

## ORIGINAL ARTICLE

# Prognostic Importance of Defibrillator Shocks in Patients with Heart Failure

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## ABSTRACT

**BACKGROUND**

Patients with heart failure who receive an implantable cardioverter–defibrillator (ICD) for primary prevention (i.e., prevention of a first life-threatening arrhythmic event) may later receive therapeutic shocks from the ICD. Information about long-term prognosis after ICD therapy in such patients is limited.

**METHODS**

Of 829 patients with heart failure who were randomly assigned to ICD therapy, we implanted the ICD in 811. ICD shocks that followed the onset of ventricular tachycardia or ventricular fibrillation were considered to be appropriate. All other ICD shocks were considered to be inappropriate.

**RESULTS**

Over a median follow-up period of 45.5 months, 269 patients (33.2%) received at least one ICD shock, with 128 patients receiving only appropriate shocks, 87 receiving only inappropriate shocks, and 54 receiving both types of shock. In a Cox proportional-hazards model adjusted for baseline prognostic factors, an appropriate ICD shock, as compared with no appropriate shock, was associated with a significant increase in the subsequent risk of death from all causes (hazard ratio, 5.68; 95% confidence interval [CI], 3.97 to 8.12;  $P < 0.001$ ). An inappropriate ICD shock, as compared with no inappropriate shock, was also associated with a significant increase in the risk of death (hazard ratio, 1.98; 95% CI, 1.29 to 3.05;  $P = 0.002$ ). For patients who survived longer than 24 hours after an appropriate ICD shock, the risk of death remained elevated (hazard ratio, 2.99; 95% CI, 2.04 to 4.37;  $P < 0.001$ ). The most common cause of death among patients who received any ICD shock was progressive heart failure.

**CONCLUSIONS**

Among patients with heart failure in whom an ICD is implanted for primary prevention, those who receive shocks for any arrhythmia have a substantially higher risk of death than similar patients who do not receive such shocks.

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**T**HE SUDDEN CARDIAC DEATH IN HEART Failure Trial (SCD-HeFT) (ClinicalTrials.gov number, NCT00000609) and the Multicenter Automatic Defibrillator Implantation Trial II (MADIT II) both showed that therapy with implantable cardioverter–defibrillators (ICDs) improves survival among patients who are at risk for sudden cardiac death but who have not previously had a sustained ventricular arrhythmia.<sup>1–3</sup> On the basis of these data, recent clinical guidelines consider the implantation of an ICD for “primary prevention” (i.e., prevention of a first life-threatening arrhythmic event) to be standard high-quality care for patients who meet the entry criteria for these trials.<sup>4</sup>

One result of this broader use of ICDs is that the natural history of the disease in these patients is modified as a consequence of the delivery of ICD therapies. Patients in whom an ICD is implanted for primary prevention and who subsequently receive an appropriate defibrillator shock may have a different prognosis from similar patients who do not receive a shock. Although data from MADIT II previously showed that patients who received appropriate ICD therapy had a risk of death that was increased by a factor of 3,<sup>5</sup> there is little evidence from current practice that the importance of these events is recognized by physicians who care for these patients. We therefore assessed the long-term prognostic significance of both appropriate and inappropriate ICD shocks in SCD-HeFT.

## METHODS

### STUDY OVERVIEW AND POPULATION

The study design, methods, and primary results of SCD-HeFT have been reported previously.<sup>1,2</sup> SCD-HeFT was a multicenter clinical trial in which 2521 patients with New York Heart Association (NYHA) class II or III heart failure and a left ventricular ejection fraction of 35% or less, but no previous sustained ventricular arrhythmia, were randomly assigned in equal proportions to receive an ICD, amiodarone therapy, or placebo. The cause of the heart failure was ischemic in 52.0% of the patients and nonischemic in 48.0%. The use of evidence-based medical therapies was at high levels both at baseline and at the final follow-up assessment.<sup>2</sup> After a median follow-up of 45.5 months, ICD therapy, as compared with medical therapy alone, was associated with a 23.0% decrease in the risk of death.

