Does the Implantable Cardioverter-Defibrillator Benefit Vary With the Estimated Proportional Risk of Sudden Death in Heart Failure Patients?

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ABSTRACT

OBJECTIVES The authors developed the Seattle Proportional Risk Model (SPRM) to estimate the proportion of total mortality due to sudden death. We prospectively validated the model in HF-ACTION (Participants in Heart Failure: A Controlled Trial Investigating Outcomes of Exercise Training) and tested whether the implantable cardioverter-defibrillator (ICD) benefit varied with the SPRM.

BACKGROUND Prediction of which heart failure patients are most likely to die of sudden death versus nonsudden death is an important factor in determining who will benefit the most from an ICD.

METHODS Among 2,331 patients enrolled, 1,947 patients were retained for analysis over a median follow-up of 2.5 years. The SPRM was calculated using age, gender, diabetes, body mass index, systolic blood pressure, ejection fraction, New York Heart Association functional class, sodium, creatinine, and digoxin use.

RESULTS An ICD (ICD or CRT-D) was in use before death in 1,204 patients (62%). SPRM was predictive of sudden death versus nonsudden death in those without an ICD (p = 0.002). The hazard ratio representing ICD versus no ICD was 0.63 for all-cause mortality (p = 0.0002). The ICD benefit varied with the SPRM for all-cause mortality (p = 0.001), with a greater benefit in those with a higher conditional probability of sudden death.

CONCLUSIONS In population of ambulatory patients with a New York Heart Association functional class II–IV HF and ejection fraction of <35%, the SPRM was predictive of the proportional risk of sudden versus nonsudden death. ICDs were associated with a decreased risk of all-cause mortality by 37% and the ICD benefit varied with the SPRM. The SPRM may be useful in risk stratifying patients for a primary prevention ICD. (Exercise Training Program to Improve Clinical Outcomes in Individuals With Congestive Heart Failure; NCT00047437) (J Am Coll Cardiol EP 2016;:–––) © 2016 by the American College of Cardiology Foundation.

Sudden death comprises one-half of all deaths in patients with chronic heart failure (1). Meta-analysis of primary prevention implantable cardioverter-defibrillator (ICD) trials suggests that ICDs decrease sudden death by approximately 60% (2) (relative risk reduction). In many patients, sudden death is a marker of the progression of their underlying heart failure. As a result, the prevention of
sudden death may merely alter the mode of death from sudden to pump failure, as seen in post myocardial infarction trials with ICDs (3). ICDs are a Class I indication by American College of Cardiology/American Heart Association/Heart Rhythm Society guidelines to prevent sudden death in New York Heart Association (NYHA) functional class II and III patients with an ejection fraction (EF) of ≤35% and other selected heart failure patients with a life expectancy of >1 year (4). However, the usefulness of a primary prevention ICD may be diminished in patients who are older, women, have chronic kidney disease, or multiple comorbidities (5–8). The 2013 guidelines were updated to include the following statement, “The usefulness of implantation of an ICD is of uncertain benefit to prolong meaningful survival in patients with a high risk of non-sudden death as predicted by frequent hospitalizations, advanced frailty, or comorbidities such as systemic malignancy or severe renal dysfunction” (Class IIb). In the National Cardiovascular Data Registry for primary prevention ICDs, one-half of patients are in NYHA functional class III/IV (9) and one-third are ≥75 years of age, patients in whom a primary prevention ICD may have a diminished benefit (7).

Prediction of which heart failure patients are most likely to die of sudden death versus nonsudden death may provide better risk stratification than NYHA functional class and EF. For example, at the same annual mortality a patient who has a 75% likelihood of dying from sudden death, conditional on dying, would be expected to derive more benefit from an ICD than a similar patient who has a 30% likelihood of dying from sudden death (10). To facilitate incorporating such information into treatment decisions, we derived the Seattle Proportional Risk Model (SPRM) in a separate cohort of patients without an ICD (9,985 patients with 2,552 deaths and 48% sudden death) not to predict the risk of death, but rather if a patient dies, the mode of death (sudden vs. nonsudden) (11). The model found the proportion of sudden death was greater with younger age, male gender, lack of diabetes mellitus, lower EF, better NYHA functional class (i.e., II vs. III or IV), higher body mass index, digoxin use, and values of systolic blood pressure (SBP), sodium, and creatinine closer to the normal range (Figure 1).

