Mortality Reduction in Relation to Implantable Cardioverter Defibrillator Programming in the Multicenter Automatic Defibrillator Implantation Trial-Reduce Inappropriate Therapy (MADIT-RIT)

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Background—The benefit of novel implantable cardioverter defibrillator (ICD) programming in reducing inappropriate ICD therapy and mortality was demonstrated in Multicenter Automatic Defibrillator Implantation Trial-Reduce Inappropriate Therapy (MADIT-RIT). However, the cause of mortality reduction remains incompletely evaluated. We aimed to identify factors associated with mortality, with focus on ICD therapy and programming in the MADIT-RIT population.

Methods and Results—In MADIT-RIT, 1500 patients with a primary prophylactic indication for ICD or cardiac resynchronization therapy with defibrillator were randomized to 1 of 3 different ICD programming arms: conventional programming (ventricular tachycardia zone ≥170 beats per minute), high-rate programming (ventricular tachycardia zone ≥200 beats per minute), and delayed programming (60-second delay before therapy ≥170 beats per minute). Multivariate Cox models were used to assess the influence of time-dependent appropriate and inappropriate ICD therapy (shock and antitachycardia pacing) and randomized programming arm on all-cause mortality. During an average follow-up of 1.4±0.6 years, 71 of 1500 (5%) patients died: cardiac in 40 patients (56.3%), noncardiac in 23 patients (32.4%), and unknown in 8 patients (11.3%). Appropriate shocks (hazard ratio, 6.32; 95% confidence interval, 3.13–12.75; P<0.001) and inappropriate therapy (hazard ratio, 2.61; 95% confidence interval, 1.28–5.31; P=0.01) were significantly associated with an increased mortality risk. There was no evidence of increased mortality risk in patients who experienced appropriate antitachycardia pacing only (hazard ratio, 1.02; 95% confidence interval, 0.36–2.88; P=0.98). Randomization to conventional programming was identified as an independent predictor of death when compared with patients randomized to high-rate programming (hazard ratio, 2.0; 95% confidence interval, 1.06–3.71; P=0.03).

Conclusions—In MADIT-RIT, appropriate shocks, inappropriate ICD therapy, and randomization to conventional ICD programming were independently associated with an increased mortality risk. Appropriate antitachycardia pacing was not related to an adverse outcome.

Clinical Trial Registration—URL: clinicaltrials.gov; Unique identifier: NCT00947310.
(Circ Arrhythm Electrophysiol. 2014;7:785-792.)

Key Words: arrhythmias, cardiac ■ mortality

Implantable cardioverter-defibrillator (ICD) and cardiac resynchronization therapy with defibrillator (CRT-D) have been shown to reduce mortality in patients at high risk for ventricular tachycardia or fibrillation (VT or VF).1-4 However, many patients experience inappropriate defibrillator therapy, defined as therapy delivered for a nonventricular arrhythmia. Inappropriate shocks have been associated with reduced quality of life,5-8 myocardial injury,7-9 rare fatal proarrhythmia,10 and
increased mortality in some studies, whereas in other studies, no association between mortality and inappropriate shocks has been found. Whether inappropriate shocks are causally related to increased mortality or indirectly related to mortality by the supraventricular arrhythmias triggering them has been difficult to establish. Increasingly, device therapy programming considerations have emphasized antitachycardia pacing (ATP). Although ATP may reduce shocks and improve quality of life, the effect of ATP on mortality, if any, remains unknown.

Clinical Perspective on p 792

In the Multicenter Automatic Defibrillator Implantation Trial-Reduce Inappropriate Therapy (MADIT-RIT) study, we investigated the effect of 2 novel ICD programming strategies on inappropriate therapy. Randomization of patients to high-rate ICD device programming with ICD therapy beginning at 200 beats per minute or to delayed programming (12–60 seconds before ATP or shock) was associated with reductions in inappropriate therapy when compared with conventional programming. Mortality was higher with conventional programming than in the other 2 programming arms. In the current MADIT-RIT substudy, we investigated the factors associated with mortality in the 3 treatment arms of this randomized trial. Based on potentially harmful consequences of inappropriate therapies, we hypothesized that the higher mortality rate seen with conventional programming was because of, in part, the high frequency of inappropriate ICD therapies in this treatment arm when compared with the other 2 treatment arms.

