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Mortality benefits from implantable cardioverter-defibrillator therapy are not restricted to patients with remote myocardial infarction: an analysis from the Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT)

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Abstract

Background—The implantable cardioverter-defibrillator (ICD) is an effective therapy for preventing sudden cardiac death (SCD) in patients with prior myocardial infarction (MI) and reduced left ventricular function; however, the optimal timing of ICD implantation after MI remains unknown.

Objective—The purpose of this study was to determine whether the benefit of single-lead conservatively programmed ICD therapy varies as a function of time from MI to ICD implantation.

Methods—We compared time to all-cause death and SCD between the ICD and placebo arms in the Sudden Cardiac Death in Heart Failure Trial. Rates of appropriate shocks in the ICD arm were also assessed as a function of time after MI.

Results—Among the 712 patients with a history of MI, 274 died (38.5%), and 68 of these deaths were SCD (24.8%). Appropriate shocks were more common with increasing time after MI (adjusted hazard ratio [HR] per year after MI 1.04 [1.00–1.08]). Despite these differences, there was no evidence of differential mortality benefit with ICD implantation as a function of time after MI: continuous variable adjusted HR 1.00 [0.98,1.03] and shortest versus longest tertile adjusted HR 0.95 [0.66–1.34]. Sensitivity analyses also failed to show differential mortality benefit by quartile or with the use of an 18-month cutoff: <18 versus ≥18 months adjusted HR 1.08 [0.77, 1.51].

Conclusion—There is no evidence that ICD benefit varied with time from MI to implantation/randomization in this primary prevention population. Single-lead ICD benefit is not restricted to patients with a remote MI (>18 months).

Keywords

Implantable cardioverter defibrillator; myocardial infarction; ischemic cardiomyopathy; heart failure; sudden cardiac death

Introduction

The implantable cardioverter-defibrillator (ICD) is an effective therapy for preventing sudden cardiac death (SCD) in patients with prior myocardial infarction (MI) and reduced left ventricular function.^{1,2} Despite the increased risk of SCD in survivors of MI and the proven efficacy of the ICD for the prevention of SCD, there is a temporal paradox between (1) the risk of SCD and (2) the benefits of device implantation in this patient population.

Multiple studies have shown that the risk of SCD is greatest immediately after MI.^{3,4} Despite the predominance of SCD risk early after MI, the Defibrillator After Acute Myocardial Infarction Trial (DINAMIT) and the Immediate Risk Stratification Improved Survival (IRIS) trials failed to demonstrate significant improvement in survival with ICD implantation early after MI compared with optimal medical therapy.^{5,6} Additionally, a post hoc analysis of the Multicenter Automatic Defibrillator Implantation Trial (MADIT) II study suggested that ICD implantation was associated with decreased mortality only in those patients 18 months after MI.⁷ Given these disparate data, the optimal timing of ICD implantation after MI remains unknown. The goal of this analysis is to assess the benefit ICD therapy in patients with ischemic cardiomyopathy as a function of the time from the most recent MI.

Methods

Study design

The methods and study design of the Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT) have been published elsewhere.² Briefly, SCD-HeFT randomized patients with symptomatic heart failure (New York Heart Association functional [NYHA] class II or III) and a left ventricular ejection fraction (LVEF) $\geq$ 35% to placebo, amiodarone (Wyeth-Ayerst Pharmaceuticals, Madison, NJ), or an ICD. Patients with MI, unstable angina, or coronary revascularization within the last 30 days were not eligible for enrollment. The ICD (Medtronic model 7223) was a single-chamber, shock-only device. Tachycardia detection was programmed as a single zone ($\geq$ 188 bpm), and antibradycardia pacing was programmed at VVI 50 bpm after a hysteresis of 34 bpm. All patients received optimal medical therapy.

For the purpose of this analysis, we included only patients with ischemic cardiomyopathy randomized to placebo (n = 453) or ICD therapy (n = 431). Patients randomized to amiodarone and those with nonischemic cardiomyopathy were excluded. Additionally, patients without documentation of prior MI were excluded (n = 172), leaving 712 patients in this analysis. Patients were divided into tertiles based on the time from their most recent MI to ICD implantation/randomization, as recorded in the baseline SCD-HeFT case report form. Time from MI was also considered as a continuous variable. Finally, based on the MADIT-

If trial results,⁷ we also conducted a sensitivity analysis examining ICD benefit according to quartiles of time after MI as well as <18 months versus ≥18 months between MI and ICD implantation/randomization. The time delay from randomization to ICD implantation in those randomized to device therapy was minimal (median = 3 days).

