Published in final edited form as:

Heart Rhythm. 2013 June ; 10(6): 828–835. doi:10.1016/j.hrthm.2013.02.011.

Survival Benefit of Primary Prevention Implantable Cardioverter-Defibrillator Therapy After Myocardial Infarction: Does Time to Implant Matter?:

A Meta-Analysis Using Patient-Level Data from 4 Clinical Trials

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Abstract

Background—Whether there is an optimal time to place an implantable cardioverter-defibrillator (ICD) more than 40 days after myocardial infarction (MI) in guideline-eligible patients is unknown.

Objective—To evaluate the impact of time from MI to randomization on mortality, re-hospitalizations, and complications.

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Potential Conflicts of Interest (None unless otherwise noted below):

Alan H. Kadish, MD- Sanofi-Aventis, consulting fees/honoraria

Jonathan P. Piccini, MD, MHS- Sanofi-Aventis and Forest Pharmaceuticals, consulting fees/honoraria; Johnson and Johnson, research grants

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Methods—Individual data on patients enrolled in 9 primary and secondary prevention ICD trials were provided. Clinical trials were eligible for the current analysis if they enrolled patients with an MI more than 40 days prior to randomization to primary prevention ICD therapy versus usual care: MADIT-I, MUSTT, MADIT-II, and SCD-HeFT.

Results—ICD recipients died less frequently than non-recipients at 5 years across all subgroups of time from MI to randomization. In unadjusted Cox proportional hazards regression, a survival benefit was evident in most subgroups. Adjusted Bayesian Weibull survival modeling yielded hazard ratio (HR) 0.50, 95% posterior credible interval [PCI] 0.20–1.25 41–180 days after MI; HR 0.98, 95% PCI 0.37–2.37 181–365 days after MI; HR 0.22, 95% PCI 0.07–0.59 >1–2 years after MI; HR 0.42, 95% PCI 0.17–0.90 >2–5 years after MI; HR 0.55, 95% PCI 0.25–1.15 >5–10 years after MI; and HR 0.48, 95% PCI 0.20–1.02 > 10 years after MI. There was no evidence of an interaction between time from MI and all-cause mortality, re-hospitalizations, or complications.

Conclusions—In this meta-analysis, there was scant evidence that the efficacy of primary prevention ICD therapy and no evidence that the risks of re-hospitalizations or complications are dependent on time to implantation more than 40 days after MI.

Keywords

implantable cardioverter-defibrillator; sudden cardiac death; myocardial infarction; heart failure

Introduction

Some survivors of myocardial infarction (MI) are at high risk of sudden cardiac death.¹ The implantable cardioverter-defibrillator (ICD) is the most effective therapy available to reduce this risk.^{2–4} Since risk of sudden cardiac death is highest in the first 30 days after MI and remains elevated in the first six months,^{5, 6} it was postulated that placement of an implantable cardioverter-defibrillator (ICD) early after MI could maximize therapeutic benefit. Counter to this postulate, the Defibrillator in Acute Myocardial Infarction Trial (DINAMIT)⁷ and the Immediate Risk Stratification Improves Survival (IRIS)⁸ trial failed to demonstrate a survival benefit of ICD placement early after MI despite a reduction in arrhythmic death. Current professional guidelines therefore mandate a 40-day waiting period prior to ICD placement after acute MI.⁹

Data from DINAMIT and the IRIS trial are clear: ICD placement within 40 days of a MI is not beneficial. However, whether there is an optimal time to place an ICD more than 40 days after MI remains unknown. Subgroup analyses of three clinical trials exploring the time-dependent survival benefit of ICD therapy after MI yielded conflicting results. In the Multicenter Automatic Defibrillator Implantation Trial II (MADIT-II), ICD recipients did not acquire a survival benefit compared with those who received usual care among those enrolled less than 18 months after MI. Among patients enrolled 18 months or more after MI, however, ICD therapy was associated with a survival benefit.¹⁰ By contrast, post hoc analyses of the Multicenter Unsustained Tachycardia Trial (MUSTT) and the Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT) found no evidence of a time-dependent benefit of ICD therapy.^{11, 12} A gap in evidence regarding the subacute and chronic periods after MI therefore persists.^{13, 14}

Pooling of patient-level data from clinical trials increases the number of patients within subgroups of interest and allows for a more robust assessment of treatment effects. A collaborative consortium involving the principal investigators of 9 existing ICD therapy trials was established to explore the effectiveness of ICD therapy in various subgroups. Confined to patients enrolled in primary prevention ICD trials randomized to ICD therapy vs. usual care, the current analysis sought to assess the impact of the time from MI to randomization and corresponding ICD placement on all-cause mortality, re-hospitalizations, and complications.