We prospectively applied the SPRM to data from the HF-ACTION (Participants in Heart Failure: A Controlled Trial Investigating Outcomes of Exercise Training) clinical trial (12). Our aim was to: 1) validate whether the model predicts the proportion of sudden versus nonsudden death; and 2) determine if the benefit of an ICD varied with the estimated conditional probability of sudden death. We hypothesized that there would be a greater relative ICD benefit on sudden death and total mortality in those patients with a higher predicted proportion of mortality from sudden death.

METHODS

HEART FAILURE. The HF-ACTION was a clinical trial (NCT00047437) of exercise training in 2,331 ambulatory patients with NYHA functional class II, III, and IV heart failure and an EF of ≤35% (12). We excluded patients who received a left ventricular assist device or underwent cardiac transplantation (n = 78), patients who were missing baseline variables necessary to calculate the SPRM score (n = 281) and missing values necessary to calculate the SHFM score (n = 25), resulting in a sample of 1,947 patients. The mode of death was adjudicated by a clinical events committee (13). Sudden death was defined as unexpected and otherwise unexplained death in a previously stable patient, including patients who were comatose and then died after attempted resuscitation. Patients in this category should have had recent human contact before the event. Patients who died and had been out of contact for prolonged periods of time were classified as ‘unknown’ mode of death. For this analysis, the endpoint of sudden death included those classified by the clinical events committee as sudden death or unknown mode of death as described. We combined these endpoints because it is more similar to the methods used in the trials within which the SPRM was derived. The SPRM score was calculated as previously described (11). We defined “ICD use” if an ICD or cardiac resynchronization therapy with ICD (CRT-D) was present at baseline or implanted before the end of follow-up (death or end of the trial). It is our anticipation that the CRT benefit of a device that is already present on mortality is already reflected in the SHFM by improvements in the SBP, EF, and NYHA functional class (14). Thus, in a CRT-D device present at baseline, the additional benefit of the device is due to the ICD part of the CRT-D. Consequently, ICDs and CRT-Ds were treated as “ICDs” in this analysis as the majority of CRT-Ds were present at baseline. ICD or CRT-D had to be placed ≥6 weeks before enrollment per the HF-ACTION protocol. Patients who may have had an ICD explant remained in the ICD group. For this analysis, we used logistic regression to compare the SPRM-predicted versus the observed proportional risk of sudden death by quartiles of the SPRM among those without an ICD, in the
total cohort with an expectation that the risk of sudden death would be less in those with an ICD. Calibration was assessed by the Hosmer-Lemeshow goodness of fit test and discrimination by receiver operating characteristic area under the curve in patients without an ICD.

For the second aim, to ascertain if the benefit of an ICD varied with the estimated conditional probability of sudden death, we used a Cox proportional hazards model to examine the effect of ICDs on all-cause mortality. We used the 3-year survival in the ICD group in each SPRM quartile and the Cox model device hazard ratio (HR) to estimate life-years added with an ICD over a patients lifespan (Gompertz method), number needed to treat for 3 years, and years needed to treat to add 1 year of life (15). To examine the impact of ICDs on sudden death and nonsudden death, we applied a regression technique that uses pseudovalues from cumulative incidence functions to account for competing risks from the other modes of death (16). With both the Cox model and the pseudovalues competing risk models, we applied an interaction term to evaluate whether the effects of ICDs varied across the conditional risk of sudden death as estimated using the SPRM and included a baseline covariate representing a history of ventricular tachycardia/ventricular fibrillation (VT/VF) as a proxy for indication for ICD implantation, because the specific ICD indication was not available.