The protocol was approved by the institutional review board at each participating organization, and each patient provided written informed consent before enrollment. Sponsorship and oversight of the trial were provided by the National Heart, Lung, and Blood Institute. Study drugs and ICDs were provided free of charge by the manufacturers (Wyeth–Ayerst Laboratories [now Wyeth Pharmaceuticals] and Medtronic, respectively).

The authors designed this study, collected and analyzed the data, and made the decision to submit the results for publication. Dr. Poole wrote the manuscript, which was reviewed by all the authors. The corporate sponsors of the trial had no role in the design, analysis, or interpretation of the study. ICD-shock data and clinical data were maintained in confidential, secure databases (the ICD Core Laboratory at the Seattle Institute for Cardiac Research and the Duke Clinical Research Institute, respectively).

### ICD THERAPY

Each patient in the ICD-therapy group was assigned to receive a single-lead ICD (Medtronic Micro Jewel II model 7223Cx). This device was implanted in 804 of 811 patients (99.1%); 4 patients received other Medtronic single-lead models, and 3 patients received Medtronic dual-lead models, owing to deviations from the protocol. The protocol for the programming of the ICD was deliberately conservative, specifying that the ICD should intervene only for rapid, life-threatening ventricular tachycardia or ventricular fibrillation. A single zone of therapy was used, and an episode of tachycardia was defined as at least 18 of 24 beats at a rate of 188 beats per minute or more ( $\leq 320$  msec). Up to six shocks could be delivered per episode. Neither antitachycardia pacing nor a second zone of therapy was allowed, since patients with known sustained ventricular tachycardia were excluded from the study. Anti-bradycardia pacing was programmed at 50 beats per minute but would not be triggered to pace unless the heart rate dropped below 34 beats per minute (a process defined as hysteresis).

### FOLLOW-UP

Downloading of the information from the ICD was performed at the time of implantation, every 3 months thereafter, and after ICD shocks were delivered. Reports of the downloaded information were electronically sent or saved to a disk

and mailed to the ICD Core Laboratory. Permission to obtain data on the ICD after the death of a patient was requested from the patient's next of kin. The cause of death for all patients was determined according to preset criteria by the events committee, whose members were unaware of the therapy group to which the patient had been assigned.

#### ELECTROGRAM CLASSIFICATION

All electrograms showing events that triggered ICD shocks were assigned to two independent members of the Electrogram Review Committee (see the Appendix), who classified the events according to predetermined diagnostic criteria for cardiac rhythms. To discriminate ventricular from supraventricular rhythms, onset characteristics, electrograms recorded before detection of the arrhythmia and after delivery of the shock, and plots of RR intervals were analyzed. Shocks were considered to be appropriate if the triggering rhythm was determined to be ventricular fibrillation or ventricular tachycardia. Inappropriate triggers of ICD shocks included supraventricular tachycardias, oversensing of P or T waves as R waves, double counting of R waves, and an artifact from lead fractures or electromagnetic interference. The delivery of a shock after the spontaneous termination of nonsustained ventricular tachycardia was also considered to be inappropriate. The term "ICD shock" in this analysis refers to ICD therapy that was triggered for a single rhythm event, regardless of the total number of actual shocks that were required to satisfy the criteria for termination of tachycardia by the ICD.

#### STATISTICAL ANALYSIS

Standard descriptive statistics were used, including percentages for discrete variables and medians and quartiles for continuous variables. The relationship of ICD-shock therapy to death from any cause was examined with the use of Cox proportional-hazards models,<sup>6</sup> with adjustment for baseline prognostic factors measured in the trial. These included age, sex, cause of heart failure, NYHA class, time since the diagnosis of heart failure, left ventricular ejection fraction, distance covered on a 6-minute walk, systolic blood pressure, presence or absence of diabetes, use or nonuse of angiotensin-converting-enzyme inhibitors, use or nonuse of digoxin, presence or absence of mitral regurgitation, renal sufficiency or insuf-

ficiency, presence or absence of a history of substance abuse, baseline electrocardiographic intervals, and score on the Duke Activity Status Index.<sup>7</sup> Risk relationships were characterized as hazard ratios and 95% confidence intervals, generated with the use of the Cox model.

