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Inappropriate Implantable Cardioverter-Defibrillator Shocks in MADIT II

Frequency, Mechanisms, Predictors, and Survival Impact

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Objectives This study sought to identify the incidence and outcome related to inappropriate implantable cardioverter-defibrillator (ICD) shocks, that is, those for nonventricular arrhythmias.

Background The MADIT (Multicenter Automatic Defibrillator Implantation Trial) II showed that prophylactic ICD implantation improves survival in post-myocardial infarction patients with reduced ejection fraction. Inappropriate ICD shocks are common adverse consequences that may impair quality of life.

Methods Stored ICD electrograms from all shock episodes were adjudicated centrally. An inappropriate shock episode was defined as an episode during which 1 or more inappropriate shocks occurred; another inappropriate ICD episode occurring within 5 min was not counted. Programmed parameters for patients with and without inappropriate shocks were compared.

Results One or more inappropriate shocks occurred in 83 (11.5%) of the 719 MADIT II ICD patients. Inappropriate shock episodes constituted 184 of the 590 total shock episodes (31.2%). Smoking, prior atrial fibrillation, diastolic hypertension, and antecedent appropriate shock predicted inappropriate shock occurrence. Atrial fibrillation was the most common trigger for inappropriate shock (44%), followed by supraventricular tachycardia (36%), and then abnormal sensing (20%). The stability detection algorithm was programmed less frequently in patients receiving inappropriate shocks (17% vs. 36%, $p = 0.030$), whereas other programming parameters did not differ significantly from those without inappropriate shocks. Importantly, patients with inappropriate shocks had a greater likelihood of all-cause mortality in follow-up (hazard ratio 2.29, $p = 0.025$).

Conclusions Inappropriate ICD shocks occurred commonly in the MADIT II study, and were associated with increased risk of all-cause mortality. (J Am Coll Cardiol 2008;51:1357–65) © 2008 by the American College of Cardiology Foundation

Implantable cardioverter-defibrillator (ICD) therapy is proven to reduce mortality (1–5). However, inappropriate shocks for atrial arrhythmias with rapid ventricular conduction (6,7) or for abnormal sensing (8–10) results in multiple adverse effects (11–14) including impaired quality of life (15), psychiatric disturbances (16), and even provocation of nonfatal (17) or fatal (18) ventricular arrhythmia. Although inappropriate shocks have been studied in some ICD groups (19,20), no reports have detailed inappropriate ICD therapy in a pure primary prevention group like those in the MADIT II study.

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Methods

ICD devices and programming. The MADIT II protocol permitted implantation of U.S. Food and Drug Adminis-

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Abbreviations and Acronyms

AF = atrial fibrillation or atrial flutter
ATP = antitachycardia pacing
CHF = congestive heart failure
HR = hazard ratio
ICD = implantable cardioverter-defibrillator
SVT = supraventricular tachycardia
VF = ventricular fibrillation
VT = ventricular tachycardia

tration–approved single-chamber or dual-chamber Guidant ICDs. Each ICD stored intracardiac electrograms for arrhythmia episodes. Moreover, each unit offered 2 algorithms intended to minimize inappropriate shocks: 1) "stability," evaluating the regularity of the tachyarrhythmia; and 2) "sudden onset," the degree to which the arrhythmia began suddenly versus gradually (21). The dual-chamber devices provided additional algorithms evaluating the atrial rate (22). The ICD programming, including such discriminator usage, was left to the discretion of the investigators using standard clinical practice.

ICD therapy event analysis. The MADIT II study randomly allocated 742 patients to the ICD arm, but 1 withdrew consent and 22 never received an ICD, leaving 719 that could be evaluated for inappropriate shocks. The ICDs were interrogated quarterly and after ICD shocks. The ICD therapy was defined as either antitachycardia pacing (ATP) or ICD shock. Two investigators (J.P.D, W.Z.) categorized the rhythm prompting ATP or shock using the stored electrograms. Any ICD therapy not delivered for VT or VF was deemed inappropriate, and the rhythm triggering therapy categorized as: atrial fibrillation or atrial flutter (AF), supraventricular including sinus tachycardia (SVT), or inappropriate sensing using published criteria (9,19). A small percentage of rhythms triggering ICD therapy (2.2%) were unclassified because of missing or incomplete data. An episode's termination was defined by the ICD re-detecting sinus rhythm and thus could include more than 1 shock (and/or ATP bursts). As done previously in the AVID (Antiarrhythmics Versus Implantable Defibrillators) study, a subsequent episode beginning <5 min after episode termination was ignored for this analysis (19). Thus, an inappropriate shock episode was defined as an episode during which one or more inappropriate shocks occurred; a separate ICD episode of the same type (inappropriate or appropriate) occurring <5 min later was not counted.