Endpoints and definitions

The primary endpoint of this analysis was time from randomization to death from any cause. Secondary endpoints included SCD (arrhythmic death) and appropriate ICD shocks. A central committee, blinded to treatment randomization, adjudicated all events. This committee, using an SCD definition adapted from the Multicenter UnSustained Tachycardia Trial (MUSTT), determined the cause of death. Importantly, deaths in the context of progressive end-stage heart failure over the preceding 3–4 months (e.g., long-term survival was not expected) were not adjudicated as SCD, even if the heart failure death was associated with a terminal tachyarrhythmic event.⁸ Appropriate shocks were defined as those delivered for rapid ventricular tachycardia (VT) or ventricular fibrillation that met detection criteria (number of intervals to detect = 18/24).⁹

Statistical analysis

Time from MI was considered according to prespecified variable classifications, including time from MI as a continuous variable and by tertile groups (<2.11, 2.11–7.31, and >7.31 years). Tertile analysis was chosen in an attempt to maximize sample size in each subgroup, while maintaining adequate temporal dispersion.

When time from MI was considered as an ordinal variable, the baseline characteristics of patients in the three tertiles were compared using the Jonckheere-Terpstra test¹⁰ for continuous variables and the Mantel-Haenszel P²-test for categorical variables. Continuous variables are presented as medians with 25th and 75th percentiles, and categorical variables are presented as frequencies and percentages. Event rates per 100 years of follow-up were calculated as $100 \times (\text{number of events}) / (\text{sum of all patient follow-up times})$.

The relationships between time from MI and all-cause mortality and SCD were assessed using Cox proportional hazards modeling¹¹ after adjustment for mortality predictors established in the full SCD-HeFT cohort: randomized therapy, age, gender, NYHA class, time since heart failure diagnosis, LVEF, 6-minute walk distance, systolic blood pressure, diabetes, angiotensin-converting enzyme (ACE) inhibitor use, digoxin use, presence of mitral regurgitation, renal insufficiency, substance abuse, baseline electrocardiography [PR, QTc, interventricular conduction delay], and the Duke Activity Status Index. The Cox model for appropriate shocks (performed only in the patients who received an ICD) was unadjusted for other covariates. Baseline beta-blocker use was not included in the final models because it was not a significant predictor of all-cause mortality or SCD in the SCD-HeFT population.

When time from MI was considered as a continuous variable, the assumption of linearity within the context of the Cox model (linearity with respect to the log hazard ratio) was evaluated using restricted cubic splines to determine whether any transformations were necessary. For all three endpoints considered (all-cause death, SCD, and appropriate ICD

shocks), the relationship was approximately linear. Sensitivity analyses also explored time from MI according to quartiles and <18 versus ≥18 months.⁷

To determine whether ICD benefit varied with time from MI, we tested for two-way interactions between time from MI to implantation/randomization and ICD benefit (vs. placebo) for all-cause mortality and SCD. Event rates for all-cause mortality and SCD were summarized for placebo and ICD arms within each tertile using Kaplan-Meier estimates.¹² ICD:placebo hazard ratios within tertiles were generated using adjusted Cox models as described.

All statistical comparisons were two-sided, and $P < .05$ was considered statistically significant.

Results

Baseline characteristics

We identified 712 patients with prior MI and heart failure randomized to placebo or ICD therapy. Examination of the baseline characteristics according to the time from MI to implantation/randomization (tertiles <2.11, 2.11–7.31, and >7.31 years) revealed several differences in the three tertiles. As shown in Table 1, Figure 1 shows the distribution of time from MI at randomization. Among the 712 patients with a history of prior MI, independent of treatment, 274 died (38.5%), and 68 of these deaths were SCD (24.8%). When considering the 330 patients who were randomized to ICD therapy, 69 (20.9%) experienced one or more appropriate shocks for sustained VT or ventricular fibrillation at rates of 188 bpm or greater over the course of the study.

Comparison of outcomes according to the time from MI revealed that patients randomized to ICD therapy (vs. placebo) were less likely to experience SCD in all three tertiles: 6.2% versus 14.2% in the shortest tertile, 5.8% versus 10.3% in the middle tertile, and 2.5% versus 17.4% in the longest tertile (Table 2). Figure 2 depicts the cumulative event rates for all-cause death and SCD according to treatment (ICD vs. placebo) stratified by time from MI (by tertiles). There were no significant differences in the HRs and 95% confidence interval between groups according to time after MI. When we examined the incidence of appropriate shocks in those patients who received an ICD, the rates of appropriate shocks did not diverge until approximately 6 months after device implantation. As shown in Figure 3, patients in the upper tertile (>7.31 years after MI) had the highest cumulative incidence of appropriate ICD shocks.