Methods

Data Sources and Study Selection

Individual data on patients enrolled in 9 primary and secondary prevention ICD trials were provided. All data were previously collected as part of the primary trials and use of the de-identified dataset achieved exempt status by the Duke Institutional Review Board. Clinical trials were eligible for the current analysis if they enrolled patients with an MI more than 40 days prior to randomization to primary prevention ICD therapy versus usual care. The Antiarrhythmics Versus Implantable Defibrillators trial,¹⁵ the Cardiac Arrest Study Hamburg trial,¹⁶ the Defibrillators in Nonischemic Cardiomyopathy Treatment Evaluation trial,¹⁷ and the amiodarone arm of SCD-HeFT⁴ were therefore excluded. The Coronary Artery Bypass Graft Patch trial¹⁸ was also excluded because patients enrolled in this trial are appreciably different from patients enrolled in the other 4 trials and because of the potential favorable impact of surgical revascularization on ventricular arrhythmia. The following 4 trials were included: the Multicenter Automatic Defibrillator Implantation Trial I (MADIT-I),¹⁹ MUSTT,²⁰ MADIT-II,³ and SCD-HeFT²¹ (Table 1). Although ICD therapy was not randomized in MUSTT, the trial was included because the benefit of antiarrhythmic therapy guided by electrophysiological testing observed in MUSTT was due entirely to outcomes among patients who received an ICD.²² In the current analysis, MUSTT ICD recipients were considered to have received active intervention and non-recipients usual care. Patient inclusion criteria were left ventricular dysfunction due to prior MI, heart failure (New York Heart Association Class I-III), a left ventricular ejection fraction (LVEF) of $\geq 35\%$, and the availability of important covariates. Patients without heart failure symptoms or with New York Heart Association Class IV symptoms (53 from MADIT-II), a LVEF of $> 35\%$ (2 from MADIT-I, 108 from MUSTT, 3 from SCD-HeFT), no documented prior MI (all remaining 458 from DEFINITE, 34 from MUSTT, 913 from SCD-HeFT), an MI in the 40 days preceding randomization or whose time from randomization was unknown (15 from MADIT-I, 76 from MADIT-II, 165 from MUSTT, 50 from SCD-HeFT), or who were missing important covariates (1 from SCD-HeFT) were excluded. A total of 2,388 patients from 4 clinical trials comprised our final study population.

Data Synthesis and Analysis

Table 2 summarizes the baseline characteristics of these patients stratified by category of time from most recent MI prior to randomization. We assessed the association of each baseline characteristic with time from MI using χ^2 tests and tests of equality of medians, respectively, for categorical and continuous-valued characteristics.

Endpoints

We examined the impact of time from MI to randomization on all-cause mortality. Re-hospitalizations and complications were secondary endpoints. Admission to a hospital for any reason after ICD placement during each trial study period qualified as a re-hospitalization. Trial-specific complications included hypotension, syncope, bradycardia or conduction defect, pulmonary embolism, atrial fibrillation, pneumothorax, bleeding, venous thrombosis, problems with a defibrillator lead, defibrillator generator malfunction, MI, sustained ventricular tachycardia, ventricular fibrillation, shock (hemodynamic compromise), new or more advanced heart failure, postpericardiotomy syndrome, postoperative infection, renal failure, new or unanticipated drug therapy, and clinical events requiring surgical correction.

Statistical Analysis

Intervals of time from MI to randomization were chosen to balance interest in clinically relevant time points with the need for adequate sample sizes. Accordingly, patients were categorized into the following subgroups: 41–180 days, 181–365 days, >1 – 2 years, >2 – 5 years, >5 – 10 years, and >10 years. Categorical variables are presented as percentages, and continuous variables are presented as medians with 25th and 75th percentiles.