Statistical analysis. Clinical characteristics were compared using the Wilcoxon rank sum test for continuous variables. The chi-square test was used for dichotomous variables, except the Fisher exact test was used when 25% or more of the cells had expected cell counts fewer than 5 (sudden and nonsudden cardiac death). The Kaplan-Meier life-table method was used to graphically display the time to first event and calculate the cumulative event rates for each group and within each group by risk factors. The results were compared using the log-rank statistic.

Using printouts or ICD discs downloaded after an inappropriate shock prompted interrogation, the major tachyarrhythmia detection settings were compared for the 83 inappropriate shock patients to 83 randomly chosen subjects without inappropriate shock. The latter group was matched with the inappropriate shock group for the presence or absence of 3 variables associated with inappropriate shock, prior atrial fibrillation, smoking, and appropriate shock. Theoretically 8 combinations of these 3 variables existed. In reality, only 7 combinations of these 3 variables contained patients who had received an inappropriate shock. Next, from the pool of patients who did not receive an inappropriate shock, we randomly chose the same number of patients from each of the 7 groups defined by having the same combination of these 3 characteristics. A stratified difference-between-proportions test, with strata weights inversely proportional to variances, was used to derive p values for the binary variables. The Mann-Whitney rank statistic, likewise stratified, was used for the numerical variables. Unstratified versions were also carried out to evaluate consistency of findings.

Using the 83 patients who did experience an inappropriate shock and the 636 patients who did not experience inappropriate shocks, Cox proportional hazards regression models were developed to determine what factors predicted time to inappropriate shock. Similarly, again using the patients with and without inappropriate shock, Cox proportional hazards regression models were developed to determine whether the occurrence of inappropriate shocks predicted time to all-cause mortality. Variables from the clinical characteristics table that met the criteria of p value <0.20 were considered as candidates for the regression model of inappropriate shock. For the inappropriate shock end point, appropriate shock was modeled as a time-dependent covariate.

Both appropriate and inappropriate shock were modeled as time-dependent covariates in the all-cause mortality model. Additional commonly used risk factors were included in this model. Follow-up time began at ICD implantation. Unclassified rhythms (n = 13, 2.2% of total shocks) were not included in this analysis.

The statistical software used for the analyses was SAS version 9.13 (SAS Institute Inc., Cary, North Carolina). A 2-sided probability value of <0.05 identified statistical significance.

Results

Incidence and type of inappropriate shocks—or ATP. One or more inappropriate ICD shocks occurred in 83 of 719 patients (11.5%). After 2 years of follow-up, patients had a 13% likelihood of having experienced one or more inappropriate shocks (Fig. 1). Table 1 shows patient experience with inappropriate and appropriate shocks. Thirty-two patients had more than 1 inappropriate shock episode (Table 1), ranging up to a maximum of 16 inappropriate shock episodes during 18 months of follow-up for 1 patient. Patients experiencing an inappropriate shock had a mean number of 2.2 ± 2.5 inappropriate shock episodes.