Appropriate and inappropriate shocks were treated as two separate time-dependent covariates, allowing the risk to change after the occurrence of a shock. Thus, a patient's follow-up was credited to the no-shock group until a shock occurred, at which time the patient became part of the risk group for that shock type (i.e., appropriate or inappropriate). "Both shock types" refers to the receipt of both an appropriate and an inappropriate shock during follow-up.

The Cox model was also used to assess whether there was an interaction between appropriate and inappropriate shocks — that is, whether the prognostic effect of an appropriate shock differed if patients also received an inappropriate shock (and vice versa). Interaction terms were also used to determine whether the association of each shock type with the risk of death differed according to the cause of heart failure or NYHA class. Data for patients who had their ICD removed during follow-up were censored at the time the device was removed.

Analyses were also performed to assess the prognostic effect of multiple episodes of the same type of shock (appropriate or inappropriate) in contrast to multiple episodes consisting of both appropriate and inappropriate shocks. For this assessment, additional time-dependent covariates reflecting the occurrence of two (or more) appropriate shocks and two (or more) inappropriate shocks were also considered in the Cox model.

In addition, separate analyses were performed that included only shocks that patients survived for more than 24 hours. In this analysis, shocks that occurred 24 hours or less before death were not considered — that is, at the time of death, a patient was classified as a member of the risk group that he or she had been in before the shock.

Kaplan–Meier survival rates 1 year after a shock were calculated to compare survival after shock therapy according to the type of ICD shock received and in selected clinical subgroups. Reported P values are two-sided and have not been adjusted for multiple testing.

Table 1. Selected Baseline Clinical Characteristics of the Study Groups.\*

Characteristic	Patients Who Received Any Appropriate Shock (N = 182)	Patients Who Received Appropriate Shocks Only (N = 128)	Patients Who Received No Appropriate Shock (N = 629)	Patients Who Received Inappropriate Shocks (N = 141)	Patients Who Received Inappropriate Shocks Only (N = 87)	Patients Who Received No Inappropriate Shock (N = 670)	Patients Who Received Any Shock (N = 269)	Patients Who Received Both Types of Shock (N = 54)	Patients Who Received No Shock (N = 542)
Age — yr									
Median	63	64	60	57	54	61	59	61	61
Interquartile range	53–69	53–69	52–69	48–67	47–62	53–69	51–68	52–69	52–70
Female sex — no. (%)	38 (20.9)	30 (23.4)	147 (23.4)	29 (20.6)	21 (24.1)	156 (23.3)	59 (21.9)	8 (14.8)	126 (23.2)
NYHA class III — no. (%)	65 (35.7)	45 (35.2)	192 (30.5)	43 (30.5)	23 (26.4)	214 (31.9)	88 (32.7)	20 (37.0)	169 (31.2)
Ischemic cause of heart failure — no. (%)	93 (51.1)	66 (51.6)	327 (52.0)	52 (36.9)	25 (28.7)	368 (54.9)	118 (43.9)	27 (50.0)	302 (55.7)
Ejection fraction									
Median	20	20	25	25	25	24	20	20	25
Interquartile range	18–26	17–26	20–30	20–28	20–30	19–30	18–28	20–26	20–30
Atrial fibrillation or flutter — no. (%)	37 (20.3)	20 (15.6)	102 (16.2)	37 (26.2)	20 (23.0)	102 (15.2)	57 (21.2)	17 (31.5)	82 (15.1)
Nonsustained ventricular tachycardia — no. (%)	61 (33.5)	48 (37.5)	149 (23.7)	39 (27.7)	26 (29.9)	173 (25.8)	87 (32.3)	13 (24.1)	123 (22.7)

\* A total of 811 patients received an implantable cardioverter–defibrillator (ICD); 554 (68.3%) had New York Heart Association (NYHA) class II heart failure, and 257 (31.7%) had NYHA class III heart failure. Of the 811 patients who received an ICD, 420 (51.8%) had an ischemic cause of heart failure, and 391 (48.2%) had a nonischemic cause.

