Published in final edited form as:

JACC Clin Electrophysiol. 2017 March ; 3(3): 291–298. doi:10.1016/j.jacep.2016.09.006.

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

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Abstract

Background—Prediction of which heart failure patients are most likely to die of sudden death vs. non-sudden death is an important factor in determining who will benefit the most from an ICD.

Objective—We 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 and tested whether the ICD benefit varied with the SPRM.

Methods—Among 2331 patients enrolled, 1947 patients were retained for analysis over a median follow-up of 2.5 years. The SPRM was calculated using age, gender, diabetes, BMI, SBP, EF, NYHA, sodium, creatinine, and digoxin use.

Results—ICD use (ICD or CRT-D) was present prior to death in 1204 patients (62%). SPRM was predictive of sudden death vs. non-sudden death in those without an ICD ($P=0.002$). The

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Disclosures

Industry Relationships: Dr. Levy has received research funding from HeartWare, Medtronic, Resmed, Amgen, and GE Healthcare. He is a consultant to Novartis, GE Healthcare, Pharmin, Abbot, Relysa, and Micro Systems Engineering. There was no industry funding for this study.

Clinical [Trials.gov](https://clinicaltrials.gov) identifier: NCT00047437

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 an ambulatory NYHA II-IV HF population and EF $\geq 35\%$, the SPRM was predictive of the proportional risk of sudden vs. non-sudden 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 have utility in risk stratifying patients for a primary prevention ICD.

Keywords

Heart Failure; Sudden Death; Non-Sudden Death; Prognosis; ICD; Risk Prediction Model; Regression Analysis; Proportional Risk

Introduction

Sudden death comprises half of all deaths in chronic heart failure patients¹. Meta-analysis of primary prevention ICD trials suggests that ICDs decrease sudden death by $\sim 60\%$ 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 ICDs³. ICDs are a Class I indication by ACC/AHA/HRS guidelines to prevent sudden death in NYHA II-III patients with an ejection fraction (EF) $\geq 35\%$ and other selected heart failure patients with a life expectancy of >1 year⁴. However, the utility of a primary prevention ICD may be diminished in patients who are older, women, have chronic kidney disease, or multiple comorbidities⁵⁻⁸. 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, half of patients are NYHA III/IV⁹ and a third are ≥ 75 years old, patients in whom a primary prevention ICD may have a diminished benefit⁷.

Prediction of which heart failure patients are most likely to die of sudden death vs. non-sudden death may provide better risk stratification than NYHA class and ejection fraction. 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 death¹⁰. 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. non-sudden)¹¹. The model found the *proportion* of sudden death was greater with younger age, male gender, lack of diabetes mellitus, lower ejection fraction, better NYHA class (i.e., II vs. III or IV), higher body mass index, digoxin use, and values of systolic blood pressure, sodium, and creatinine closer to the normal range.

We prospectively applied the SPRM to data from the HF-ACTION clinical trial¹² Aim 1) to validate whether the model predicts the proportion of sudden vs. non-sudden death and Aim 2) to 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: A Controlled Trial Investigating Outcomes of Exercise Training (HF-ACTION) was a clinical trial ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT00047437) identifier NCT00047437) of exercise training in 2331 ambulatory NYHA II-IV heart failure patients with an EF of $\geq 35\%$ ¹². We excluded patients who received a LVAD or cardiac transplant (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 1947 patients. The mode of death was adjudicated by a clinical events committee (CEC)¹³. Sudden death was defined as unexpected and otherwise unexplained death in a previously stable patient. This included patients who were comatose 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 CEC as sudden death or unknown mode of death as described above. We combined these endpoints as it is more similar to the methods used in the trials within which the SPRM was derived. The SPRM score was calculated as previously described¹¹. We defined “ICD use” if an ICD or CRT-D was present at baseline or implanted prior to 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, NYHA, etc¹⁴. 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 at least 6 weeks prior to enrollment per the HF-ACTION protocol. Patient 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 vs. 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 (ROC) area under the curve (AUC) in the 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 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 one year of life¹⁵. To examine the impact of ICDs on sudden death and non-sudden death, we applied a regression technique that uses