We also adjusted for Seattle Heart Failure Model (SHFM) scores (14) to evaluate whether ICD benefits varied across individuals with varying SPRM scores when adjusting for risk of all-cause mortality (as predicted using SHFM) as previously described (11). For a sensitivity analysis, we adjusted for 18 individual variables in the Cox model for all-cause mortality. The analyses were performed using SAS version 9.3 (SAS Institute Inc., Cary, North Carolina) with p ≤ 0.05 considered significant. The analyses were approved by the Duke University Institutional Review Board.

RESULTS

Among the 1,947 patients who met the study’s inclusion criteria, the mean age was 59 years, 73% male, EF of 25%, diabetes in 33%, and NYHA functional class II or III in 99% of subjects, similar to the SCD-HeFT (Sudden Cardiac Death in Heart Failure Trial). Sixty-two percent had an ICD before the end of follow-up. Of the patients with an ICD at the end of follow-up, 893 patients (74%) had an ICD at baseline (ICD 28%, CRT-D 18% of all patients) and 311 patients (26%) received an ICD during follow-up (ICD 13%, CRT-D 5% of all patients). The baseline demographics of those with and without an ICD before the end of follow-up are shown in Table 1. Patients with an ICD were higher risk as judged by many markers, including older age, history of VT/VF, higher NYHA functional class, creatinine, diuretic dose, and lower EF and SBP. This is reflected by an approximately 33% higher SHFM estimated 1-year all-cause mortality (not including the benefit of the ICD). Patients with a CRT-D versus ICD had a higher SHFM estimated 1-year mortality with medical therapy (8.6 ± 6.5% vs. 7.5 ± 6.7%; p = 0.0033) and a lower SPRM predicted proportion of sudden death (53.8 ± 13.6% vs. 56.3 ± 14.1%; p = 0.0022).

During a mean of 2.5 years of observation, 328 patients (16.8%) died, with 138 deaths among 743 patients (18.6%) without an ICD and 190 deaths among 1,204 patients (15.8%) with an ICD. Among those who died, the distributions of the various modes of death differed between those with and without an ICD: the proportion of patients with sudden death was lower in those with an ICD compared with those without an ICD (31% vs. 59%; p ≤ 0.0001), and the proportion of patients with pump failure deaths was higher in those with an ICD compared with those without an ICD (39% vs. 18%;
TABLE 2

<table>
<thead>
<tr>
<th>The HF-ACTION Mode of Death</th>
<th>All Patients (n = 1,204)</th>
<th>No ICD (n = 743)</th>
<th>ICD (n = 461)</th>
<th>p Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sudden cardiac death</td>
<td>140 (43)</td>
<td>81 (59)</td>
<td>59 (31)</td>
<td></td>
</tr>
<tr>
<td>Pump failure death</td>
<td>99 (30)</td>
<td>25 (18)</td>
<td>74 (39)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Other cardiovascular death</td>
<td>32 (10)</td>
<td>10 (7)</td>
<td>22 (12)</td>
<td></td>
</tr>
<tr>
<td>Noncardiovascular death</td>
<td>57 (17)</td>
<td>22 (16)</td>
<td>35 (18)</td>
<td></td>
</tr>
</tbody>
</table>

Values are n (percent of total deaths). A chi-square test was used to compare distributions between patients with and without implantable cardiac defibrillators (ICDs).

HF-ACTION = Participants in Heart Failure: A Controlled Trial Investigating Outcomes of Exercise Training.
beta blockers, aldosterone antagonists, statins, serum sodium, total cholesterol, hemoglobin, lymphocytes, uric acid, and VT/VF in the all-cause mortality Cox model, the ICD overall benefit was 0.62 (\(p = 0.0002\)) and the SPRM had an interaction p value of 0.0002, very similar to the SHFM-adjusted model. The life-years added with ICD treatment for a lifetime for the lowest to highest SPRM quartile is estimated at 0.9, 1.5, 2.7, and 5.7 years. The number needed to treat for 3 years was 16.9, 18.2, 21.2, and 9.1. An alternative metric, the years needed to treat to add 1 year of life is 6.7, 5.5, 4.4, and 2.3 (Online Table 1).