Adjusted outcomes stratified by time from MI to implantation/randomization

When analyzing time from MI as a continuous variable or as an ordinal variable (by tertile), there was no detectable association between time from MI and all-cause death or SCD independent of treatment (Table 3). As Shown in Table 3, appropriate ICD shocks were more common with increasing time from MI, such that the adjusted HR for appropriate ICD shocks per year after MI was 1.04 (1.002–1.08), $P = .040$.

Time from MI to implantation/randomization and ICD benefit

When examining the effect of ICD therapy on all-cause mortality and SCD (ICD vs. placebo), there was no significant difference according to time after MI (Figure 2, Table 4). As shown in Table 4, there was no evidence of any interaction between treatment (ICD vs. placebo) and time from MI (by tertiles) for either endpoint, suggesting that the reduction in all-cause mortality and SCD associated with ICD implantation did not depend on the length of time after MI. Interaction tests for ICD benefit and time from MI to randomization as a continuous variable (death $P = .76$, SCD $P = .35$) also failed to identify differential treatment effects.

Sensitivity analyses

Since prior published data from MADIT-II have suggested time dependence of ICD benefit using a cutoff of 18 months, we conducted a post hoc sensitivity analysis examining SCD and all-cause death in patients with MI <18 months and MI ≥ 18 months. There was no evidence of an interaction between time from MI <18 or ≥ 18 months and ICD benefit for all-cause death ($P = .57$) or SCD ($P = .39$). Finally, we also examined the time according to MI by quartiles, as used in the MADIT-II analyses. As shown in Table 5,^{7,13} we found no evidence of differential treatment effect across quartiles of time from MI to implantation/randomization.

Discussion

Prior work has suggested that the mortality benefit associated with ICD implantation is limited to those who are more than 18 months from their MI.^{7,13} To ascertain whether treatment benefit from ICD implantation varies as a function of time after MI, we conducted an analysis of those patients with a history of MI enrolled in the SCD-HeFT trial. Despite multiple analyses that examined the relationship between time from MI to implantation/randomization and multiple outcomes, we did not find evidence of differential ICD benefit according to the time elapsed since MI.

The risk of SCD is greatest immediately after MI and declines in the weeks to months after infarction.^{4,14} In the Valsartan In Acute Myocardial Infarction (VALIANT) trial, which enrolled patients with symptomatic heart failure or left ventricular dysfunction after MI, the risk of SCD decreased with time after MI; from 1.37% in the month after discharge (until 30 days), to 0.54% per month in the first 6 months after MI, and finally to 0.21% per month thereafter.³ Given the increased risk of SCD early after MI, the Defibrillator in Acute Myocardial Infarction Trial (DINAMIT) trial was designed to determine whether prophylactic ICD implantation early after MI led to improved survival. Despite a decrease in arrhythmic death, ICD implantation within 40 days of an MI did not reduce all-cause mortality in patients with an LVEF <35% and abnormal heart rate variability.⁵

It is important to note that the devices used in the DINAMIT trial were programmed to treat VT 175–200 bpm with antitachycardia pacing. It is possible that differences in ICD programming may have led to the increased risk of nonarrhythmic death in the device patients in DINAMIT.¹⁵ Similar to the DINAMIT trial, the IRIS trial also randomized

patients to optimal medical therapy or ICD implantation early after MI (5–31 days). Patients in IRIS were included based on the presence of (1) an LVEF $\geq 40\%$ with a resting heart rate >90 bpm, (2) the presence of nonsustained VT >150 bpm on Holter monitoring, or (3) both. ICD programming was similar to that in SCD-HeFT, with single-chamber demand pacing (VVI 40) and shock-only therapy for VT/VF ≥ 200 bpm.⁶ Although similar in some regards to SCD-HeFT, the patient selection process was considerably different. Consequently, the results of these and other studies have led to a controversy about the relationship between ICD benefit and time after MI.