pseudovalues from cumulative incidence functions to account for competing risks from the other modes of death¹⁶. 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 VT/VF as a proxy for indication for ICD implantation, as the specific ICD indication was not available. We also adjusted for Seattle Heart Failure Model (SHFM) scores¹⁴ 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 described¹¹. 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*-values ≤ 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 demographics were mean age 59, male 73%, ejection fraction 25%, diabetes 33%, and NYHA 2 or 3 in 99% of subjects, similar to SCD-HeFT. Sixty-two percent had an ICD prior to 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 prior to 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 class, creatinine, diuretic dose, and lower ejection fraction and systolic blood pressure. This is reflected by a ~33% higher SHFM estimated 1 year all-cause mortality (not including the benefit of the ICD). Patients with a CRT-D vs. ICD had a higher SHFM estimated 1-year mortality with medical therapy ($8.6 \pm 6.5\%$ vs. $7.5 \pm 6.7\%$), $P=0.0033$ and a lower SPRM predicted proportion of sudden death ($53.8 \pm 13.6\%$ vs. $56.3 \pm 14.1\%$, $P=0.0022$).

During a mean of 2.5 years of observation, 328 (16.8%) patients died, with 138 (18.6%) deaths in 743 patients without an ICD and 190 (15.8%) deaths in 1,204 patients 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 to 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 to those without an ICD (39% vs. 18%, $P<0.0001$). Other modes of death were similar (Table 2).

Aim 1- Determine whether SPRM predicts the proportion of sudden vs. non-sudden death.

Overall, the SPRM-predicted conditional probability of sudden death was 56%. The SPRM-predicted conditional risk of sudden death was 57% in patients alive at the end of follow-up in the trial, 55% in those who died of sudden death, 46% in those with pump failure death and 48% in those who died of other cardiovascular or non-cardiovascular death ($P<0.0001$). Among patients without an ICD, the predicted and observed proportions of deaths that were sudden were similar (57% vs. 59%). The SPRM was predictive sudden vs. non-sudden death

in patients without an ICD (logistic regression, odds ratio 2.05, $P=0.002$) providing validation of the SPRM for prediction of sudden vs. non-sudden death. The Hosmer-Lemeshow goodness of fit test in the patients without an ICD showed adequate SPRM calibration ($p=0.51$). The ROC AUC for sudden vs. non-sudden death was 0.64 in cohort of patients who never had an ICD, the same as the SPRM derivation cohort (0.64). For comparison, EF $\geq 35\%$ and NYHA 2 & 3 had a ROC AUC of 0.52 in the SPRM derivation cohort. Among patients with ICDs, the observed proportions of deaths attributable to sudden death were lower than predicted (odds ratio 0.32, $P<0.0001$), representative of the ICD benefit on sudden death (Figure 2).