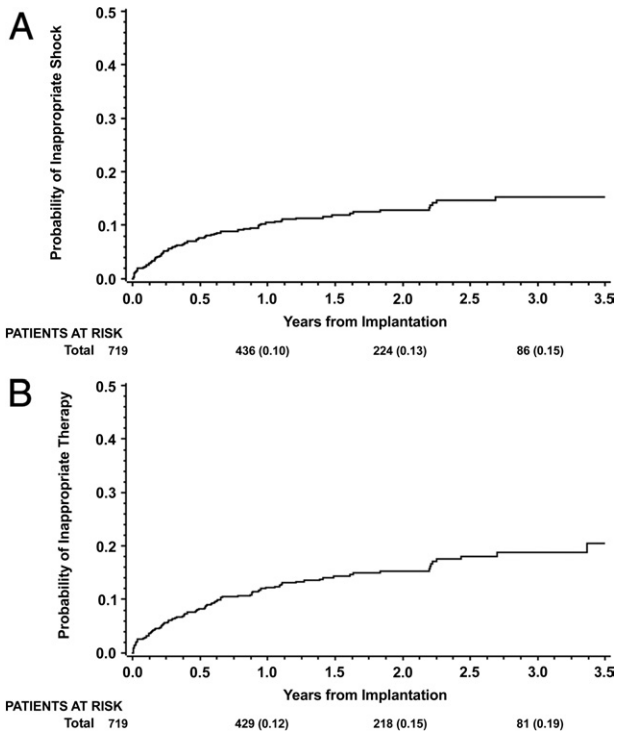

Figure 1 Survival Free of Inappropriate Shock/Therapy

(A) The cumulative proportion of patients who experienced a first inappropriate shock (due to any mechanism) is plotted versus time. **(B)** The cumulative proportion of patients who experienced a first inappropriate therapy, antitachycardia pacing (ATP) or shock (due to any mechanism) is plotted versus time. The number of patients at risk at a given time point of follow-up is indicated below the x axis. The proportion of the population experiencing the event in question is given in **parentheses** at the 1-, 2-, and 3-year time points.

Table 2 delineates the inappropriate shocks by episode rather than by patient and shows the subclassification of inappropriate shock by mechanism. As noted above, shock episodes were counted and multiple shocks within an episode were not tallied, nor were episodes caused by the same mechanism beginning within 5 min of a prior episode

Table 1 Patients Experiencing Inappropriate ICD Shocks

Shock Therapy Group	Patients (n)	Percent
One or more inappropriate shock episodes	83	11.5
1 inappropriate shock episode	51	7.1
2–4 inappropriate shock episodes	23	3.2
≥5 inappropriate shock episodes	9	1.3
Both inappropriate and appropriate shock episodes	27	3.8
Inappropriate but not appropriate shock episode(s)	56	7.8
No inappropriate shock episodes	636	88.5
Appropriate shock episode(s)	101	14.1
No appropriate shock episodes	535	74.4
Total patients	719	100.0

Shock episodes consisted of an ICD detection during which 1 or more shocks occurred; episodes caused by the same type of arrhythmia beginning within 5 min of another episode were not counted or reanalyzed.
ICD = implantable cardioverter-defibrillator.

Table 2 Rhythm Responsible for ICD Shock Episodes

Shock Type	Shock Episodes (n)	Percent
Appropriate	393	66.6
Inappropriate	184	31.2
Atrial fibrillation/flutter	81	13.7
SVT	67	11.4
Abnormal sensing	36	6.1
Unclassified	13	2.2
Total	590	100.0

This table analyzes shock episodes from the standpoint of shock rather than by patient; a given patient could receive 1 or more inappropriate shock(s) (from any or all of the subcategories) and/or one or more appropriate shock(s). Shock episodes consisted of an ICD detection during which 1 or more shock(s) occurred; episodes caused by the same type of arrhythmia beginning within 5 min of another episode were not counted or reanalyzed.
ICD = implantable cardioverter-defibrillator; SVT = supraventricular tachycardia.

(19). Table 2 thus reflects separate ICD shock episodes rather than the total number of shocks. Atrial fibrillation or atrial flutter was the most common mechanism for inappropriate shock, followed by SVT, with inappropriate sensing the least common mechanism for inappropriate shock in the MADIT II study. The time-dependent occurrence of a patient's first inappropriate shock caused by any of the 3 mechanisms is shown in Figure 2, illustrating that the time course of the occurrence of the 3 types of inappropriate shocks is similar. In the cohort of 719 patients with ICDs included in this analysis, 79 (11.0%) of patients had one type of inappropriate shock, 3 (0.4%) had 2 types of inappropriate shock mechanism, and 1 (0.1%) of the patients experienced ICD shock for all 3 types of inappropriate therapy mechanism.