To assess the relationship between time from MI to randomization and all-cause mortality, unadjusted Cox proportional hazards regression models were fitted. Time to death was evaluated from the day of randomization. All-cause mortality event rates were summarized with Kaplan-Meier survival curves, and differences in survival between ICD recipients compared with non-recipients were assessed with logrank tests. To combine trial data and address missingness, we used Bayesian Weibull survival regression modeling.²³ Missing covariate values were imputed based on their trial-specific empirical distribution. We adjusted for the following covariates: sex, race, age, left ventricular ejection fraction, New York Heart Association class, QRS duration, history of coronary artery bypass grafting, and use of cardiac medications including angiotensin converting enzyme inhibitors, β -blockers, and diuretics. Assuming random effects for trial-specific treatment effects and for parameters defining trial-specific baseline hazard functions, a model including the main effects of ICD therapy and time from MI as well as the multiplicative interaction of ICD therapy with time from MI was fitted. Statistical significance for hazard ratios was established by whether the posterior credible interval did not include the unity value.

In sensitivity analyses, time from MI to randomization was categorized according to quintiles¹⁰, 6 months vs. > 6 months¹¹, and tertiles.¹² We also examined the secondary endpoints of re-hospitalizations and complications with logistic regression modeling using the same groups described in the primary analysis. MUSTT was excluded in the latter analyses given a preponderance of missing values. A main effects model with continuously-valued time from MI was fitted. Analyses were performed using R version 2.15.1 and WinBUGS version 1.4.3.²⁴

Results

Baseline characteristics

A total of 2,388 patients with a prior MI and left ventricular dysfunction due to prior MI were randomized to ICD therapy or placebo. Inspection of baseline characteristics as a function of time from MI to randomization demonstrated some differences (Table 2). Patients with longer periods from MI to randomization were older (median age 67 vs. 63.5 years), more commonly male (92.1% vs. 85.0%), less likely to have received percutaneous intervention (31.1% vs. 36.8%), and less likely to be taking a β -blocker at enrollment (50.6% vs. 65.0%). By contrast, there were no notable differences in race, LVEF, functional status by New York Heart Association classification, major comorbidities, or use of an angiotensin converting enzyme inhibitor, diuretic, or antiarrhythmic medications.

Unadjusted Outcomes

Among 2,388 patients with a history of MI, the Kaplan Meier estimate of the probability of death during follow-up was 65.1% in the 1212 patients receiving usual care as compared with 41.0% in the 1176 ICD recipients. The median duration of follow-up was 2.38 years. Patients randomized to ICD therapy in comparison to usual care were less likely to die by 5 years among all subgroups of time from MI to randomization (Table 3). Figure 1 illustrates cumulative event rates for all-cause mortality stratified according to time from MI to randomization. A survival benefit was evident by 1 year after MI and became more striking over time in most subgroups. Among patients randomized 181 to 365 days after MI, however, a survival benefit was not evident ($p=0.746$).

A total of 1,243 (67.4%) patients were re-hospitalized one or more times and 318 (17.8%) patients experienced one or more complications. Comparison of re-hospitalizations according to time from MI to randomization showed that patients receiving ICD therapy in comparison to those who were randomized to usual care were more likely to be re-hospitalized during follow-up. Similarly, more complications were observed during the follow-up period in patients receiving an ICD versus usual care in all subgroups of time from MI to randomization (Table 3).

Adjusted Outcomes

After adjustment for baseline characteristics, the point estimates for the effect of ICD therapy in comparison to usual care on all-cause mortality estimates for most subgroups were consistent with a survival benefit (Table 4). The absence of benefit in most subgroups was not ruled out, however. Notable exceptions were among patients receiving ICD therapy >1 to 2 years after MI (hazard ratio [HR] 0.22, posterior credible interval [PCI] (0.07, 0.59) and >2 to 5 years after MI (HR 0.42, PCI 0.17, 0.90). Overall, there was no evidence of an interaction between time from MI to randomization and all-cause mortality. Likewise, there was no evidence of an interaction between time from MI and re-hospitalizations or complications.

Sensitivity Analyses

A difference in ICD therapy effect in comparison to usual care according to MI was not detected when time from MI was categorized according to quintiles, 6 months versus > 6 months, tertiles, or analyzed as a continuous value. In a main effects model, the hazards of death related to continuously-valued time from MI was 1.01, 95% PCI (0.99, 1.02).

Discussion

The principal findings of our analysis are twofold. First, when pooling individual patient data from 4 trials to enhance estimation of treatment effects, there is scant evidence that time to implantation more than 40 days after MI impacts ICD efficacy. Second, there is no evidence that time more than 40 days after MI influences the likelihood of re-hospitalization or complication after ICD placement.