Aim 2 – Evaluate whether ICD Benefit varies with the SPRM Score

In the Cox proportional hazards model, 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 37% reduction in all-cause mortality (hazard ratio (HR): 0.63, $P=0.0002$). When an interaction term was added to test whether the benefit of ICDs varied across SPRM scores, the results indicated that ICDs were associated with a lower relative risk of death to among patients with higher SPRM scores (higher proportion of sudden death - hazard ratio 0.58, interaction $P=0.001$ with SPRM modeled as a continuous variable – Figure 3A). The SPRM interaction was similar for both ICD (hazard ratio 0.56, $P=0.002$) and CRT-D (hazard ratio 0.61, $P=0.029$). When modeling the risk of all-cause death using SPRM quartile groups instead, treatment effects of ICDs varied across SPRM quartiles with the greatest benefit in the highest SPRM quartile (Figure 3A), validating the hypothesis. The point of no ICD benefit in the fitted Cox model occurred at a SPRM of $\sim 32\%$ (Figure 3A). Within the first quartile of SPRM, patients with a SPRM $\leq 32\%$ predicted sudden death had a trend for ICD harm (HR: 1.44, $P=0.31$) while those with SPRM $>32\%$ within the first quartile had a trend for ICD benefit (HR: 0.73, $P=0.23$ – interaction P value=0.10). If we adjust for age, sex, EF, NYHA, SBP, ischemic etiology, diuretic dose, ACEI, ARB, 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 above 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 one year of life is 6.7, 5.5, 4.4, and 2.3. (Supplement 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 non-sudden death, an ICD was not associated with an increase in the hazard of non-sudden death (HR: 1.05, $P=0.81$ -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 non-sudden 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 non-sudden death and did not predict patients with a greater proportion of sudden vs. non-sudden 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 prior to the end of follow-up and ICD at baseline). The relative ICD benefit remained greater in those with a higher SPRM scores (interaction $P=0.011$ –See Supplement Figure 1A & 1B). If we start a typical HF-ACTION patient, a 58 y/o male, NYHA class 2, EF 27%, SBP 118, sodium 138, creatinine 1.2 mg/dL, no diabetes mellitus, no digoxin, and a BMI of 31, the SPRM is ~64% predicted proportion sudden death. Changing any one of the following variables has a similar effect on the SPRM predicted proportion of sudden death and will decrease it by ~7% (NYHA 3 vs. 2, EF 42% vs. 27%, female vs. male, aging 12 years, BMI 25 vs. 31, SBP 88 vs. 118 mm Hg, adding diabetes mellitus, sodium 132 vs. 138, or increasing creatinine by 0.6 mg/dL). Adding 0 to 4 of the above risk change for the above patient would change the SPRM from ~64% to ~57%, ~51%, ~44% and ~37%. From the fitted curve in Figure 1, the associated ICD hazard ratio with the previous SPRM values would be ~0.51, ~0.58, ~0.65, ~0.74, and ~0.84. 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 analyses has 1) validated that the previously derived SPRM predicts the proportion of patients who will die of sudden death within HF-ACTION (Figure 1), and more importantly 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 II-III patients with EF 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 prior to 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 variable¹¹. More importantly, 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 model¹⁰.

Prior research has shown the proportion of sudden death varies based on the clinical scenario. The proportion of sudden death is ~50% in chronic systolic heart failure,¹ ~33% in the first year after a myocardial infarction¹⁸, and ~25% in patients with heart failure with preserved ejection fraction¹⁹. Many clinicians assume with such a high risk of sudden death, that an ICD will abrogate this increased risk of sudden death and reduce total mortality. In the DINAMIT trial that tested the effects of ICDs in patients following a myocardial infarction, ICDs decreased sudden death by 67%. However, there was a corresponding 70% increase in non-arrhythmic death and no benefit on total mortality³.

In chronic heart failure patients, the proportion of deaths attributable to sudden death varies by NYHA class: from ~1/3 in NYHA IV to ~2/3 in NYHA II patients¹. The proportion of clinically adjudicated sudden death due to a tachyarrhythmic event is 1/2 of clinically adjudicated sudden death in hospitalized heart failure patients and as high 2/3 clinically adjudicated sudden death in ambulatory heart failure patients¹. Thus, the proportion of total mortality due to a tachyarrhythmic event that may be prevented by an ICD is ~17% (50% of the 33% sudden death) in NYHA IV patients and ~50% (~67% of the ~67% sudden death) in 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, SCD-HeFT, or observationally in HF-ACTION.

There are numerous limitations to the current analysis. This post hoc analysis was not in 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 $\geq$ 35% (HR 0.33 for sudden death and HR 0.63 for all-cause mortality) is similar to the meta-analyses of primary prevention ICDs (HR 0.40 for sudden death and 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 years of observation in HF-ACTION as shown in Supplement 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, as 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 benefit¹⁰.

Conclusion

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 <32% predicted proportion of total mortality due to sudden death had no benefit of the ICD on total mortality. The SPRM may help identify those patients who will derive the greatest benefit from a primary prevention ICD and allow more appropriate utilization of this effective but expensive therapy.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Grants: Drs. Reed, Li, Schulman and Levy received funding from grant 5R01NR011873 from the National Institute of Nursing Research. HF-ACTION was funded by grants 5U01HL063747, 5U01HL066461, 5U01HL068973, 5U01HL066501, 5U01HL066482, 5U01HL064250, 5U01HL066494, 5U01HL064257, 5U01HL066497, 5U01HL068980, 5U01HL064265, 5U01HL066491, and 5U01HL064264 from the National Heart, Lung, and Blood Institute; and grants R37AG018915 and P60AG010484 from the National Institute on Aging.