We analyzed the heart rate at the time of a patient's first inappropriate shock for either AF or SVT. Inappropriate sensing episodes were excluded from this analysis only,

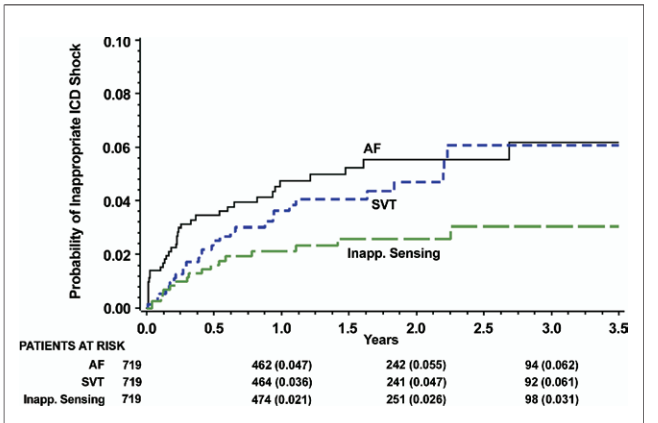

Figure 2 Time-Dependent Occurrence of Inappropriate Shock by Type

The cumulative proportion of patients experiencing a first inappropriate (Inapp.) shock due to the 3 subcategories of inappropriate shock is plotted with respect to time. The number of patients at risk at a given time point of follow-up is indicated below the x axis. The proportion of the population experiencing the event in question is given in **parentheses** at the 1-, 2-, and 3-year time points. AF = atrial fibrillation or atrial flutter; ICD = implantable cardioverter-defibrillator; SVT = supraventricular tachycardia.

because the true ventricular rate was actually normal for these, and not what the device reported. The mean ventricular rate triggering inappropriate shock for AF or SVT was 174 ± 22 beats/min (Fig. 3). The number of patients experiencing inappropriate shock at a given rate is shown on the y axis. For instance, 3 patients had a (first) inappropriate shock for atrial fibrillation with a heart rate of 200 beats/min, and 1 patient had a heart rate of 200 beats/min because of SVT prompting inappropriate shock. At the time of inappropriate shock, the ventricular rate exceeded 160 beats/min in 78% of episodes.

Considering any inappropriate therapy, that is inappropriate shock or ATP, this occurred in 100 of 719 (13.9%) patients (Fig. 1B), of whom 17 patients experienced inappropriate ATP therapy without having at least 1 inappropriate shock during follow-up.

Clinical characteristics of patients receiving inappropriate ICD shocks. Inappropriate shock recipients differed statistically from nonrecipients (Table 3) for 3 baseline clinical characteristics: 1) prior atrial fibrillation (18.1% vs. 7.4%, $p = 0.001$), 2) smoking history (89.2% vs. 78.4%, $p = 0.022$), and 3) diastolic blood pressure ≥80 mm Hg (37.3% vs. 26.3%, $p = 0.033$). Considering interim events, appropriate therapy occurred more commonly in the inappropriate shock group than in those without inappropriate shocks (42.2% vs. 21.1%, $p < 0.001$). Notably, the proportion of patients receiving a dual-chamber ICD in the inappropriate shock group versus those without inappropriate shock was not appreciably different (Table 3), suggesting that dual-chamber ICD systems were not less prone to inappropriate shocks in MADIT II.

Cox proportional hazards analysis found the baseline characteristics of prior atrial fibrillation (hazard ratio [HR] 2.90, $p < 0.01$), smoking history (HR 2.18, $p = 0.03$), and diastolic blood pressure ≥80 (HR 1.61, $p = 0.04$) independently predicted the occurrence of inappropriate shock (Table 4). Considering time-dependent factors, prior interim appropriate shock predicted the occurrence of an inappropriate shock (HR 2.25, $p = 0.03$), as did interim atrial fibrillation (HR 3.45, 95% confidence interval 1.55 to 7.69, $p < 0.01$).

Programmed parameters in patients with inappropriate shocks. The SVT–VT discriminator stability function had been activated less frequently in inappropriate shock recipients (17%) than in those not receiving inappropriate shocks (36%, $p = 0.030$). Among dual-chamber devices, a trend toward the V>A criterion being used less frequently was seen in patients with inappropriate shocks (31% vs. 50%, $p = 0.054$). We did not observe other significant differences in these parameters, such as the lowest zone detection rate (Table 5).