Methods

MADIT-RIT Randomization, Programming, and Interrogation

MADIT-RIT enrolled 1500 patients with guideline-indicated, primary prevention ICD or CRT-D devices at 98 centers in the United States, Canada, Europe, Israel, and Japan from September 15, 2009, to October 10, 2011. Commercially available dual-chamber ICD or CRT-D Boston Scientific devices were used as appropriate. Dual-chamber ICD devices were used to permit the same programming discriminators in patients with CRT-D and ICD devices and to optimize arrhythmia adjudication. Subjects were randomized to 1 of 3 different programming arms. Arm A, conventional programming, used VT detection 170 to 199 beats per minute with a 2.5-second delay before therapy (ATP or shock) and a faster VT and VF zone >200 beats per minute with a 1-second delay before therapy. Arm B, high-rate programming, had a monitor-only zone from 170 to 199 beats per minute and a therapy zone at ≥200 beats per minute with a 1-second delay before therapy. Arm B, high-rate programming, had a monitor-only zone from 170 to 199 beats per minute and a therapy zone at ≥200 beats per minute with a 2.5-second delay before therapy. Arm C, delayed therapy, consisted of 3 therapy zones: zone 1 provided therapy from 170 to 199 beats per minute after a 60-second delay; zone 2, 200 to 249 beats per minute, used a 12-second delay before therapy; and zone 3 treated VT/VF >250 beats per minute after a 2.5-second delay. Atrial discriminators were turned on in all arms. For the conventional and high-rate programming arms, onset and stability detection were used, whereas in the delayed programming arm, Rhythm ID detection algorithms were used. Physician investigators were encouraged to follow optimal pharmacological treatment for the enrolled patients according to current guidelines.

The protocol allowed reprogramming of the devices after an inappropriate ICD therapy. Device interrogations were conducted every 3 months the first year and every 6 months thereafter. Postmortem device interrogation was encouraged.

The current data represent version 2 of the MADIT-RIT data, with follow-up conducted until July 10, 2012.

MADIT-RIT was approved by an institutional review committee, and all patients gave informed consent before being enrolled in the study.

End Points

The primary end point of MADIT-RIT was first occurrence of inappropriate therapy; all-cause mortality was a secondary end point. For the current analysis, all-cause mortality was used as the primary end point. An independent morbidity and mortality committee adjudicated and classified deaths as cardiac, noncardiac, or unknown based on an assessment of all the information provided by the enrolling centers, including medical history, description of the circumstances surrounding the death from family members and hospital personnel, physician’s determination of the cause of death, death records, and, when available, postmortem ICD interrogation.

ICD Therapy and Arrhythmia Definitions

All ICD therapies from in-clinic and available postmortem interrogations (18 of 71 deaths; 25%) were adjudicated by an independent device interrogation committee. Appropriate ICD therapy was defined as any ICD therapy rendered for VT or VF. Inappropriate ICD therapy was defined as any ICD therapy delivered where VT or VF was not present. Appropriate and inappropriate ICD therapies were subdivided as ATP or shock. If both ATP and shock occurred in an episode, it was considered a shocked episode.

Pharmacotherapy

Cardiovascular pharmacotherapy, including β-blockers, statins, diuretics, digitalis, angiotensin II receptor blocker, angiotensin-converting enzyme inhibitor, aldosterone antagonists, and amiodarone, was recorded at each visit. The influence of pharmacotherapy on all-cause mortality was investigated by incorporating either baseline or in-trial use into multivariate Cox proportional hazard regression models. Time-dependent pharmacotherapy throughout the study period was adjusted for by creating variables for each drug taking into account the time each patient was either on or off the specific drug.