RESULTS

ICD IMPLANTATION AND PROGRAMMING

Of the 829 patients who were randomly assigned to ICD therapy, 811 patients had an ICD implanted, 17 declined to undergo implantation, and 1 died before implantation. In 31 of the patients in whom an ICD was implanted (3.8%), the ICD was subsequently removed and not replaced, owing to complications with the device (8 patients), other medical problems (3), or heart transplantation (20). Deviations from the protocol occurred in patients who received a dual-lead ICD at initial implantation (3 patients) or who received a dual-lead ICD (15) or biventricular ICD (7) as a replacement for the original ICD. Deviations from the protocol with respect to ICD programming included a second zone of therapy in 64 patients (as well as antitachycardia pacing in 58 of those patients). The pacing rate was increased in 66 patients. Patients whose only detected events over the course of the study were the result of ICD therapy delivered in deviation from the protocol (arrhythmia events detected at <188 beats per minute and antitachycardia pacing) were not included in this analysis.

ICD-SHOCK THERAPY

During the follow-up period (median, 45.5 months), 269 of the 811 patients with devices (33.2%) received at least one episode of ICD-shock therapy, whereas 542 patients (66.8%) received no known ICD-shock therapy. Either ventricular tachycardia or ventricular fibrillation was the only rhythm trigger for shocks in 128 of the 269 patients who received shocks (47.6%), and inappropriate triggers were the only cause of shocks in 87 (32.3%); 54 (20.1%) received both appropriate and inappropriate shocks. In total, 182 of the 811 patients with ICDs (22.4%) received shocks for ventricular tachycardia or ventricular fibrillation, with ventricular tachycardia or ventricular fibrillation recurring in 97 of those patients (53.3%). A total of 141 patients (17.4%) received inappropriate shocks, with recurrent inappropriate shocks delivered in 61 of those patients (43.3%).

SELECTED CLINICAL CHARACTERISTICS AT STUDY ENTRY

Baseline characteristics of each shock group are shown in Table 1. Patients who received appropriate shocks had a lower ejection fraction, were

in a higher NYHA class, and were more likely to have atrial fibrillation than those who did not receive appropriate shocks (Table 1). Patients who received inappropriate shocks were more likely to have atrial fibrillation and were less likely to have ischemic heart failure than those who did not receive inappropriate shocks (Table 1).

**DEATHS**

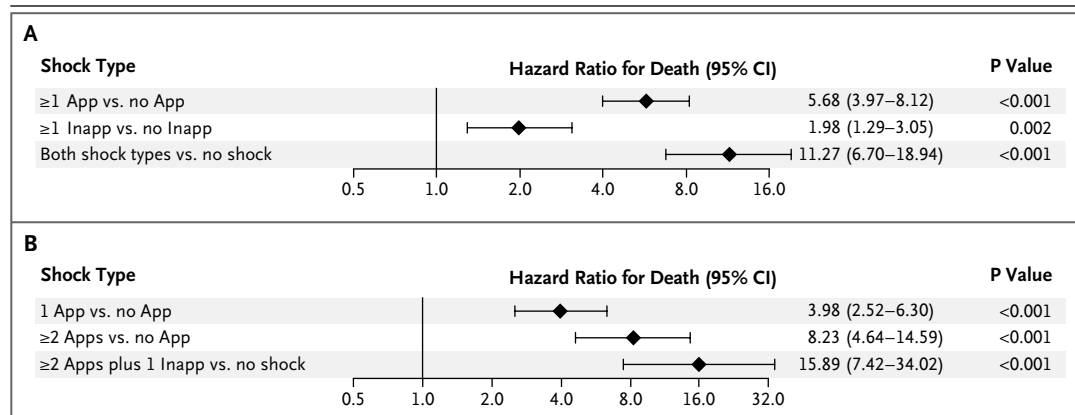
A total of 182 patients died among the 829 patients who were randomly assigned to the ICD group. Of the 18 patients in the ICD group who did not receive an ICD, 9 died, and of the 811 patients in whom an ICD was implanted, 173 died. Ten of these deaths occurred among the 31 patients whose ICDs were removed during the study. Among the 182 patients who received one or more appropriate shocks, there were 67 deaths (36.8%) (54 of the 182 patients also received one or more inappropriate shocks). Ten additional deaths occurred among the 87 patients who received only one or more inappropriate shocks (11.5%). Finally, 86 deaths occurred among the 542 patients who were not recorded as having received an ICD shock (15.9%). Postmortem data on the ICD were available for only 64 of the 173 patients with ICDs who died (37.0%). According to postmortem review, 20 patients died within 24 hours after their first ICD shock for ventricular tachycardia