Impact of inappropriate shocks on outcomes. Inappropriate shock recipients tended to have a higher percent total mortality than those patients not experiencing inappropriate shocks (16.9% vs. 12.9%, $p = 0.317$, Table 3). Because appropriate shock occurrence was one predictor of inappropriate shocks (Table 4), Cox proportional hazards regression analysis was used to evaluate the

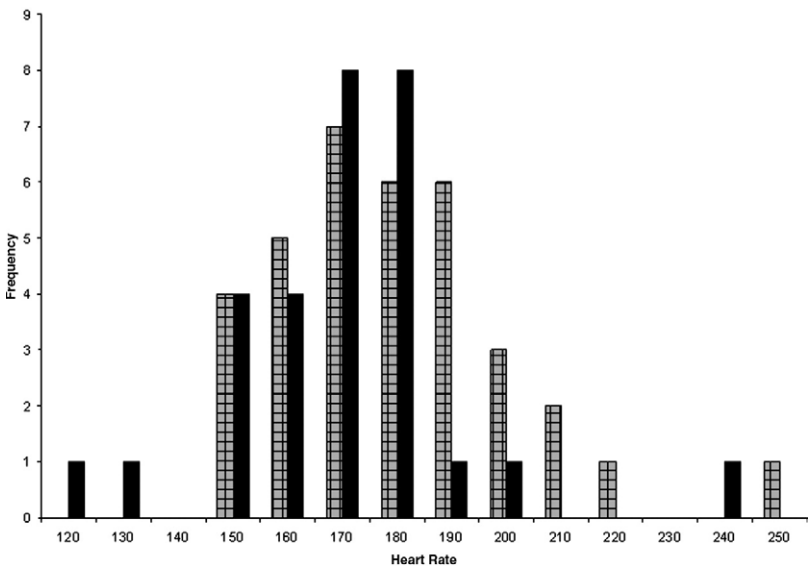

Figure 3 Ventricular Rate Precipitating Inappropriate Shock

The heart rate at the time of the ICD detection resulting in a patient's first inappropriate shock is shown in the bar graph in groups of 10 beats/min. Atrial fibrillation episodes are shown with **cross-hatched bars**, and SVT episodes are shown with **solid bars**. Inappropriate shocks caused by abnormal sensing are excluded because the device has by definition misconstrued the actual ventricular rate (typically normal in these cases). The events relate to shocks, not patients, in this figure. Abbreviations as in figure 2.

Table 3 Clinical Characteristics of Patients With Versus Without Inappropriate ICD Shock

Clinical Characteristic	No Inappropriate Shock n = 636 (%)	Inappropriate Shock n = 83 (%)	p Value
Characteristics at baseline			
Age at randomization ≥65 yrs	52.5	59.0	0.263
Female gender	16.0	12.0	0.346
History of smoking	78.4	89.2	0.022
Canadian Class Angina Grade II to IV	28.6	27.7	0.864
NYHA functional CHF class II to IV	66.0	64.6	0.802
Prior coronary bypass surgery	59.4	49.4	0.081
History of diabetes	34.4	28.9	0.318
Atrial fibrillation	7.4	18.1	0.001
Heart rate ≥80 beats/min	28.9	36.1	0.175
Systolic blood pressure ≥130 mm Hg	35.8	31.3	0.417
Diastolic blood pressure ≥80 mm Hg	26.3	37.3	0.033
QRS >0.12 s	39.6	33.7	0.301
Left bundle branch block (yes/no)	19.7	14.1	0.235
Right bundle branch block (yes/no)	9.0	9.0	0.991
Blood urea nitrogen >25	29.7	20.7	0.091
Ejection fraction <0.25	47.3	49.4	0.722
Medications at baseline			
Beta-blocker therapy	64.9	57.8	0.204
ACE inhibitor therapy	76.7	84.3	0.118
Angiotensin receptor blocker therapy	13.8	7.2	0.093
Statin therapy	64.0	63.9	0.980
Characteristics/events after enrollment			
Dual-chamber ICD implanted*	44.4	38.6	0.313
Appropriate ICD therapy	21.1	42.2	<0.001
CHF requiring hospitalization	23.0	26.8	0.436
CHF requiring hospitalization or death	28.9	35.4	0.230
Angina or MI requiring hospitalization	13.1	18.1	0.210
Death during follow-up	12.9	16.9	0.317
Cardiac death (total)†	10.9	8.4	0.495
Cardiac death, sudden†	3.3	4.9	0.518
Cardiac death, nonsudden†	6.5	2.4	0.215

*A dual-chamber or single-chamber device was implanted at the investigator's discretion. †A blinded committee adjudicated deaths using a modified Hinkle-Thaler classification.