Statistics

Baseline characteristics were compared between patients who died and survivors. Comparisons between groups used χ² or Fisher exact tests for categorical variables and Wilcoxon rank-sum test for continuous measures.

The cumulative proportion of all-cause mortality was calculated using the method of Kaplan–Meier. In-trial mortality risk was analyzed in all 1500 patients by multivariate Cox proportional hazards regression models, adjusting for baseline predictors of death found by best subset analysis, setting the limit for inclusion in the model at P<0.05. The selected model was then used to analyze the influence of: ICD therapy throughout the study, pharmacotherapy throughout the study, and randomized programming arm on the end point of all-cause mortality. We created time-dependent variables for appropriate shock, appropriate ATP only, inappropriate shock, and inappropriate ATP only. The shock and ATP-only groups were defined based on the assumption that appropriate and inappropriate ICD therapies were different entities, and therefore, any potential overlaps between appropriate and inappropriate ICD therapies were not included in the definition. Furthermore, shocks were assumed to be more detrimental than ATP, and therefore, patients in the ATP-only groups were defined as ATP without prior shock. They contributed with risk time in the ATP-only group until they received a shock, and afterward they contributed with risk time in the shock groups.

The proportional hazards assumption was checked in the multivariate models by the use of time-dependent covariates created by interacting survival time with the various covariates and testing for statistical significance using the likelihood ratio test.

Covariate interactions were systematically investigated between programming arms and baseline variables, ICD therapies, and pharmacotherapies. Interactions were also checked between the specific types of ICD therapy (appropriate therapy [ATP only or shock] and inappropriate therapy [ATP only or shock]), baseline variables, and
pharmacotherapy. A significance limit for interactions was set at $P<0.01$, to account for multiple comparisons. No significant interactions were found.

Hazard ratios with their 95% confidence intervals and 2-sided $P$ values are reported. A 2-tailed $P$ value <0.05 was considered statistically significant.

Analyses were performed using SAS software version 9.3 (SAS Institute, Cary, NC).

**Results**

During a mean follow-up period of 1.4±0.6 years, 71 of 1500 (5%) enrolled patients died with 34, 16, and 21 deaths in the conventional, high-rate, and delayed programming arms, respectively (Figure 1). The 2.5-year cumulative probability of death was 9%. The adjudicated cause of death was cardiac in 40 patients (56.3%), noncardiac in 23 patients (32.4%), and unknown in 8 patients (11.3%; Figure 1). The majority of cardiac deaths were because of heart failure, closely followed by sudden cardiac death (Figure 1). The proportions of cardiac deaths were equally distributed among the programming arms, whereas the percentage of noncardiac deaths was higher in the conventional and delayed programming arms compared with the high-rate programming arm. Most of the noncardiac death in the conventional programming arm was related to cancer (n=8).

**Baseline Factors and All-Cause Mortality**

Patients who died were significantly older, had lower left ventricular ejection fraction, lower diastolic blood pressure, and were more likely to have ischemic cardiomyopathy, diabetes mellitus, and to receive amiodarone and digitalis at baseline compared with patients who survived (Table 1).

Similarly, in multivariate analysis, older age, lower diastolic blood pressure, New York Heart Association class III (compared with lower New York Heart Association class), lower left ventricular ejection fraction, ischemic cardiomyopathy, diabetes mellitus, and implantation of an ICD (compared with a CRT-D) were significantly associated with an increased risk of all-cause mortality (Table 2).

**ICD Therapy and All-Cause Mortality**

During follow-up, appropriate ICD therapy occurred in 186 of 1500 patients (12.4%). Inappropriate ICD therapy, largely because of atrial tachyarrhythmia, occurred in 152 of 1500 patients (10.1%). Patients in the conventional ICD programming arm received a higher frequency of both appropriate and inappropriate therapies compared with patients in the other 2 treatment arms. Figure 2 shows the breakdown of patients who died with known antecedent appropriate or inappropriate ICD therapies.