Motivated by the evolving therapeutic landscape in the treatment of MI, including improved revascularization and pharmacotherapy, Wilber et al⁷ examined the time dependence of ICD benefit after MI in MADIT-II. After dividing the time after MI into quartiles (<18 , 18–59, 60–119, and ≥ 120 months), the MADIT-II investigators examined the risk of all-cause death associated with ICD implantation (vs. control) in 1,159 patients. They found an increase in the mortality benefit associated with ICD implantation with longer times after MI. After adjustment for important confounders, they observed decreased mortality with ICD implantation in patients with a remote MI (HR 0.55 [0.39–0.78]) that was not observed in patients with a more recent MI (<18 months, HR 0.97 [0.51–1.81]). The MADIT-II investigators concluded that the survival benefit associated with ICD implantation appeared to be greater for patients with a remote MI. While the MADIT-II analysis was a critical step forward in the evaluation of the time dependence of ICD benefit after an MI, their analysis did not consider time after MI as a continuous variable and was restricted to all-cause mortality.

In a similar population of patients with significant left ventricular dysfunction after MI, we could not demonstrate a difference in ICD benefit as a function of time after MI. SCD rates were reduced across all three tertiles of time after MI. More importantly, ICD implantation was not associated with a differential treatment effect within 18 months of MI and beyond 18 months as demonstrated by the overlapping treatment estimates. Despite formal interaction testing, we did not observe heterogeneity of treatment effect across the range of time since MI in any analysis (continuous, by tertile, by quartile, or by 18 month cutoff). While we did find an increased risk of appropriate shocks with increasing time after MI, ICD shocks are a limited surrogate for SCD and all-cause mortality.¹⁷

Within a clinical trial population, subgroups of those at risk are often analyzed in hopes of identifying patients who are more likely to benefit from a given intervention or, conversely, to identify those who will not benefit. However, subgroup analyses must be viewed with caution.^{18,19} More often than not, the best treatment effect estimate for a given subpopulation is the overall treatment effect, rather than those derived from subgroups.²⁰ Accordingly, and consistent with the results of our analyses, ICD benefit does not appear to be restricted to patients remote (>18 months) from their MI. However, it is also possible (although perhaps less likely) that this observation could be explained by important differences between SCD-HeFT and other ICD trials. MADIT-II enrolled patients with an LVEF of 30% or less, while SCD-HeFT used a cutoff of 35%. In MADIT-II, device programming was left to the discretion of the implanting physician and included antitachycardia pacing, as opposed to the single-zone shock-only program used in SCD-

HeFT. The use of dual-chamber ICDs in MADIT-II may have also contributed to different outcomes, since dual-chamber devices (depending on programming) could lead to greater right ventricular pacing burden and increased mortality as suggested by the DAVID trial.¹⁶ Again, while not directly comparable to SCD-HeFT, but notable for the absence of a mortality benefit early after MI, both the DINAMIT and IRIS trials also had different device programming from SCD-HeFT. In DINAMIT, the programming of a VT zone may have led to more ICD therapies, which may or may not have exerted a harmful effect. Finally, both the DINAMIT and IRIS trial (in part) selected patients on the basis of impaired autonomic tone. Therefore, these patients may have a higher likelihood of progressive heart failure death rather than arrhythmic death. Unlike DINAMIT and IRIS, MADIT-II and SCD-HeFT enrolled few patients who were less than 6 months post-MI ($n = 81$ in this analysis). These and other differences between SCD-HeFT and other trial populations can make drawing inferences across trials challenging.

Limitations

When considering the results of this analysis, several important limitations must be kept in mind. This study is a retrospective analysis and thus is subject to bias and the other well-known limitations of nonexperimental designs. While we adjusted for factors known to be associated with both all-cause death and SCD, it is possible (and likely) that there were unobserved and unrecorded variables that may have influenced the observed outcomes. When compared with the overall populations of primary prevention trials, this cohort represents a smaller sample size and therefore may have been limited by reduced power to detect small but real differences in the benefits of ICD therapy as a function of time after MI. Additionally, the vast majority of patients analyzed were more than 6 months from their most recent MI, thus limiting our ability to definitively characterize risk and benefit in those patients who have a recent history of MI. Nonetheless, over 10% of the cohort did have a recent MI, and the reductions observed in SCD and all-cause death did not differ according to the time after MI to randomization, including time from MI via tertiles, quartiles, or <18 months or as a continuous variable.