ACE = angiotensin-converting enzyme; CHF = congestive heart failure; ICD = implantable cardioverter-defibrillator; MI = myocardial infarction; NYHA = New York Heart Association.

independent survival impact of inappropriate ICD shocks (Table 6). In multivariate analysis, mortality was predicted by blood urea nitrogen >25 (HR 2.07, $p < 0.01$), absence of beta-blocker therapy (HR 1.64, $p = 0.02$), and interim congestive heart failure (CHF) hospitalization (HR 4.23, $p < 0.01$) Because inappropriate and appropriate shocks were intertwined in their occurrence, we examined them independently and together (Table 6). The occurrence of both inappropriate and appropriate shock was associated with an over 4-fold increase in probability of mortality for a given follow-up period (HR 4.08, $p < 0.01$). The occurrence of an inappropriate shock was associated with an HR for mortality of 2.29 ($p = 0.02$). Prior appropriate shock alone portended an HR of 3.36 for mortality ($p < 0.01$). On the other hand, neither appropriate nor inappropriate ATP was associated with a significant mortality increase (Table 6). Inappropriate shocks were not a predictor of subsequent CHF hospitalization (data not shown), although appropriate shocks were identified as a predictor of CHF events as previously reported (23).

Table 4 Predictors of Inappropriate Shock by Cox Proportional Hazards Regression Analysis

Variable	Hazard Ratio	95% Confidence Interval	p Value
Baseline characteristics			
Atrial fibrillation	2.90	1.65–5.09	<0.01
Smoking	2.18	1.09–4.35	0.03
Diastolic blood pressure ≥80 mm Hg	1.61	1.03–2.52	0.04
Interim events			
Interim appropriate shock	2.25	1.09–4.67	0.03

Other covariates tested but not found significant in multivariate analysis included absence of beta-blocker therapy, prior coronary artery bypass graft procedure, blood urea nitrogen >25, and interim hospitalization for either congestive heart failure, myocardial infarction, or unstable angina. An alternative analysis that also included interim atrial fibrillation found this to be a highly significant predictor of inappropriate shock (hazard ratio 3.45, 95% confidence interval 1.55 to 7.69, $p < 0.01$); the other variables remained significant.

Table 5 ICD Programming in Patients With and Without Inappropriate ICD Shocks

Programming	Inappropriate Shock	No Inappropriate Shock	p Value*
Single-chamber and dual-chamber devices			
Number of patients	83	83†	
Lowest VT zone (beats/min)	169.3 ± 19.9	171.9 ± 14.5	0.540
Lowest VT zone detection time (s)	2.45 ± 1.99	2.42 ± 2.07	0.830
Stability on, % (n)	17 (14)	36 (30)	0.030
Sudden onset on, % (n)	16 (13)	23 (19)	0.160
Dual-chamber devices only			
Number of patients	32	36	
V>A on, % (n)	31 (10)	50 (18)	0.054
Atrial fibrillation discriminator on, % (n)	34 (11)	44 (16)	0.210

*p values from stratified Mann-Whitney rank test and difference-between-proportions test, for continuous and dichotomized measures, respectively. Values were consistent with corresponding ones from nonstratified tests. †Selected randomly from among the 635 patients without inappropriate shocks, matching on history of atrial fibrillation, smoking, and appropriate shock; see text for details.

ICD = implantable cardioverter-defibrillator; VT = ventricular tachycardia.

Discussion

Inappropriate shock epidemiology. In the MADIT II study, inappropriate ICD shocks were common, occurring in 11.5% of patients and with a cumulative 1- and 2-year event rate of 10% and 13%, respectively (Fig. 1A). Overall, 184 inappropriate shock episodes occurred compared with a total of 393 appropriate shock episodes. An AF caused 44.0% of inappropriate shock episodes; SVT and inappropriate sensing were less common.