Abbreviation List

ICD	implantable cardioverter defibrillator
CRT-D	cardiac resynchronization therapy with ICD
EF	ejection fraction
NYHA	New York Heart Association
SPRM	Seattle Proportional Risk Model
SHFM	Seattle Heart Failure Model
LVAD	left ventricular assist device
VT	ventricular tachycardia
VF	ventricular fibrillation

References

1. Effect of metoprolol cr/xl in chronic heart failure: Metoprolol cr/xl randomised intervention trial in congestive heart failure (merit-hf). *Lancet*. 1999; 353:2001–2007. [PubMed: 10376614]
2. 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; 12:1564–1570. [PubMed: 20974768]
3. Hohnloser SH, Kuck KH, Dorian P, Roberts RS, Hampton JR, Hatala R, Fain E, Gent M, Connolly SJ, Investigators D. Prophylactic use of an implantable cardioverterdefibrillator after acute myocardial infarction. *The New England journal of medicine*. 2004; 351:2481–2488. [PubMed: 15590950]

4. Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE Jr, Drazner MH, Fonarow GC, Geraci SA, Horwich T, Januzzi JL, Johnson MR, Kasper EK, Levy WC, Masoudi FA, McBride PE, McMurray JJ, Mitchell JE, Peterson PN, Riegel B, Sam F, Stevenson LW, Tang WH, Tsai EJ, Wilkoff BL. 2013 accf/aha guideline for the management of heart failure: A report of the american college of cardiology foundation/american heart association task force on practice guidelines. *Journal of the American College of Cardiology*. 2013; 62:e147–239. [PubMed: 23747642]
5. Lee DS, Tu JV, Austin PC, Dorian P, Yee R, Chong A, Alter DA, Laupacis A. Effect of cardiac and noncardiac conditions on survival after defibrillator implantation. *Journal of the American College of Cardiology*. 2007; 49:2408–2415. [PubMed: 17599603]
6. Ghanbari H, Dalloul G, Hasan R, Daccarett M, Saba S, David S, Machado C. Effectiveness of implantable cardioverter-defibrillators for the primary prevention of sudden cardiac death in women with advanced heart failure: A meta-analysis of randomized controlled trials. *Arch Intern Med*. 2009; 169:1500–1506. [PubMed: 19752408]
7. Mezu U, Adelstein E, Jain S, Saba S. Effectiveness of implantable defibrillators in octogenarians and nonagenarians for primary prevention of sudden cardiac death. *Am J Cardiol*. 2011; 108:718–722. [PubMed: 21640321]
8. Williams ES, Shah SH, Piccini JP, Sun AY, Koontz JI, Al-Khatib SM, Hranitzky PM. Predictors of mortality in patients with chronic kidney disease and an implantable defibrillator: An epgen substudy. *Europace*. 2011; 13:1717–1722. [PubMed: 21821855]
9. Hammill SC, Stevenson LW, Kadish AH, Kremers MS, Heidenreich P, Lindsay BD, Mirro MJ, Radford MJ, Wang Y, Lang CM, Harder JC, Brindis RG. Review of the registry's first year, data collected, and future plans. *Heart rhythm : the official journal of the Heart Rhythm Society*. 2007; 4:1260–1263.
10. Owens DK, Sanders GD, Heidenreich PA, McDonald KM, Hlatky MA. Effect of risk stratification on cost-effectiveness of the implantable cardioverter defibrillator. *American heart journal*. 2002; 144:440–448. [PubMed: 12228780]
11. Shadman R, Poole JE, Dardas TF, Mozaffarian D, Cleland JG, Swedberg K, Maggioni AP, Anand IS, Carson PE, Miller AB, Levy WC. A novel method to predict the proportional risk of sudden cardiac death in heart failure: Derivation of the seattle proportional risk model. *Heart rhythm : the official journal of the Heart Rhythm Society*. 2015
12. O'Connor CM, Whellan DJ, Lee KL, Keteyian SJ, Cooper LS, Ellis SJ, Leifer ES, Kraus WE, Kitzman DW, Blumenthal JA, Rendall DS, Miller NH, Fleg JL, Schulman KA, McKelvie RS, Zannad F, Pina IL, Investigators H-A. Efficacy and safety of exercise training in patients with chronic heart failure: Hf-action randomized controlled trial. *JAMA*. 2009; 301:1439–1450. [PubMed: 19351941]
13. Reed SD, Li Y, Dunlap ME, Kraus WE, Samsa GP, Schulman KA, Zile MR, Whellan DJ. In-hospital resource use and medical costs in the last year of life by mode of death (from the hf-action randomized controlled trial). *Am J Cardiol*. 2012; 110:1150–1155. [PubMed: 22762718]
14. Levy WC, Mozaffarian D, Linker DT, Sutradhar SC, Anker SD, Cropp AB, Anand I, Maggioni A, Burton P, Sullivan MD, Pitt B, Poole-Wilson PA, Mann DL, Packer M. The seattle heart failure model: Prediction of survival in heart failure. *Circulation*. 2006; 113:1424–1433. [PubMed: 16534009]
15. Levy WC, Mozaffarian D, Linker DT, Kenyon KW, Cleland JG, Komajda M, Remme WJ, Torp-Pedersen C, Metra M, Poole-Wilson PA, Investigators C. 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; 11:256–263. [PubMed: 19164422]
16. Klein JP, Andersen PK. Regression modeling of competing risks data based on pseudovalues of the cumulative incidence function. *Biometrics*. 2005; 61:223–229. [PubMed: 15737097]
17. Bardy GH, Lee KL, Mark DB, Poole JE, Packer DL, Boineau R, Domanski M, Troutman C, Anderson J, Johnson G, McNulty SE, Clapp-Channing N, Davidson-Ray LD, Fraulo ES, Fishbein DP, Luceri RM, Ip JH. Sudden Cardiac Death in Heart Failure Trial I. Amiodarone or an implantable cardioverter-defibrillator for congestive heart failure. *The New England journal of medicine*. 2005; 352:225–237. [PubMed: 15659722]
18. Pouleur AC, Barkoudah E, Uno H, Skali H, Finn PV, Zelenkofske SL, Belenkov YN, Mareev V, Velazquez EJ, Rouleau JL, Maggioni AP, Kober L, Califf RM, McMurray JJ, Pfeffer MA,