or ventricular fibrillation; 19 of them had ischemic heart failure.

**RISK OF DEATH ASSOCIATED WITH ICD SHOCKS**

In a multivariable Cox model, both appropriate and inappropriate ICD shocks were significant predictors of death (Fig. 1A). An appropriate shock, as compared with no appropriate shock, was associated with a risk that was increased by a factor of more than 5 (hazard ratio, 5.68; 95% confidence interval [CI], 3.97 to 8.12;  $P < 0.001$ ), and an inappropriate shock, as compared with no inappropriate shock, was associated with a near doubling of the risk of death (hazard ratio, 1.98; 95% CI, 1.29 to 3.05;  $P = 0.002$ ). The relative risk of death associated with an appropriate shock in patients who had not received a previous inappropriate shock did not differ significantly from that in patients who had received a previous inappropriate shock ( $P = 0.59$  for the interaction). We therefore estimated that in patients who received both shock types, the risk of death was increased by a factor of 11, as compared with the risk in patients who received no shocks (hazard ratio, 11.27; 95% CI, 6.70 to 18.94;  $P < 0.001$ ).

Analyses performed to refine these results and account for multiple shocks of the same type (Fig. 1B) showed that one appropriate shock was associated with a risk of death that was increased



**Figure 1. Hazard Ratios for the Association of ICD Shock with the Risk of Death, According to Shock Type.**

Panel A shows the hazard ratios for the association of shock types with the risk of death, adjusted for baseline prognostic factors identified in the trial (age, sex, cause of heart failure, New York Heart Association class, time since the diagnosis of heart failure, left ventricular ejection fraction, distance covered on a 6-minute walk, systolic blood pressure, presence or absence of diabetes, use or nonuse of angiotensin-converting-enzyme inhibitors, use or nonuse of digoxin, presence or absence of mitral regurgitation, renal sufficiency or insufficiency, presence or absence of a history of substance abuse, baseline electrocardiographic intervals, and score on the Duke Activity Status Index<sup>7</sup>). Panel B shows the adjusted hazard ratios for the risk of death according to the number of appropriate or inappropriate shocks. App denotes appropriate defibrillator shock, CI confidence interval, and Inapp inappropriate defibrillator shock.

by a factor of approximately 4 (hazard ratio, 3.98; 95% CI, 2.52 to 6.30;  $P < 0.001$ ), whereas a second appropriate shock was associated with a further significant increase by a factor of 2 ( $P = 0.005$ ), resulting in an overall risk of death that was increased by a factor of 8 for patients with two or more appropriate shocks as compared with patients who did not receive any shock (hazard ratio, 8.23; 95% CI, 4.64 to 14.59;  $P < 0.001$ ). After adjustment for the occurrence of multiple appropriate shocks, an inappropriate shock continued to have important prognostic significance and was associated with a risk that was increased by a factor of approximately 2 ( $P = 0.01$ ). The net result is that for patients with two or more appropriate shocks plus an inappropriate shock, the risk of death was increased by a factor of more than 15 (hazard ratio, 15.89; 95% CI, 7.42 to 34.02;  $P < 0.001$ ). Additional inappropriate shocks were not associated with a further increase in risk ( $P = 0.69$ ).