Frequent inappropriate ICD shocks and ATP occurred in other series (7,19,20), such as the AVID study with 20% of patients experiencing an inappropriate shock or ATP in follow-up and 9% by 2 years of follow-up (19). Enrolling patients with prior sustained VT or VF, a higher proportion of patients experienced appropriate therapy, so the overall percent of events that were inappropriate was lower in the AVID study. Swerdlow et al. (24) had previously predicted that the proportion of inappropriate shocks of the total shock count would be higher in primary prevention ICD patients because of a lower appropriate shock rate. Enrolling a diverse ICD population, the Pain Free Study found that 15% of patients experienced inappropriate therapy (20), with the proportion of all events being inappropriate trending higher in the primary prevention subset than in the secondary prevention group (46% vs. 34%, p = 0.09) (20). In the Multicenter InSync ICD Randomized Clinical Evaluation (MIRACLE ICD) study, 32% of primary prevention biventricular ICD patients had inappropriate detections, although not all of these led to shocks, and unlike in the MADIT II study and most studies, inappropriate detections for sinus tachycardia exceeded atrial arrhythmias (19,20,25,26).

Inappropriate shocks: root causes. Inappropriate shock patients more commonly had a history of atrial fibrillation, smoking, and/or diastolic hypertension and were more likely to also have had a prior appropriate ICD shock (Table 3).

Table 6 Predictors of All-Cause Mortality by Cox Proportional Hazards Regression Analysis

Variable	Hazard Ratio	95% Confidence Interval	p Value
Baseline characteristics			
Blood urea nitrogen >25	2.07	1.38–3.11	<0.01
No beta-blocker	1.64	1.09–2.47	0.02
Interim events			
Interim CHF hospitalization	4.23	2.70–6.62	<0.01
Appropriate and inappropriate shock	4.08	1.71–9.75	<0.01
Appropriate shock only	3.36	2.04–5.55	<0.01
Inappropriate shock only	2.29	1.11–4.71	0.02
Appropriate and inappropriate therapy	3.12	1.38–7.03	<0.01
Appropriate therapy only	2.53	1.54–4.15	<0.01
Inappropriate therapy only	2.01	0.97–4.13	0.06
Appropriate ATP but not shock	0.412	0.148–1.150	0.0903
Inappropriate ATP but not shock	0.729	0.213–2.496	0.6145

Other covariates that were evaluated but not found significant predictors included atrial fibrillation, smoking, congestive heart failure, New York Heart Association class at baseline ≥2, prior non–coronary artery bypass graft revascularization, diastolic blood pressure ≥80 mm Hg, QRS duration >0.12 s, prior angina, history of atrial arrhythmia, diabetes mellitus, age ≥65 years, ejection fraction <0.25, systolic blood pressure ≥130 mm Hg, left bundle branch block, and interim myocardial infarction/unstable angina. The effect of a second appropriate shock episode, when present, is not adjusted for in this model.

ATP = antitachycardia pacing; CHF= congestive heart failure.

Alter et al. (27) reported that young age and nonischemic cardiomyopathy predicted inappropriate shocks. Other investigators have found that prior history of atrial fibrillation and appropriate therapy were predictors of inappropriate shocks, similar to our findings (26). Because AF was the most common inappropriate shock mechanism, its association as a predictive factor is expected. Smoking was recently found to increase the incidence of both appropriate and inappropriate shocks in the MADIT II study, possibly because of a myriad of adverse consequences such as sympathetic stimulation, increased platelet reactivity, vasoconstriction, endothelial dysfunction, and tachycardia (28). Hypertension is a potent risk factor for AF and may act in this way to promote the likelihood of an inappropriate shock. The link between appropriate and inappropriate therapy likely stems from a combination of several factors: 1) ventricular arrhythmia or its treatment (ATP or shock) provoking atrial fibrillation (29,30); 2) inappropriate therapy causing VT, that is, proarrhythmia (18,27); 3) a common factor or factors predisposing to both VT/VF and AF or SVT; or 4) incorrect categorization of some appropriate episodes in a given patient as inappropriate or vice versa.

Outcomes of patients experiencing inappropriate shocks. The prior occurrence of an inappropriate shock was associated with a doubled risk of total mortality in this study even after accounting for the known association between appropriate shock and increased mortality (23) (Table 6). Possible explanations for the increased mortality in the cohort with inappropriate shocks include: 1) potential direct mechanical, arrhythmic, or hemodynamic adverse effect of the shocks themselves, such as fatal proarrhythmia (18,27) or other effects (11); and 2) baseline characteristics or interim events, such as AF, causing both inappropriate shocks and an increased risk of mortality. Because shocks bore a greater association with mortality than ATP (Table 6), explanation one may be favored. However, an alternative inference is that a more recalcitrant, persistent, rapid, or recurrent arrhythmia may have led to a shock, whereas a brief flurry of the arrhythmia may have led to ATP and not required a shock.