Solomon SD, Investigators V. Pathogenesis of sudden unexpected death in a clinical trial of patients with myocardial infarction and left ventricular dysfunction, heart failure, or both. *Circulation*. 2010; 122:597–602. [PubMed: 20660803]

19. Zile MR, Gaasch WH, Anand IS, Haass M, Little WC, Miller AB, Lopez-Sendon J, Teerlink JR, White M, McMurray JJ, Komajda M, McKelvie R, Ptaszynska A, Hetzel SJ, Massie BM, Carson PE, Investigators IP. Mode of death in patients with heart failure and a preserved ejection fraction: Results from the irbesartan in heart failure with preserved ejection fraction study (i-preserve) trial. *Circulation*. 2010; 121:1393–1405. [PubMed: 20231531]
20. Al-Khatib SM, Greiner MA, Peterson ED, Hernandez AF, Schulman KA, Curtis LH. Patient and implanting physician factors associated with mortality and complications after implantable cardioverter-defibrillator implantation, 2002-2005. *Circ Arrhythm Electrophysiol*. 2008; 1:240–249. [PubMed: 19169382]

Clinical Competency Milestones

PC5 (Request and provides consultative care), MK2 (Knowledge of diagnostic testing and procedures), and SBP3 (identifies factors that impact the cost of healthcare, and advocates for, and practices cost-effective care).

Translational Outlook

The Seattle Proportional Risk Model is a method to integrate common clinical variables into a risk model to predict the proportion of sudden death and potentially to assist in selection of patients who are most appropriate for primary prevention ICDs.

Observational ICD use in HF-ACTION suggests patients with a greater predicted proportion of death due to sudden death derive more benefit from an ICD. Other co-morbidities, that may not be prevalent in clinical trial databases such as cancer, dementia, cirrhosis, are likely to decrease the proportion of sudden death similar to the effect of diabetes mellitus.

