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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;■:■-■)

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

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ABBREVIATIONS AND ACRONYMS

CRT-D = cardiac resynchronization therapy with ICD

EF = ejection fraction

HR = hazard ratio

ICD = implantable cardioverter-defibrillator

NYHA = New York Heart Association

SBP = systolic blood pressure

SHFM = Seattle Heart Failure Model

SPRM = Seattle Proportional Risk Model

VF = ventricular fibrillation

VT = ventricular tachycardia

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 70% 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 the first aim—to validate the SPRM—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