Implications for minimizing inappropriate therapy. We found a statistically different, lower utilization rate of the stability SVT–VT discriminator in patients with inappropriate shocks compared with patients not having inappropriate shocks, raising the possibility that more aggressive use of the available SVT discriminators could reduce the incidence of inappropriate detection. Stability was used in a minority of the overall population (Table 5), likely reflecting standard clinical practice at the time of this study. The SVT–VT discriminator usage carries the theoretical risk of underdetection of true ventricular arrhythmias, although current data suggest that underdetection due to stability usage is infrequent (9,21,31,32). Nevertheless, the stability discriminator's effectiveness in preventing therapy for atrial fibrillation is markedly reduced at rates above 170 beats/min (9). In fact, Figure 3 shows that most of the rapidly conducted atrial fibrillation episodes causing inappropriate shocks were indeed 170 beats/min or faster. Thus, even if this discriminator had been uniformly programmed, it may not have had a major impact. Other parameters were not statistically different in the 2 groups, further arguing against programming aberrations explaining the inappropriate shocks (Table 5). Although programming a higher detection rate likely reduces the detection of atrial arrhythmias and misinterpretation of them as ventricular arrhythmias, it is clear that programming too high a rate cutoff could lead to underdetection of relatively slow monomorphic VTs or underdetection of polymorphic ventricular arrhythmias or ventricular fibrillation due to intermittent undersensing (31,33,34). Although there is an incidence of sudden death in any ICD population, the extent to which this could have been prevented by the ICD or whether some of these sudden deaths are caused by underdetection of ventricular arrhythmias remains unknown.

Dual-chamber ICD systems were used approximately as commonly in patients who experienced an inappropriate shock (38.6%) as in those who did not (44.4%, Table 3). Prior studies have often failed to show a benefit of dual-chamber devices in preventing inappropriate detections of supraventricular arrhythmias (22,26,35,36). The Detect Supraventricular Tachycardia Study (DETECT SVT) recently showed a reduction in the percent of total SVT episodes that were inappropriately classified as VT in the dual-chamber detection group (30.9%) than the single-chamber group (39.5%) (37). However, this means that almost one-third of the SVT episodes were still misclassified despite the dual-chamber criteria, and furthermore that total inappropriate shocks were not reduced in the dual-chamber arm (37,38). Future enhancements of SVT–VT discrimination systems may yield improvements (9,33,38–42).

The role of medications in preventing inappropriate shocks is mixed, with a prior study failing to find beta-blocker therapy protective from inappropriate shocks in the MADIT II study (43). However, sotalol and amiodarone have reduced inappropriate shocks by as much as 78% in a secondary prevention population (27,44,45). Recently introduced continuous wireless ICD monitoring (46,47) could reduce inappropriate therapies.

Study limitations. Total shocks were not counted, but rather ICD episodes containing one or more shocks were tallied. The potential additional prognostic importance of the total number of shocks cannot be evaluated. The ICD programming was not protocol specified, and although the VT cutoff rate was collected prospectively, the other parameters analyzed (Table 5) were obtained retrospectively, and the difference in stability programming must be interpreted cautiously. Moreover, parameter changes and possible effects on inappropriate shocks could not be analyzed in a time-dependent fashion. Electrogram interpretation to adjudicate appropriate versus inappropriate shocks was based on available data, which differs for single-chamber and

dual-chamber systems (48). Furthermore, errors in classification may occur (49). This MADIT II substudy's findings may not pertain to other ICD populations. Lastly, although quality of life data were collected in MADIT II and initial analysis has been performed (50), the association of inappropriate shocks and quality of life is not yet available.

Conclusions

Inappropriate shocks were common in the MADIT II study, as in other recently reported trials, occurring in 83 (11.5%) of the 719 MADIT II ICD patients and constituting 31.2% of all shock episodes. Smoking, atrial fibrillation, diastolic hypertension, and prior appropriate shocks were associated with an increased chance of inappropriate shock. Inappropriate shock occurrence was associated with increased probability of mortality in follow-up. Coupled with potential effects on quality of life, this association with increased mortality heightens the importance of efforts to reduce the occurrence of inappropriate shocks.

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