When applying the competing risks analysis to examine the risk of sudden death, adjusted for a history of VT/VF, all-cause mortality (per SHFM), and proportion of mortality due to sudden death (per SPRM), an ICD was associated with a 67% reduction in the hazard of sudden death (HR: 0.33; \(p < 0.0001\)). When an interaction term between SPRM scores and ICDs was included in the model, the results suggested that ICDs may impart a greater relative reduction on the risk of sudden death in individuals with higher SPRM scores (i.e., higher proportion of mortality from sudden death) to a greater extent than individuals with lower SPRM scores (interaction \(p = 0.07\) with SPRM modeled as a continuous variable) (Figure 3B).

When applying the competing risks analysis to examine the risk of nonsudden death, an ICD was not associated with an increase in the hazard of nonsudden death (HR: 1.05; \(p = 0.81\), and adjusted for VT/VF, SHFM score, and SPRM score).

A history of VT/VF was associated with a 1.7-fold increased risk of all-cause mortality (\(p = 0.0006\)), a 1.8-fold increased risk of sudden death (\(p = 0.05\)), and a 1.6-fold increased risk of nonsudden death (\(p = 0.01\)). Thus, within this cohort, a history of VT/VF was associated with a similar increase in the risk of sudden and nonsudden death and did not predict patients with a greater proportion of sudden versus nonsudden death.

To address confounding by ICD placement during the trial, a sensitivity analysis was performed with exclusion of patients who received an ICD after randomization (i.e., comparison of no ICD before the end of follow-up and ICD at baseline). The relative ICD benefit remained greater in those with a higher SPRM scores (interaction \(p = 0.011\)) (Online Figures 1A and 1B).

If we start a typical HF-ACTION patient, a 58-year-old male, NYHA functional class II, EF 27%, SBP 118 mm Hg, sodium 138 mEq/l, creatinine 1.2 mg/dl, no diabetes mellitus, no digoxin, and a body mass index of 31 kg/m², the SPRM is approximately 64% predicted proportion of sudden death. Changing any 1 of the following variables has a similar effect on the SPRM predicted proportion of sudden death and will decrease it by approximately 7% (NYHA functional class III vs. II, EF 42% vs. 27%, female vs. male, aging 12 years, body mass index 25 vs. 31 kg/m², SBP 88 vs. 118 mm Hg, adding diabetes mellitus, sodium 132 mEq/L vs. 138 mEq/L, or increasing creatinine by 0.6 mg/dl). Adding 1 to 4 of these risk changes for this patient would change the SPRM from approximately 64% to 57%, 51%, 44%, and a 37%, respectively. From the fitted curve in Figure 2, the associated ICD HR with the previous SPRM values would be 0.51, 0.58, 0.65, 0.74, and approximately 0.84, respectively. It is the combination of several risk markers, rather than a single risk marker, that is associated with an attenuation of the ICD benefit.

**DISCUSSION**

Our analysis has: 1) validated that the previously derived SPRM predicts the proportion of patients who will die of sudden death within HF-ACTION (Figure 2); and, more important, 2) demonstrated a highly significant interaction of benefit of an ICD with the SPRM on all-cause mortality (Figure 3A). There was a
2.7-fold greater relative ICD benefit (63% vs. 23%) in those with a higher conditional probability of sudden death (SPRM quartile 4 vs. 1) within a cohort of largely NYHA functional class II and III patients with an EF of ≥35% who were considered eligible to participate in an exercise training program. In the fitted Cox model, patients with a SPRM estimated ≥32% proportional risk of sudden death had no ICD benefit on total mortality. This is similar to the 31% residual risk of clinically adjudicated sudden death in those who had an ICD present before death in this cohort.

Many prior analyses have suggested ICD interactions with many of the SPRM variables (5–8,17). The SPRM is a method to allow integration of these multiple variables into a single variable (11). More important, the ICD benefit varied with the SPRM with greater ICD benefit in those with a higher predicted proportion of sudden death consistent with a prior Markov model (10).