Post-MI scar formation may lead to the development of intramyocardial reentry circuits days or years after the initial insult.²⁵ Over time, neurohormonal pathway activation causes ventricular remodeling and dysfunction in some MI survivors. Changes in ventricular architecture in turn set the stage for temporal dispersion and further reentrant arrhythmias.^{26, 27} Post-MI arrhythmic risk profiles therefore vary over time.²⁸ Parallel to the evolving post-MI arrhythmic milieu concomitant with the development of heart failure, the survival benefit of ICD therapy benefit has been hypothesized to vary with time after MI.^{13, 14}

Since adverse ventricular remodeling is associated with a greater risk of mortality,^{29, 30} the MADIT-II subgroup analysis¹⁰ may be consistent with the aforementioned pathophysiologic model. In this setting, the survival benefit of ICD therapy may be restricted to patients with a more remote MI.³¹ By contrast, subgroup analyses from MUSTT¹¹ and SCD-HeFT¹² suggest that ICD therapy is beneficial over all post-MI periods outside of 40 days.¹⁴ Based on adjusted point estimates, the findings of the current study appear to support the latter view. However, we cannot rule out lack of benefit from ICD therapy in most of the studied categories.

The disparate findings between the unadjusted analysis suggesting reduced ICD efficacy among those who received an ICD 181 to 365 days after MI and the adjusted Bayesian Weibull survival analysis suggesting a greater benefit from an ICD >1 to 2 years after MI merit mention. These findings reflect the inherent difference between unadjusted and adjusted analyses. In contrast to the former, the latter account for covariates that may impact the outcome.³² The reduced ICD treatment effect among patients 181–365 days after MI in the adjusted analysis may result from variability in competing causes of mortality such as recurrent MI or heart failure over time after MI. They may also be due to unmeasured factors known to have prognostic significance such as bundle branch block. That there was no evidence of an interaction between the time from MI to randomization and all-cause mortality, complications, or re-hospitalizations suggests the observation in adjusted analysis more likely represents the play of chance.

To our knowledge, our study is the first to examine whether re-hospitalizations or complications after ICD placement vary with time after MI. These events have a direct impact on quality of life and thus may influence patients' decisions regarding ICD placement. The increased risk for re-hospitalization among ICD recipients compared to non-recipients is likely due to shocks requiring further investigation or therapy, complications after ICD placement, and shock-associated heart failure exacerbations.^{33, 34} The absence of evidence that the risks of re-hospitalization or complication are dependent on time from MI is reassuring.

The current analysis has important clinical implications. First, guideline-eligible post-MI patients need not wait an extended period of time prior to device placement in order to derive the maximal survival benefit. Rather, patients with a recent MI experience a survival benefit comparable to patients with a remote MI. Second, time from MI outside of 40 days should not alter patient consent or procedural planning.

Limitations

The current study was performed retrospectively; however, data were collected prospectively in the context of very well-conducted and monitored clinical trials. The factors by which we adjusted our analysis were limited to those which were common to all included trials. It is therefore possible that residual confounding from trial-specific variables we could not include such as atrial fibrillation, diabetes mellitus, bundle-branch block, and other unrecorded ones may have influenced our estimation of treatment effects. Patients with an MI within 40 days of randomization were excluded, and thus the current study neither confirms nor disproves the findings of DINAMIT or the IRIS trial. Despite pooling of individual patient data from 4 trials, the number of patients in each subgroup was still modest. Hence, the study may have been underpowered to detect small differences in ICD efficacy among subgroups. In comparison to prior subgroup analyses, however, the current study had the largest sample size and thus allowed for better characterization of patients with a recent MI. Although a prospective randomized trial could best ascertain whether there is an optimal time to place an ICD after MI, sample size considerations and corresponding costs limit the feasibility of such an endeavor.

Conclusions

In this meta-analysis of 2,388 patients in 4 clinical trials, there was scant evidence that the efficacy of primary prevention ICD therapy is dependent on time to implantation more than 40 days after MI. Similarly, there was no evidence that time more than 40 days after MI influences re-hospitalization or complication rates after ICD placement.

Acknowledgments

Sources of Funding: Primary funding was provided by the Agency for Healthcare Research and Quality (5 R01 HS018505-03). P.L.H. was funded by NIH T-32 training grant HL069749-09. The funding sources had no role in the design, analysis, or interpretation of the data or in the decision to submit the manuscript for publication.