Clinical implications

These results have important clinical implications. At the present time, we know that ICD therapy can prevent SCD, but we do not know when to initiate primary prevention device therapy after an MI to optimize efficacy and minimize patient risk. Previous work has suggested that despite a higher risk of SCD early after MI, the benefit from ICD therapy is optimal more than 18 months after MI. Our results suggest otherwise, by showing no differences in device benefit according to time after MI. This may reflect more the types of patients enrolled (MADIT-II also enrolled NYHA class I patients) or the type of ICD programming and therapy implemented more than anything else. Very simply, conservatively programmed devices, as in SCD-HeFT, may prove valuable early post-MI (outside of 40 days). Therefore, device therapy should not be restricted to those patients remote from MI. Future, prospective trials are needed to determine the optimal time for ICD implantation after MI and the optimal programming of primary prevention devices.

Conclusions

In this heart failure population, there is no evidence that ICD benefit varied with time after MI to implantation/randomization. Differences observed between SCD-HeFT and other clinical trials of ICD therapy after MI may be explained by differential ICD programming and therefore require further investigation. While further work must be done to characterize ICD implantation in the postacute and intermediate time periods, ICD implantation should not be restricted to patients with a remote MI (>18 months).

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Abbreviations

DINAMIT	Defibrillator After Acute Myocardial Infarction Trial
HR	hazard ratio
ICD	implantable cardioverter-defibrillator
IRIS	Immediate Risk Stratification Improved Survival
LVEF	left ventricular ejection fraction
MADIT	Multicenter Automatic Defibrillator Implantation Trial
MI	myocardial infarction
MUSTT	Multicenter UnSustained Tachycardia Trial
NYHA	New York Heart Association
SCD	sudden cardiac death
SCD-HeFT	Sudden Cardiac Death in Heart Failure Trial
VT	ventricular tachycardia

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Figure 1.
Distribution of time between myocardial infarction and randomization/implantation. Each bar represents 3-month intervals.

Figure 2. Kaplan-Meier event rates in patients treated with an ICD vs. placebo according to time from MI to implantation/randomization (tertiles) for (A) all-cause mortality and (B) sudden cardiac death.

Figure 3.
Kaplan-Meier rates of appropriate ICD therapy according to the time from myocardial infarction to implantation/randomization.

Table 1

Baseline characteristics according to the time from MI (tertiles)

	Time from MI			
Baseline characteristic	<2.11 years (n = 238)	2.11–7.31 years (n = 237)	>7.31 years (n = 237)	<i>pa</i>
Randomized to ICD	41 (97)	51 (121)	51 (122)	.019
Age	61 (52, 68)	60 (52, 68)	66 (58, 72)	>.0001
Female	17 (40)	19 (46)	6 (15)	.0011
Nonwhite race	18 (42)	17 (41)	13 (31)	.18
Weight, Lbs	190 (162, 224)	184 (161, 211)	187 (164, 216)	.67
NYHA class III	34 (82)	34 (80)	32 (75)	.52
Ejection fraction	25 (20, 30)	25 (20, 30)	24 (20, 29)	.0099
Prior coronary artery bypass grafting	45 (106)	59 (139)	57 (134)	.0087
Prior percutaneous coronary intervention	48 (113)	43 (101)	36 (85)	.010
Diabetes	42 (100)	35 (84)	30 (70)	.0045
Pulmonary disease	18 (44)	19 (46)	19 (45)	.89
Hyperlipidemia	73 (174)	74 (174)	68 (162)	.25
Hypertension	59 (140)	59 (140)	56 (133)	.55
Atrial fibrillation/flutter	13 (31)	18 (42)	18 (42)	.16
Nonsustained VT	17 (41)	21 (50)	20 (48)	.41
Syncope	10 (23)	6 (14)	5 (13)	.075
Electrophysiological study	13 (31)	18 (42)	13 (30)	.91
QRS duration &&& 120 ms	30 (72)	38 (90)	52 (124)	>.0001
Systolic blood pressure, HHmg	114 (104, 128)	118 (104, 130)	118 (110, 135)	.015
Diastolic blood pressure, HHmg	70 (60, 78)	70 (62, 78)	70 (60, 78)	.34
Heart rate, bpm	72 (64, 80)	72 (64, 82)	71 (62, 80)	.41
Serum sodium, mEq/L	139 (137, 141)	139 (137, 141)	139 (137, 141)	.28
Serum creatinine, mg/dL	1.2 (1.0, 1.4)	1.1 (1.0, 1.4)	1.2 (1.0, 1.4)	.11
ACE inhibitor or angiotensin receptor Blocker	95 (226)	96 (227)	94 (223)	.67
Beta-blocker	79 (188)	70 (165)	63 (149)	.0001
Digoxin	61 (145)	62 (148)	60 (142)	.82
Aspirin	76 (181)	70 (165)	72 (170)	.29
Statin	60 (143)	62 (147)	50 (119)	.030
Aldosterone Antagonist	17 (41)	13 (30)	17 (41)	.98

Note. Data are % (n) unless otherwise specified.

