A novel method to predict the proportional risk of sudden cardiac death in heart failure: Derivation of the Seattle Proportional Risk Model

Ramin Shadman, MD,[*] Jeanne E. Poole, MD, FHRS,[†] Todd F. Dardas, MD, MS,[†] Dariush Mozaffarian, MD, DrPH,[‡] John G.F. Cleland, MD,[§] Karl Swedberg, MD, PhD,[‖¶] Aldo P. Maggioni, MD,[#] Inder S. Anand, MD,[**] Peter E. Carson, MD,[††] Alan B. Miller, MD,[‡‡] Wayne C. Levy, MD[†]

From the [*]Southern California Permanente Medical Group, Los Angeles, California, [†]University of Washington, Seattle, Washington, [‡]Harvard School of Public Health, Boston, Massachusetts; Brigham and Women's Hospital and Harvard Medical School, Boston Massachusetts, [§]Hull York Medical School, University of Hull, Kingston-upon-Hull, United Kingdom, [‖]University of Gothenburg, Gothenburg, Sweden, [¶]Imperial College, London, United Kingdom, [#]Italian Association of Hospital Cardiologists, Florence, Italy, [**]Veterans Affairs Health Care System and University of Minnesota, Minneapolis, Minnesota,, Minneapolis, Minnesota, [††]Veterans Affairs Medical Center, Washington, DC and [‡‡]University of Florida, Jacksonville' Florida.

BACKGROUND Patients with heart failure are at increased risk of both sudden death and pump failure death. Strategies to better identify those who have greatest net benefit from implantable cardioverter-defibrillator (ICD) implantation could reduce morbidity and maximize cost-effectiveness of ICDs.

OBJECTIVE We aimed to identify baseline variables in patients with cardiomyopathy that are independently associated with a disproportionate fraction of mortality risk attributable to sudden death vs nonsudden death.

METHODS We used data from 9885 patients with heart failure without ICDs, of whom 2552 died during an average follow-up of 2.3 years. Using commonly available baseline clinical and demographic variables, we developed a multivariate regression model to identify variables associated with a disproportionate risk of sudden death.

RESULTS We confirmed that lower ejection fraction and better functional class were associated with a greater proportion of mortality due to sudden death. Younger age, male sex, and higher body mass index were independently associated with a greater proportional risk of sudden death, while diabetes mellitus, hyper/hypotension, higher creatinine level, and hyponatremia were associated with a disproportionately lower risk of sudden death. The use of several heart failure medications, left ventricular end-diastolic dimension, or NT-pro brain natriuretic peptide concentrations were not associated with a disproportionate risk of sudden death.

CONCLUSION Several easily obtained baseline demographic and clinical variables, beyond ejection fraction and New York Heart Association functional class, are independently associated with a disproportionately increased risk of sudden death. Further investigation is needed to assess whether this novel predictive method can be used to target the use of lifesaving therapies to populations who will derive greatest mortality benefit .

KEYWORDS Sudden death; Nonsudden death; Proportional risk; ICD; ICD benefit; Heart failure; Seattle Proportional Risk Model (SPRM); Regression analysis

ABBREVIATIONS **ACE-I** = angiotensin-converting enzyme inhibitor; **ARB** = angiotensin receptor blocker; **BMI** = body mass index; **CKD** = chronic kidney disease; **ICD** = implantable cardioverter-defibrillator; **LVEF** = left ventricular ejection fraction; **NYHA** = New York Heart Association; **SHFM** = Seattle Heart Failure Model; **NT-proBNP** = N-terminal of the prohormone brain natriuretic peptide; **OR** = odds ratio; **SCD-HeFT** = Sudden Cardiac Death in Heart Failure Trial; **MADIT-II** = Multicenter Automatic Defibrillator Implantation Trial II

(Heart Rhythm 2015;0:-1–9)

Dr Poole is on speakers bureau for Biotronik, Boston Scientific, Medtronic, and St Jude Medical. Dr Levy has received research grant from GE Healthcare, Heartware, Thoratec, Epocrates, National Heart, Lung, and Blood Institute, Medtronic, and ResMed; he also serves as a consultant to GE Healthcare, CDMI, Novartis, and Biotronik. Dr Miller serves as a consultant to St Jude Medical, Medtronic, Biocontrol, Biotronik, Corthera, CardioMEMS, Pfizer, and Columbia/VA; he is also on speakers bureau for Gilead, Bristol-Myers Squibb, and Sanofi. Dr Swedberg serves as a consultant to Medtronic, Novartis, and Servier; he has also received research grant from Amgen, Pfizer, and Servier. The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree with the written manuscript. **Address reprint requests and correspondence:** Dr Ramin Shadman, Division of Cardiology, Southern California Permanente Medical Group, 1526 N Edgemont, 2nd Floor, Los Angeles, CA 90027. E-mail address: ramin.x.shadman@kp.org.