Glossary of abbreviations

CABG-Patch	Coronary Artery Bypass Graft Patch
DINAMIT	Defibrillator in Acute Myocardial Infarction Trial
HR	hazard ratio
ICD	implantable cardioverter-defibrillator
IRIS	Immediate Risk Stratification Improves Survival
LVEF	left ventricular ejection fraction
MADIT-I	Multicenter Automatic Defibrillator Implantation Trial I
MADIT-II	Multicenter Automatic Defibrillator Implantation Trial II
MI	myocardial infarction
MUSTT	Multicenter UnSustained Tachyarrhythmia Trial
OR	odds ratio
PCI	posterior credible interval
SCD-HeFT	Sudden Cardiac Death in Heart Failure

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Figure 1.
Unadjusted Kaplan-Meier Survival Curves in ICD Recipients vs. Non-recipients According to Time From MI

Table 1

Design and Eligibility Criteria of Primary Prevention ICD Trials

Clinical Trial	Dates of Recruitment	Participating Countries	Year of Main Publication Countries	No. of participants	Mean duration of follow-up (mos)	Eligible age range at entry (yrs)	Eligible LVEF	Factorial Comparison	Placebo Control
MADIT-I	Dec 1990 – Mar 1996	USA, Italy, Germany	1996	196	26.8	25–80	35%	ICD v. conventional medical therapy	No
MUSTT	Nov 1990 – Oct 1996	USA, Canada	1999	2202	39.0	<80	40%	ICD or antiarrhythmic v. drugs v. placebo	No
MADIT-II	Jul 1997 – Nov 2001	USA, Netherlands, Germany, Israel	2002	1232	20.2	>21	30%	ICD v. conventional medical therapy	No
SCD-HeFT	Sep 1997 – Jul 2001	USA, Canada	2005	2521	40.2	>18	35%	ICD v. placebo v. amiodarone	Yes

Table 2

Baseline Characteristics According to Time From MI

Characteristic	Time from MI					p-value
	41–180 days (n=300)	181–365 days (n=197)	>1 – 2 years (n=237)	>2 – 5 years (n=484)	>5 – 10 years (n=585)	
Randomized to ICD, %	42.3	43.7	48.5	51.9	52.5	0.034
Age, median (IQR)	63.5 (55, 70)	61 (52, 68)	61 (53, 69)	61 (53, 69)	67 (61, 73)	<0.001
Male, %	85.0	82.7	86.5	83.1	92.1	<0.001
Race						0.317
White	86.6	81.7	88.2	86.8	88.7	
Black	10.0	12.2	8.4	8.7	6.3	
Other	3.3	6.1	3.4	4.5	5.0	
Left ventricular ejection fraction, median (IQR)	26 (20.8, 30)	25 (20, 30)	25 (20, 30)	25 (20, 30)	25 (20, 30)	<0.001
New York Heart Association Class						0.056
I	26.2	21.9	27.0	21.0	26.5	
II	46.9	50.3	47.4	46.4	45.6	
III	26.9	27.8	25.6	32.5	27.9	
Serum creatinine, median (IQR)	1.1 (1.0, 1.4)	1.1 (0.9, 1.4)	1.1 (0.9, 1.4)	1.1 (1.0, 1.4)	1.2 (1.0, 1.4)	0.746
Medical history, %						
Atrial fibrillation	3.8	6.1	3.7	6.1	6.4	0.649
Diabetes	34.2	37.7	30.5	34.7	31.3	0.261
Hypercholesterolemia	50.0	50.0	66.7	38.7	48.4	0.811
Hypertension	54.7	58.3	54.2	52.4	52.4	0.808
Peripheral vascular disease	12.5	9.5	18.2	26.3	14.6	0.446
Percutaneous coronary intervention	36.8	51.5	50.2	41.0	36.1	<0.001
Pulmonary disease	17.4	22.6	18.5	19.8	17.9	0.945
Smoking	79.8	83.0	80.0	81.2	80.5	0.711
Medication, %						
Angiotensin converting enzyme inhibitor	79.0	82.7	78.9	81.0	79.8	0.108
β-blocker	65.0	65.0	59.1	57.4	53.8	<0.001
Diuretic	70.9	72.1	73.8	75.2	74.0	0.249
Antiarrhythmic	12.7	7.1	8.0	6.2	8.9	0.040

Characteristic	Time from MI					p-value
	41–180 days (n=300)	181–365 days (n=197)	>1 – 2 years (n=237)	>2 – 5 years (n=484)	>5 – 10 years (n=585)	
Included Patients, n						
MADIT-I	32	21	11	38	41	36
MADIT-II	123	88	111	221	281	279
MUSTT	66	22	34	60	107	108
SCD-HeFT	79	66	81	165	156	162

IQR = interquartile range.