^aP-value from Mantel-Haenszel χ^2 test for categorical variables and Jonckheere-Terpstra test for continuous variables. Continuous variables are shown as median (25th, 75th percentiles).

Table 2

Outcomes according to time from MI by tertiles

	Time from MI to randomization					
	<2.11 years (n = 238)		2.11–7.31 years (n = 237)		>7.31 years (n = 237)	
	Placebo (n = 141)	ICD (n = 97)	Placebo (n = 116)	ICD (n = 121)	Placebo (n = 115)	ICD (n = 122)
SCD, % (n)	14.2 (20)	6.2 (6)	10.3 (12)	5.8 (7)	17.4 (20)	2.5 (3)
Death, % (n)	36.9 (52)	23.7 (23)	27.6 (32)	27.3 (33)	41.7 (48)	29.5 (36)
Event rates per 100 person-years of follow-up						
SCD	4.49	1.87	3.10	1.81	5.44	0.73
Death	11.67	7.17	8.28	8.52	13.06	8.71

Table 3

Relationship between time from MI to randomization and outcomes

	Death	SCD	Appropriate shock (ICD arm only)
N	712	712	330
Events	274	68	69

Coding for time between MI and randomization		HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P
Continuous		1.00 (0.98, 1.03) per year increase	.97	1.00 (0.95, 1.05) per year increase	.88	1.04 (1.00, 1.08) per year increase	.040
Tertiles:							
Shortest vs. longest		0.95 (0.66, 1.34)	.78	0.89 (0.45, 1.69)	.73	0.63 (0.35, 1.15)	.13
Shortest vs. middle		0.99 (0.69, 1.41)	.95	1.00 (0.51, 1.92)	.99	0.98 (0.51, 1.89)	.95
Dichotomous, >18 vs. 18 months		1.08 (0.77, 1.51)	.66	1.31 (0.74, 2.31)	.36	0.99 (0.54, 1.80)	.96

Note: HR: hazard ratio. Cox regression models included the following covariates that are shown to predict mortality in the full SCD-HcFT cohort: randomized therapy, age, gender, NYHA class, time since heart failure diagnosis, LVEF, 6-minute walk distance, systolic blood pressure, diabetes, ACE inhibitor use, digoxin use, presence of mitral regurgitation, renal insufficiency, substance abuse, baseline electrocardiography [PR, QTc, interventricular conduction delay], and the Duke Activity Status Index.

Table 4

Treatment effect according to time elapsed after MI to implantation/randomization

Time from MI	HR ^a	95% Confidence interval for the HR	P-Value for MI time × ICD interaction
All-cause mortality			
Shortest tertile, >2.11 years	0.70	0.42–1.17	.34
Middle tertile, 2.11–7.31 years	0.94	0.56–1.59	
Longest tertile, <7.31 years	0.69	0.43–1.11	
SCD			
Shortest tertile, >2.11 years	0.44	0.16–1.17	.16
Middle tertile, 2.11–7.31 years	0.50	0.18–1.37	
Longest tertile, <7.31 years	0.12	0.03–1.45	

^a Adjusted HR reported for ICD vs. placebo.

Table 5

Quartile sensitivity analysis of treatment effect according to time elapsed after MI to randomization/implantation^{*^}

	Time from MI (n=178 in each quartile)	ICD:placebo HR	95% CI	P for interaction
All-cause mortality	1 st quartile < 18 months	0.70	0.37, 1.31	0.33
	2 nd quartile 18 – 52 months	0.54	0.30, 0.98	
	3 rd quartile 52 – 111 months	1.47	0.75, 2.87	
	4 th quartile > 111 months	0.75	0.44, 1.29	
Sudden cardiac death	1 st quartile < 18 months	0.47	0.16, 1.42	0.68
	2 nd quartile 18–52 months	0.28	0.073, 1.10	
	3 rd quartile 52 – 111 months	0.24	0.063, 0.89	
	4 th quartile > 111 months	0.25	0.065, 0.97	

* Adjusted HR reported for ICD vs. placebo.

[^] The quartiles of time from MI as reported in the MADIT II analysis were: < 18 mo, 18–59 mo, 60–119 mo, ≥120 mo.(10)