at Yale University and the American College of Cardiology for their assistance in facilitating the present analysis.

ADDRESS FOR CORRESPONDENCE: Dr. Kenneth C. Bilchick, UVA Health System, Cardiovascular Division, P.O. Box 800158, Charlottesville, Virginia 22908. E-mail: bilchick@virginia.edu.

PERSPECTIVES

COMPETENCY IN PATIENT CARE AND

PROCEDURAL SKILLS: Patients with ischemic or non-ischemic cardiomyopathy face competing risks of heart failure and ventricular arrhythmias, limiting the benefit of ICD therapy to those at higher risk of sudden death.

COMPETENCY IN INTERPERSONAL AND

COMMUNICATION SKILLS: Shared decision-making

about ICD therapy should address both overall survival and the proportional risk of death from ventricular arrhythmias.

TRANSLATIONAL OUTLOOK: Further studies are needed to assess the value of ICD therapy for patients with heart failure and a low proportional risk of death from ventricular arrhythmia.

REFERENCES

1. Roger VL, Weston SA, Redfield MM, et al. Trends in heart failure incidence and survival in a community-based population. *JAMA* 2004;292:344-50.
2. Levy D, Kenchaiah S, Larson MG, et al. Long-term trends in the incidence of and survival with heart failure. *N Engl J Med* 2002;347:1397-402.
3. Haldeman GA, Croft JB, Giles WH, Rashidee A. Hospitalization of patients with heart failure: National Hospital Discharge Survey, 1985 to 1995. *Am Heart J* 1999;137:352-60.
4. Bardy GH, Lee KL, Mark DB, et al. Amiodarone or an implantable cardioverter-defibrillator for congestive heart failure. *N Engl J Med* 2005;352:225-37.
5. Moss AJ, Zareba W, Hall WJ, et al. Prophylactic implantation of a defibrillator in patients with myocardial infarction and reduced ejection fraction. *N Engl J Med* 2002;346:877-83.
6. Theuns DA, Smith T, Hunink MG, Bardy GH, Jordaens L. Effectiveness of prophylactic implantation of cardioverter-defibrillators without cardiac resynchronization therapy in patients with ischaemic or non-ischaemic heart disease: a systematic review and meta-analysis. *Europace* 2010;12:1564-70.
7. Stevenson LW. Implantable cardioverter-defibrillators for primary prevention of sudden death in heart failure: are there enough bangs for the bucks? *Circulation* 2006;114:101-3.
8. Levy WC, Lee KL, Hellkamp AS, et al. Maximizing survival benefit with primary prevention implantable cardioverter-defibrillator therapy in a heart failure population. *Circulation* 2009;120:835-42.
9. Levy WC, Mozaffarian D, Linker DT, et al. The Seattle Heart Failure Model: prediction of survival in heart failure. *Circulation* 2006;113:1424-33.
10. Kober L, Thune JJ, Nielsen JC, et al. Defibrillator implantation in patients with nonischemic systolic heart failure. *N Engl J Med* 2016;375:1221-30.
11. Goldenberg I, Vyas AK, Hall WJ, et al. Risk stratification for primary implantation of a cardioverter-defibrillator in patients with ischemic left ventricular dysfunction. *J Am Coll Cardiol* 2008;51:288-96.
12. Greenberg H, Case RB, Moss AJ, Brown MW, Carroll ER, Andrews ML. Analysis of mortality events in the Multicenter Automatic Defibrillator Implantation Trial (MADIT-II). *J Am Coll Cardiol* 2004;43:1459-65.
13. Shadman R, Poole JE, Mozaffarian D, et al. Predicting the proportional risk of sudden cardiac death in a multicenter cohort [abstract]. *Circulation* 2011;124:A17819.
14. Levy WC, Poole JE, Hellkamp AS, et al. Benefits of ICD therapy: connecting treatment decisions to individualized SCD risk estimates within SCD-HEFT - Seattle Proportional Risk Model [abstract]. *J Interv Card Electrophys* 2015;42:208.
15. Levy WC, Li Y, Reed SD, et al. Does the implantable cardioverter-defibrillator benefit vary with the estimated proportional risk of sudden death in heart failure patients? *J Am Coll Cardiol EP* 2017;3:291-8.
16. Sullivan MD, Levy WC, Crane BA, Russo JE, Spertus JA. Usefulness of depression to predict time to combined end point of transplant or death for outpatients with advanced heart failure. *Am J Cardiol* 2004;94:1577-80.
17. Fabbri G, Gorini M, Maggioni AP, Cacciatore G, Di Lenarda A. Italian Network on Congestive Heart Failure: ten-year experience (in Italian). *G Ital Cardiol* 2006;7:689-94.
18. Jonsson A, Edner M, Alehagen U, Dahlstrom U. Heart failure registry: a valuable tool for improving the management of patients with heart failure. *Eur J Heart Fail* 2010;12:25-31.
19. Poole-Wilson PA, Swedberg K, Cleland JG, et al. Comparison of carvedilol and metoprolol on clinical outcomes in patients with chronic heart failure in the Carvedilol Or Metoprolol European Trial (COMET): randomised controlled trial. *Lancet* 2003;362:7-13.
20. Cohn JN, Tognoni G. A randomized trial of the angiotensin-receptor blocker valsartan in chronic heart failure. *N Engl J Med* 2001;345:1667-75.
21. Packer M, O'Connor CM, Ghali JK, et al. Effect of amlodipine on morbidity and mortality in severe chronic heart failure. Prospective Randomized Amlodipine Survival Evaluation Study Group. *N Engl J Med* 1996;335:1107-14.
22. Tracy CM, Epstein AE, Darbar D, et al. 2012 ACCF/AHA/HRS focused update of the 2008 guidelines for device-based therapy of cardiac rhythm abnormalities: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol* 2012;60:1297-313.
23. Levy WC, Mozaffarian D, Linker DT, et al. Years-needed-to-treat to add 1 year of life: a new metric to estimate treatment effects in randomized trials. *Eur J Heart Fail* 2009;11:256-63.
24. Al-Khatib SM, Hellkamp AS, Fonarow GC, et al. Association between prophylactic implantable cardioverter-defibrillators and survival in patients with left ventricular ejection fraction between 30% and 35%. *JAMA* 2014;311:2209-15.
25. Rho RW, Patton KK, Poole JE, et al. Important differences in mode of death between men and women with heart failure who would qualify for a primary prevention implantable cardioverter-defibrillator. *Circulation* 2012;126:2402-7.
26. Woods B, Hawkins N, Mealing S, et al. Individual patient data network meta-analysis of mortality effects of implantable cardiac devices. *Heart* 2015;101:1800-6.
27. Moss AJ, Hall WJ, Cannom DS, et al. Cardiac-resynchronization therapy for the prevention of heart-failure events. *N Engl J Med* 2009;361:1329-38.

KEY WORDS heart failure, implantable cardioverter-defibrillator, risk models

APPENDIX For a supplemental table, please see the online version of this article.