Data are presented as % unless otherwise indicated and are based on patients with available data.

Table 4

Treatment Effect of ICD Therapy According to Time From MI

Event	Trial	Time From MI					
		41–180 days (n=366)	181–365 days (n=223)	>1 – 2 years (n=263)	>2 – 5 years (n=534)	>5 – 10 years (n=644)	>10 years (n=674)
All-cause mortality (HR, 95% PCI)	MADIT-I	0.47 (0.23, 0.89)	0.92 (0.42, 1.89)	0.21 (0.09, 0.47)	0.38 (0.21, 0.69)	0.51 (0.28, 0.89)	0.45 (0.24, 0.77)
	MUSTT	0.28 (0.13, 0.56)	0.54 (0.23, 1.15)	0.12 (0.05, 0.28)	0.23 (0.12, 0.40)	0.31 (0.16, 0.52)	0.27 (0.14, 0.47)
	MADIT-II	0.60 (0.39, 1.16)	1.19 (0.65, 2.15)	0.28 (0.13, 0.52)	0.51 (0.33, 0.76)	0.67 (0.47, 0.96)	0.59 (0.39, 0.87)
	SCD-HeFT	0.74 (0.47, 1.39)	1.45 (0.79, 2.57)	0.34 (0.17, 0.65)	0.63 (0.40, 0.91)	0.82 (0.57, 1.21)	0.72 (0.50, 1.01)
	Overall	0.50 (0.20, 1.25)	0.98 (0.37, 2.37)	0.22 (0.07, 0.59)	0.42 (0.17, 0.90)	0.55 (0.25, 1.15)	0.48 (0.20, 1.02)
Rehospitalizations (OR, 95% PCI)	MADIT-I	1.38 (0.71, 2.93)	1.69 (0.72, 3.61)	0.73 (0.34, 1.57)	1.28 (0.65, 2.36)	1.21 (0.68, 2.32)	1.47 (0.76, 2.56)
	MADIT-II	2.59 (1.50, 5.18)	3.15 (1.55, 6.17)	1.34 (0.77, 2.46)	2.36 (1.54, 3.65)	2.30 (1.53, 3.63)	2.71 (1.77, 4.24)
	SCD-HeFT	1.56 (0.90, 2.96)	1.90 (0.94, 3.91)	0.83 (0.44, 1.48)	1.44 (0.90, 2.24)	1.39 (0.90, 2.22)	1.63 (1.04, 2.59)
Complications (OR, 95% PCI)	Overall	1.82 (0.66, 5.18)	2.19 (0.77, 6.91)	0.95 (0.36, 2.55)	1.66 (0.70, 4.23)	1.61 (0.67, 4.39)	1.89 (0.80, 5.05)
	MADIT-I	0.65 (0.29, 1.50)	2.02 (0.57, 8.19)	8.52 (2.33, 41.05)	2.28 (0.98, 5.46)	2.37 (1.09, 5.27)	2.32 (1.01, 5.15)
	MADIT-II	1.10 (0.53, 2.30)	3.54 (1.12, 12.88)	14.44 (4.76, 63.85)	3.89 (2.01, 8.36)	4.11 (2.29, 7.93)	4.04 (2.27, 7.21)
	SCD-HeFT	0.56 (0.27, 1.27)	1.83 (0.56, 7.15)	7.47 (2.30, 33.76)	2.00 (0.98, 4.25)	2.14 (1.09, 4.29)	2.09 (1.12, 3.99)
	Overall	0.74 (0.25, 2.19)	2.34 (0.55, 11.29)	9.61 (2.19, 53.68)	2.62 (0.92, 7.75)	2.76 (0.91, 8.64)	2.71 (1.01, 7.69)

Abbreviations: HR, hazard ratio; OR, odds ratio; PCI, posterior credible interval.

Bayesian Weibull survival regression models are adjusted for age, gender, race, New York Heart Association class, left ventricular ejection fraction, QRS duration, medication use (angiotensin converting enzyme inhibitor, β -blocker, diuretic), and coronary artery bypass grafting.

Statistical significance is established by whether posterior credible interval includes the unity value.