Seattle Proportional Risk Model

Figure 1. Impact of clinical risk factors on the mode of death

The SPRM is a logistic regression model that provides a patient level estimate of the proportion (not the absolute risk) of sudden vs. non-sudden death based on age, gender, EF, NYHA, diabetes mellitus, SBP, sodium, creatinine, digoxin use, and BMI.

Figure 2. Observed Versus SPRM-Predicted Conditional Risk of Sudden Death

The SPRM predicted vs. observed proportion of sudden death within the patients who died is shown for SRPM quartiles for patients with and without ICDs. The diagonal line is the line of identity.

Figure 3A &B. Effect of ICDs on All-Cause Mortality and Sudden Death Across SPRM Score Quartiles

The benefit associated with an ICD on all-cause mortality is shown in Figure 3A. The points are the hazard ratio for the quartiles and the associated 95% CI. The ICD was associated with an overall mortality benefit of 37% ($P=0.0002$). There was greater benefit in the patients with a higher predicted proportion of sudden death (interaction P value in the fitted Cox model = 0.001). The overall benefit of the ICD on all-cause mortality is illustrated by the dotted line (no interaction) and the interaction with the SPRM in an adjusted Cox model is shown with the solid line. The benefit associated with an ICD on sudden death is shown in Figure 3B. The points are the hazard ratio for the quartiles and the associated 95% CI. The ICD was associated with an overall sudden death benefit of 67% (i.e., $HR=0.33$; $P<0.0001$). There was a suggestion of potentially greater benefit in the patients with a higher predicted proportion of sudden death (interaction P value in the fitted model with SPRM as a continuous variable = 0.07). The overall benefit of the ICD on sudden death is illustrated by the dotted line (no interaction) and the interaction with the SPRM is shown with the solid line.

Table 1

Baseline Demographics

Mean (Standard Deviation) or % for categorical variables	No ICD (n=743)	ICD (n=1204)	P value *
Age (Years)	58 (13)	60 (12)	0.03
Male (%)	492 (66%)	926 (77%)	<0.0001
Ejection Fraction, mean (SD)	27 (8)	24 (7)	<0.0001
Systolic Blood Pressure, mean (SD)	118 (19)	112 (18)	<0.0001
NYHA Class (%)			
II	517 (70%)	720 (60%)	
III	221 (30%)	469 (40%)	<0.0001
IV	5 (1%)	15 (1%)	
History of VT/VF (%)	16 (2%)	283 (24%)	<0.0001
Diabetes Mellitus (%)	227 (31%)	413 (34%)	
Body Mass Index (kg/m ²), mean (SD)	31 (8)	31 (7)	0.54
Sodium (meq/L), mean (SD)	139.4 (3.1)	139.1 (3.7)	0.07
Creatinine (mg/dL), mean (SD)	1.24 (0.74)	1.39 (0.87)	<0.0001
ACEI/ARB (%)	707 (95%)	1130 (94%)	0.23
Beta Blocker (%)	702 (94%)	1143 (95%)	0.66
Aldosterone Blocker (%)	285 (38%)	587 (49%)	<0.0001
Digoxin (%)	279 (38%)	603 (50%)	<0.0001
Furosemide equivalent dose (mg/kg/day), mean (SD)	0.5 (0.6)	0.7 (0.7)	<0.0001
SPRM- predicted risk of SCD conditional on death	57% (15%)	55% (14%)	0.01
SHFM- predicted risk of 1-year mortality [†]	5.9% (4.7%)	7.9% (6.7%)	<0.0001

SCD, sudden cardiac death

* t-test for continuous variables and Chi-square test for categorical variable.

[†] estimated without the effect of ICD implantation included.

Table 2

HF-ACTION - Mode of Death

Number Percent of Total Deaths	All Patients (n= 328)	No ICD (n=138)	ICD (n=190)	P-value
Sudden Cardiac Death	140 (43%)	81 (59%)	59 (31%)	<0.0001
Pump Failure Death	99 (30%)	25 (18%)	74 (39%)	
Other Cardiovascular Death	32 (10%)	10 (7%)	22 (12%)	
Non Cardiovascular Death	57 (17%)	22 (16%)	35 (18%)	

A chi-square test was used to compare distributions between pts with and without ICDs.