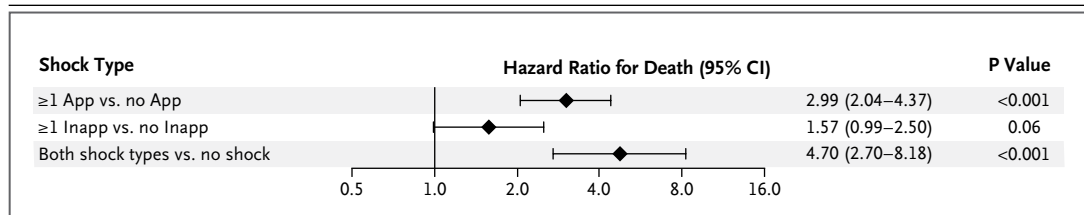
Significant interactions between the receipt of a shock and the cause of heart failure were noted ( $P < 0.001$  for the interaction with appropriate shocks, and  $P = 0.05$  for the interaction with inappropriate shocks). The hazard ratios for an appropriate shock among patients with ischemic heart failure and among those with nonischemic heart failure were 8.72 (95% CI, 5.68 to 13.39) and 2.61 (95% CI, 1.42 to 4.78), respectively, and the hazard ratios for inappropriate shocks were 2.97 (95% CI, 1.73 to 5.10) and 1.22 (95% CI, 0.59 to 2.51), respectively. No significant interactions between the receipt of a shock and the NYHA class were

observed ( $P = 0.62$  for the interaction with appropriate shocks, and  $P = 0.46$  for the interaction with inappropriate shocks).

ICD shocks remained an important predictor of the outcome among patients who survived for at least 24 hours after a first ICD shock of either type (Fig. 2). An appropriate shock was associated with a risk of death that was increased by a factor of 3 (hazard ratio, 2.99; 95% CI, 2.04 to 4.37;  $P < 0.001$ ). An inappropriate shock was associated with a trend toward an increased risk (hazard ratio, 1.57; 95% CI, 0.99 to 2.50;  $P = 0.06$ ). As was the case when all shocks were considered, there was no significant interaction between appropriate and inappropriate shock types when shocks that occurred 24 hours or less before death were not considered ( $P = 0.60$ ). We therefore estimated that patients who received both types of shocks and survived longer than 24 hours had a risk of death that was increased by a factor of nearly 5, as compared with patients who received no ICD shocks (hazard ratio, 4.70; 95% CI, 2.70 to 8.18;  $P < 0.001$ ). No significant interaction was found between the receipt of a shock and the cause of heart failure ( $P = 0.18$  for an appropriate shock, and  $P = 0.24$  for an inappropriate shock) or NYHA class ( $P = 0.11$  and  $P = 0.12$ , respectively).

#### SURVIVAL AFTER ICD SHOCKS

One-year Kaplan–Meier survival rates ( $\pm$ SE) after the first ICD shock were compared among patients with a first shock of any type ( $82.5 \pm 2.4\%$ ), all patients with one or more appropriate shocks



**Figure 2. Hazard Ratios for the Risk of Death among Patients Who Survived at Least 24 Hours after a First ICD Shock.**

The association of shock types with the risk of death among patients who survived at least 24 hours after a first ICD shock of either type is shown, adjusted for baseline prognostic factors identified in the trial (age, sex, cause of heart failure, New York Heart Association class, time since the diagnosis of heart failure, left ventricular ejection fraction, distance covered on a 6-minute walk, systolic blood pressure, presence or absence of diabetes, use or nonuse of angiotensin-converting-enzyme inhibitors, use or nonuse of digoxin, presence or absence of mitral regurgitation, renal sufficiency or insufficiency, presence or absence of a history of substance abuse, baseline electrocardiographic intervals, and score on the Duke Activity Status Index<sup>7</sup>). App denotes appropriate defibrillator shock, CI confidence interval, and Inapp inappropriate defibrillator shock.