Introduction

The current guidelines recommend primary prevention implantable cardioverter-defibrillator (ICD) therapy for patients with ischemic or nonischemic cardiomyopathy with ejection fraction ≤35%, New York Heart Association (NYHA) functional class II or III heart failure symptoms, and NYHA functional class I ischemic cardiomyopathy with ejection fraction ≤30%.[1,2] However, "the usefulness of implantation of an ICD is of uncertain benefit to prolong meaningful survival in patients with a high risk of nonsudden death."[1] In addition, there are some patients who currently do not qualify for primary prevention ICD therapy who would likely derive a net mortality benefit, given that the majority of their overall mortality risk is attributable to sudden death. The lack of a more nuanced selection tool for physicians to use when counseling patients is reflected in the poor ICD compliance rates.[3] Consequently, better identification of patients who are likely to benefit from this potentially lifesaving therapy is an important area of ongoing investigation.[4,5]

The Seattle Heart Failure Model (SHFM) is a validated multivariate model originally developed to predict all-cause mortality in the population with heart failure using commonly available clinical and demographic variables.[6] Following its original publication, subsequent analysis demonstrated that an individual's SHFM score can also predict mode of death (sudden death vs pump failure death).[7] Patients with the highest SHFM risk scores predominantly die of progressive pump failure, whereas patients with a lower risk score predominantly die suddenly. Therefore, although many patients with severe heart failure will qualify for an ICD on the basis of the current guidelines and some may receive appropriate ICD therapy, a subgroup of these patients will instead die of progressive pump failure rather than from arrhythmia, suggesting that ICD implantation may simply change the *mode* of death (sudden death to pump failure death) rather than substantially reducing *overall* mortality. This hypothesis of a differential all-cause mortality benefit from ICD implantation was tested prospectively in the Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT) using the SHFM. Lower-risk patients (<5% predicted annual mortality rate based on the SHFM score) had an 88% reduction in sudden death and an approximately 50% decrease in all-cause mortality after ICD implantation. In contrast, higher-risk patients (~25% annual mortality rate) had no net reduction in all-cause mortality with primary prevention ICD therapy.

In clinical practice, individual clinicians informally consider patient-specific factors such as extremes of age, poor heart failure prognosis, and comorbidities when applying the existing primary prevention ICD implantation guidelines to their patients. However, this approach is subjective and may not identify those variables, which truly have the greatest independent influence on mortality-specific risk, and ultimately cannot be applied to improve broad clinical guidelines. Hence, our primary objective was to formally characterize those baseline demographic and clinical variables independently associated with a *disproportionate* fraction of mortality risk attributable to either sudden death or nonsudden death. On the basis of these specific variables, we developed a novel multivariate proportional risk model, the Seattle Proportional Risk Model, which we anticipate will proved to a more nuanced tool to clinicians to better identify those patients who would benefit the most from primary prevention ICD therapy.

Methods

Population

The analysis used prospectively collected information from 5 previously described cohorts of ambulatory patients with heart failure with predominantly systolic dysfunction. The cohorts included PRAISE, Val-HeFT, COMET, Italian HF Registry, and a University of Washington cohort and have been described previously in detail.[6,8–12] Each of the studies had previously been approved by the institutional boards of their participating institutions, and all participants gave informed written consent. Patients with an ICD were excluded from this analysis.

Cause of death classification

Mortality and mode of death were independently adjudicated within each study by review of medical records by the study investigators or a centralized adjudication committee. As described previously,[7] "sudden death" was defined as unexpected death in a clinically stable patient or death from documented or presumed cardiac arrhythmia without a clear noncardiovascular cause. All other causes of death were classified as "nonsudden death."

Statistical analysis

Commonly available demographic and clinical variables were used for model development, including age, sex, systolic blood pressure, diabetes mellitus, ischemic etiology for cardiac dysfunction, NYHA functional class, left ventricular ejection fraction (LVEF), angiotensin-converting enzyme inhibitor/angiotensin receptor blocker (ACE-I/ARB) use, β-blocker use, furosemide equivalent weight–based daily dose, digoxin use, creatinine level, and body mass index (BMI). Other variables were not available in the combined data set, such as electrocardiograms, and comorbidities such as cancer, peripheral vascular disease, chronic obstructive pulmonary disease, and stroke. Baseline comparisons between the 2 mortality subgroups for individual variables were first performed using analysis of variance and χ^2 analysis. To better evaluate for suspected nonlinear relationships between some continuous variables and mortality outcomes, univariate logistic regression analyses were performed between each continuous variable and whether the subject died of sudden death vs nonsudden death (including only those patients who died during the analysis). These variables were each fitted to a quadratic function and