In multivariate analyses, both appropriate and inappropriate therapies were significantly associated with increased risk of all-cause mortality (Table 3). Increased risk of mortality was associated with the delivery of appropriate shock, inappropriate shock, and inappropriate ATP only (Table 3). No increased risk of mortality was found in the 112 patients who experienced appropriate ATP only (Table 3). The significant associations persisted after adjustment for programming arm and time-dependent pharmacotherapy (results not shown).

![Figure 1](http://circres.ahajournals.org/)

**Figure 1.** Mode of death by programming arm. Bar chart showing the number of patients who died within each programming arm. All-cause mortality is shown along with the subdivision into cardiac, noncardiac, and unknown cause of death.
Heart Association.
artery bypass grafting; CRT-D, cardiac resynchronization therapy with
Comorbidities at baseline
Delayed programming arm 21 (30) 465 (33)
High-rate programming arm 16 (23) 484 (34)*
Conventional programming arm 34 (48) 480 (34)*
Resting heart rate, beats per min 72.1±12.0 72.1±12.5
Systolic blood pressure, mm Hg 120.8±21.5 123.7±19.1
Diastolic blood pressure, mm Hg 69.5±13.3 73.1±11.7*
Body mass index, kg/m² 29.5±9.0 29.3±6.7
Left ventricular ejection fraction 25% 43 (61) 683 (48)*
Female sex 17 (24) 419 (29)
History of atrial arrhythmias 12 (17) 191 (13)
History of ventricular arrhythmias 1 (1) 47 (3)
Currently smoking 10 (15) 237 (18)
Myocardial infarction 35 (50) 603 (44)
Digitalis 15 (21) 178 (12)*
ACEi/angiotensin II receptor blocker 12 (17) 191 (13)
Calcium channel blocker 4 (6) 118 (8)
β-Blocker 64 (90) 1340 (94)
Aldosterone antagonist 30 (42) 514 (36)
Digitalis 15 (21) 178 (12)*
Method of rendered appropriate ICD therapies (in 6 patients) induced VT/VF requiring appropriate
Ishemic cardiomyopathy 1.76 1.04–3.00 0.036
Lower ejection fraction (per 10% reduction) 1.74 1.25–2.43 0.001
Diabetes mellitus 1.64 1.02–2.65 0.043
Increasing age (per decade) 1.36 1.08–1.72 0.009
Lower diastolic blood pressure (per 10 mm Hg decrease) 1.28 1.03–1.60 0.029
*Based on a multivariate Cox model with these 7 covariates identified by best subset regression, setting the limit for entry into the model at P<0.05.

Compared with first ICD events, multiple ICD therapies of the same type did not result in an additional increase in mortality risk considering appropriate shocks, inappropriate shocks, inappropriate ATP only, or appropriate ATP only (P=0.30–0.75). However, only limited numbers of deaths were present in patients with multiple ICD therapies (events: appropriate shock=5, inappropriate shock=1, appropriate ATP=1, inappropriate ATP=2). When considering the number of specific ICD therapies within each ICD therapy episode, the number of rendered inappropriate therapies was twice as high as the number of rendered appropriate ICD therapies (Table 5).

Pharmacotherapy and All-Cause Mortality
In multivariate analysis, after adjusting for baseline predictors of death and for ICD therapy, the time-dependent use of amiodarone (hazard ratio, 2.52; 95% confidence interval, 1.34–4.74; P=0.004) and the lack of angiotensin-converting enzyme inhibitor/angiotensin II receptor blocker use (hazard ratio, 2.59; 95% confidence interval, 1.56–4.31; P<0.001) were associated with increased mortality risk. No other pharmacological treatment was significantly associated with mortality. No differential antiarrhythmic treatment throughout the study was evident between the programming arms. This was confirmed in multivariate analysis where the results were consistent within each programming arm (interaction P=0.12–0.78). Importantly, the influence of ICD therapy on mortality was not altered when adjusting for time-dependent amiodarone and angiotensin-converting enzyme inhibitor/angiotensin II receptor blocker use, and the results were similar when further adjustments were made for randomized programming arm (results not shown).