(76.9±3.2%), and those with only one or more inappropriate shocks (94.9±2.5%) (Table 2). Median times from shock to death for patients who received any shock were 204 days (interquartile range, 1 to 630); for patients with one or more appropriate shocks, 168 days (interquartile range, 1 to 797); and for patients with only one or more inappropriate shocks, 294 days (interquartile range, 28 to 509) (Table 2). One-year survival was lower and the time from shock to death shorter for patients with appropriate shocks who were in NYHA class III than for those who were in class II, for those in whom the cause of heart failure was ischemic than for those in whom the cause was nonischemic (Table 2), and for those whose first shock was for ventricular fibrillation than for those whose first shock was for ventricular tachycardia.

**CAUSE OF DEATH IN PATIENTS WITH ICD SHOCKS**

The most common cause of death among patients who had any ICD shock was progressive heart failure (accounting for 33 of 77 deaths [42.9%]) (Table 3). However, sudden death from arrhythmia did occur among patients who received ICD shocks for ventricular tachycardia or ventricular fibrillation (14 of 67 deaths [20.9%]).

**DISCUSSION**

This study showed that in patients with heart failure who received an ICD for primary prevention, the occurrence of an appropriate ICD shock was associated with a markedly increased risk of death. This relationship was independent of other covariates that are predictive of the outcome and was

**Table 2. Time from ICD Shock to Death among Patients Who Received at Least One Shock.\***

Type of Shock	All Patients	Patients Who Died	Time from Shock to Death			Kaplan–Meier Survival Rate 1 Year after Shock %
			Median	Interquartile Range	Full Range	
			days			
Any shock	269	77	204	1–630	0–1872	82.5±2.4
One or more inappropriate shocks only	87	10	294	28–509	0–735	94.9±2.5
One or more appropriate shocks	182	67	168	1–797	0–1872	76.9±3.2
NYHA class II	117	31	206	1–977	0–1872	84.0±3.5
NYHA class III	65	36	168	7–626	0–1343	64.2±6.1
Ischemic heart failure	93	49	96	0–443	0–1872	62.6±5.2
Nonischemic heart failure	89	18	622	204–908	1–1785	91.6±3.0
First shock for ventricular fibrillation	77	33	3	0–622	0–1872	74.6±5.0
First shock for ventricular tachycardia	105	34	258	59–797	0–1785	78.5±4.2

\* Plus–minus values are survival rates ±SE. ICD denotes implantable cardioverter–defibrillator, and NYHA New York Heart Association.

**Table 3. Cause of Death According to Type of Shock.**

Type of Shock	All Patients	Patients Who Died*	Cause of Death				
			Sudden Arrhythmia	Heart Failure	Other Cardiac Causes	Noncardiac Causes	Unknown
			number of patients				
Any shock	269	77	16	33	9	17	2
Any appropriate shock	182	67	14	29	8	14	2
Inappropriate shock only	87	10	2	4	1	3	0
No shock	542	86	13	34	6	29	4

\* Ten additional patients whose ICDs were removed during the study died.

seen both in patients with ischemic heart disease and in those with nonischemic heart disease. Although the response by physicians to ICD shocks is commonly a sense of relief that sudden death was averted, our findings highlight the need for a more thoughtful consideration of this patient group, directed in particular at a reassessment of the therapeutic options that might modify the prognosis.

Our study also identified an increased risk for patients who received inappropriately triggered ICD shocks. The cause of this association is uncertain, but several possibilities may be considered. First, patients with heart failure in whom atrial fibrillation develops have been shown to be at an increased risk for death.<sup>8-10</sup> Second, in certain vulnerable patients, it may be postulated that the negative inotropic consequences of the shock itself could increase the risk of death, especially when the patient receives multiple shocks owing to oversensing or ongoing supraventricular tachycardia.<sup>11-16</sup>

The hazard ratios for the risk of death were lower when only patients who survived longer than 24 hours after a shock were considered. In some cases, the firing of the device may occur during the patient's fatal arrhythmia; such ICD shocks are not predictive in the sense of providing information about the likelihood of a subsequent event. The data from analyses that included only patients who survived longer than 24 hours after a shock may therefore represent a more accurate picture of the consequences of surviving an arrhythmia.