Prior research has shown the proportion of sudden death varies based on the clinical scenario. The proportion of sudden death is approximately 50% in chronic systolic heart failure (1), approximately 33% in the first year after a myocardial infarction (18), and approximately 25% in patients with heart failure with preserved EF (19). Many clinicians assume that, with such a high risk of sudden death, an ICD will abrogate this increased risk of sudden death and reduce total mortality. The DINAMIT (Defibrillator in Acute Myocardial Infarction Trial) trial tested the effects of ICDs in patients after a myocardial infarction; ICDs decreased sudden death by 67%. However, there was a corresponding 70% increase in nonarrhythmic death and no benefit to total mortality (3).

In patients with chronic heart failure, the proportion of deaths attributable to sudden death varies by NYHA class: from approximately one-third in NYHA functional class IV to approximately two-thirds in NYHA functional class II patients (1). The proportion of clinically adjudicated sudden death due to a tachyarrhythmic event is one-half of clinically adjudicated sudden death in hospitalized heart failure patients and as high two-thirds of clinically adjudicated sudden death in ambulatory heart failure patients (1). Thus, the proportion of total mortality due to a tachyarrhythmic event that may be prevented by an ICD is approximately 17% (50% of the 33% sudden death) in NYHA functional class IV patients and approximately 50% (approximately 67% of the approximately 67% of sudden deaths) in

![FIGURE 3](image-url)
ambulatory heart failure patients. These observations likely explain why we saw an interaction of the SPRM with both sudden death (p = 0.07) and total mortality (p = 0.001) with greater benefit in patients with a higher proportional risk of sudden death.

In the average Medicare patient receiving an ICD, the mortality in the first year after an ICD is 13.5% (20). It is anticipated the average Medicare patient will have a much lower proportion of deaths due to sudden death than seen in clinical trials, due to older age and higher creatinine and the relative benefit of an ICD is likely lower than was observed in MADIT II (Multicenter Automatic Defibrillator Implantation), SCD-HeFT, or observationally in HF-ACTION.

There are numerous limitations to the current analysis. This post hoc analysis was not a randomized trial of primary prevention ICDs. The reason for ICD and CRT-D implantation (primary vs. secondary prevention) and ICD programming was not available. However, the magnitude of ICD benefit within this ambulatory largely NYHA II-III HF population with an EF of ≤35% (HR: 0.33 for sudden death; HR: 0.63 for all-cause mortality) is similar to the meta-analyses of primary prevention ICDs (HR: 0.40 for sudden death; HR: 0.73 all-cause mortality). The benefit of an ICD over the lifespan of the device and the patient lifespan may be greater than observed during the 2.4 yrs of observation in HF-ACTION (Online Table 1). It is possible that patients who were otherwise potentially eligible for a primary prevention ICD (essentially all patients in HF-ACTION) had unmeasured differences that we could not account for in our risk adjustment models. The benefit from a primary prevention ICD can be better identified by applying the SPRM to randomized ICD trials. The SPRM should not be used for decision making for secondary prevention ICDs.

The goal of a model like SPRM within a validation cohort is not to predict the absolute or relative risk of sudden death, because that can vary with the definition of sudden death used by an adjudication committee. Rather, the goal is to demonstrate that a model like SPRM can identify patients who will derive the most all-cause mortality benefit from a primary prevention ICD, as well as those who will derive no meaningful mortality benefit (10).

CONCLUSIONS

Patients who have a higher SPRM proportional risk of sudden death derive greater relative all-cause mortality benefit from an ICD than their counterparts with a lower predicted risk. Patients with a <32% predicted proportion of total mortality due to sudden death had no benefit of the ICD on total mortality. The SPRM may help to identify those patients who will derive the greatest benefit from a primary prevention ICD and allow more appropriate use of this effective but expensive therapy.

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REFERENCES


KEY WORDS heart failure, ICD, nonsudden death, prognosis, proportional risk, regression analysis, risk prediction model, sudden death

APPENDIX For supplemental figures and tables, please see the online version of this article.