ICD Programming and All-Cause Mortality
Randomization to conventional programming compared with high-rate programming remained significantly associated with increased risk of mortality even after further adjustment for time-dependent ICD therapies and time-dependent use of amiodarone and angiotensin-converting enzyme inhibitor/angiotensin II receptor blocker (Table 6). A significant mortality risk was not present when comparing conventional programming
with delayed programming (Table 6). The results were consistent when considering cardiac mortality (Table 6).

During follow-up, 166 patients (11%) deviated from the allocated randomized programming arm on the parameters of rate cut-off, delay before therapy and ATP on/off, with 70 patients randomized to conventional programming, 54 randomized to high-rate programming, and 42 randomized to delayed programming. Of the patients who deviated within the abovementioned parameters, only 9 patients died, with equal distribution among the programming arms (3 events in each arm).

Discussion
In MADIT-RIT, randomization to conventional ICD programming, inappropriate ICD therapy, and appropriate ICD shocks were each independently associated with increased mortality risk after adjustment for relevant risk covariates.

Several mechanisms could potentially explain the association of conventional programming with increased mortality. Inappropriate therapy may have contributed to the differential mortality rates between arms. The sum total of inappropriate and appropriate shocks in the conventional treatment arm was almost twice the number of delivered shock therapies in the high-rate and delayed treatment arms. Thus, the increased frequency of shocks in the conventional treatment arm could contribute additional myocardial injury to an already compromised myocardium with increase in the subsequent risk for heart failure and life-threatening ventricular tachyarrhythmias, as previously suggested. However, inappropriate ATP and shock therapy cannot be the only factor responsible for the increased mortality in the conventional arm. Total deaths numbered 34 in conventional versus 16 in the high-rate and 21 in the delayed therapy arm. However, the number of patients dying after experiencing a confirmed inappropriate therapy was 8 versus 0 versus

Table 3. Influence of ICD Therapy on the Risk of Mortality

<table>
<thead>
<tr>
<th>Influence of ICD Therapy by Different Heart Rate Ranges on Mortality</th>
<th>Deaths/Total Patients With the Specific ICD Therapy</th>
<th>HR</th>
<th>95% CI</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall inappropriate therapy</td>
<td>10/152</td>
<td>2.61</td>
<td>1.28–5.31</td>
<td>0.008</td>
</tr>
<tr>
<td>Inappropriate shock</td>
<td>4/60</td>
<td>2.88</td>
<td>1.02–8.17</td>
<td>0.046</td>
</tr>
<tr>
<td>Inappropriate ATP-only</td>
<td>6/92</td>
<td>3.25</td>
<td>1.33–7.94</td>
<td>0.010</td>
</tr>
<tr>
<td>Overall appropriate therapy</td>
<td>15/186</td>
<td>2.66</td>
<td>1.45–4.88</td>
<td>0.002</td>
</tr>
<tr>
<td>Appropriate shock</td>
<td>11/74</td>
<td>6.32</td>
<td>3.13–12.75</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Appropriate ATP only</td>
<td>4/112</td>
<td>1.02</td>
<td>0.36–2.88</td>
<td>0.977</td>
</tr>
</tbody>
</table>

Adjusted for age, left ventricular ejection fraction, diastolic blood pressure, diabetes mellitus, ischemic cardiomyopathy, New York Heart Association (NYHA) class III compared with lower NYHA class and implanted device (implantable cardioverter defibrillator [ICD]/cardiac resynchronization therapy with defibrillator). ATP indicates antitachycardia pacing; CI, confidence interval; and HR, hazard ratio.