The MADIT II investigators were the first to describe an adverse prognosis associated with ICD therapy that is used for primary prevention.<sup>5,17,18</sup> In MADIT II, among 719 patients with ischemic heart disease, an ICD shock or antitachycardia pacing was reported to be appropriate in 23.5% and inappropriate in 13.9%. Absolute rates of ICD use in MADIT II were similar to those in our study, despite a shorter follow-up (21 months, vs. 45.5 months in our study), use of dual-chamber ICDs in 43.6% of the patients, ICD programming that included antitachycardia pacing in 59% of the patients, and inclusion of patients with NYHA class I disease.<sup>3,5</sup> Further analyses by the MADIT II investigators identified a risk of death that was increased by a factor of more than 3 among patients who received ICD shocks or antitachycardia pacing for ventricular tachycardia or ventricular fibrillation,<sup>5</sup> as well as increased risks of

heart failure and of death related to heart failure.<sup>17</sup> The risk of death with appropriate ICD shocks was higher in our study (increased by a factor of more than 5) than in their study. This difference may be due to the longer follow-up and the exclusion of patients with NYHA class I disease in our study. We also identified a risk of death with inappropriate shocks that was increased by a factor of 2, which was similar to that in MADIT II.<sup>18</sup>

It is important to emphasize that our results reflect our use of primarily single-lead ICDs, a single zone of therapy, and shock-only programming for high-rate arrhythmias that were most likely to be life-threatening. Although decreasing the rate of painful ICD shocks for ventricular tachycardia is an accepted reason to activate antitachycardia pacing, inappropriate intervention for self-terminating rhythms such as nonsustained ventricular tachycardia may occur when antitachycardia pacing is used empirically.<sup>19,20</sup> In shock-only programming, the delay of 5 to 10 seconds during the charging of the capacitors for the delivery of the shock allows some rhythms to normalize spontaneously and minimizes the likelihood of pacing-induced acceleration of rhythms that are best left alone.<sup>19,20</sup>

There are several limitations of our study. The episodes of ICD shock that were analyzed in this trial may not represent all ICD-detected events. It was not possible to guarantee that all ICD-detected events were transmitted to the ICD Core Laboratory, despite careful review of follow-up data forms to identify any missed events.

A second limitation, which was inherent in the design of the study, was our inability to record sustained rhythms with rates of less than 188 beats per minute, except in the few cases of deviation from the protocol. The goal of this design feature was to minimize false positive interventions in a population that was not known to have sustained ventricular tachycardia at the time of enrollment. In addition, the number of postmortem reports that were collected was limited, since family members often failed to provide notification of a patient's death in time to gather the data. Therefore, some patients may have had shock events associated with death that were not identified. Finally, the limited memory capacity of the device resulted in overwritten data in patients who had repetitive arrhythmic events occurring over a short period of time.

In conclusion, in patients with heart failure



who receive an ICD for primary prevention, both appropriate and inappropriate ICD shocks are associated with a marked increase in the subsequent risk of death, particularly death from progressive heart failure. Our results do not establish what further therapies, if any, might be effective in reducing this risk.

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#### APPENDIX

The Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT) ICD Electrogram Review Committee consisted of the following members: J.E. Poole (University of Washington, Seattle), M.H. Raitt (Portland Veterans Affairs Medical Center and Oregon Health Sciences University, Portland), R.K. Reddy (Oregon Cardiology Associates, Eugene), D. Callans and F.E. Marchlinski (University of Pennsylvania, Philadelphia), M. Talajic (Institut de Cardiologie de Montréal, Montreal), D.J. Wilber (Loyola University Medical Center, Maywood, IL), T. Guarnieri (Johns Hopkins University, Baltimore), R. Yee (University Hospital, London, ON, Canada).

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