Table 4. Influence of ICD Therapy by Different Heart Rate Ranges on Mortality

<table>
<thead>
<tr>
<th>Influence of ICD Therapy by Different Heart Rate Ranges on Mortality</th>
<th>Deaths/Total Patients With the Specific ICD Therapy</th>
<th>HR</th>
<th>95% CI</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inappropriate therapy 170–199 beats per min</td>
<td>9/122</td>
<td>3.16</td>
<td>1.47–6.81</td>
<td>0.003</td>
</tr>
<tr>
<td>Inappropriate therapy ≥200 beats per min</td>
<td>1/39</td>
<td>0.46</td>
<td>0.06–3.61</td>
<td>0.462</td>
</tr>
<tr>
<td>Appropriate therapy 170–199 beats per min</td>
<td>5/97</td>
<td>0.98</td>
<td>0.37–2.55</td>
<td>0.961</td>
</tr>
<tr>
<td>Appropriate therapy ≥200 beats per min</td>
<td>11/123</td>
<td>3.22</td>
<td>1.59–6.54</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Adjusted for age, left ventricular ejection fraction, diastolic blood pressure, diabetes mellitus, ischemic cardiomyopathy, New York Heart Association (NYHA) class III compared with lower NYHA class and implanted device (implantable cardioverter defibrillator [ICD]/cardiac resynchronization therapy with defibrillator). CI indicates confidence interval; and HR, hazard ratio.
Table 5. Frequency of Different Implantable Cardioverter Defibrillator Therapies per Treated Episode

<table>
<thead>
<tr>
<th>Variable</th>
<th>Total Episodes</th>
<th>Mean Therapies±SD</th>
<th>Median Therapies (IQR)</th>
<th>Minimum Number of Therapies</th>
<th>Maximum Number of Therapies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Appropriate ATP</td>
<td>169</td>
<td>1.28±0.89</td>
<td>1.00 (0.0)</td>
<td>1</td>
<td>6.5</td>
</tr>
<tr>
<td>Inappropriate ATP</td>
<td>149</td>
<td>2.52±2.32</td>
<td>1.67 (2.0)</td>
<td>1</td>
<td>15.0</td>
</tr>
<tr>
<td>Appropriate shock</td>
<td>74</td>
<td>1.29±0.72</td>
<td>1.00 (0.0)</td>
<td>1</td>
<td>4.0</td>
</tr>
<tr>
<td>Inappropriate shock</td>
<td>60</td>
<td>2.39±2.38</td>
<td>1.00 (2.0)</td>
<td>1</td>
<td>12.0</td>
</tr>
</tbody>
</table>

ATP indicates antitachycardia pacing; and IQR, interquartile range.

2, respectively, and therefore other factors must have contributed to the increased mortality. In multivariate analyses, when adjusted for appropriate and inappropriate therapy, assignment to conventional programming remained an independent predictor of mortality, indicating the presence of an unknown entity in patients programmed to conventional programming that contributed to increased mortality. As seen in Figure 1, there was a sizable difference in noncardiac deaths between the programming arms, and this was mostly because of cancer-related deaths as adjudicated by the mortality review committee. Although an element of chance might have involved in the higher frequency of cancer-related deaths in the conventional programming arm, it is also possible that cancer patients are especially vulnerable to the increased occurrence of adverse appropriate and inappropriate shocks in the 170 to 199 beats per minute range potentially compromising their limited medical reserve.

Inappropriate ATP only was very frequent in the conventional programming arm, consistent with the increased risk of mortality associated with inappropriate therapy in the 170 to 199 beats per minute range. This association between inappropriate ATP and increased mortality risk was also reported in a recent substudy of the MADIT-CRT trial. However, the mechanism by which inappropriate ATP, by itself, contributed to increased mortality risk is still unclear, because in both the current study and in MADIT-CRT trial, inappropriate ATP was not associated directly with any harm. In the current study, inappropriate ATP only was not a marker for risk related to supraventricular tachyarrhythmias, because device interrogations revealed that the cumulative frequency of these arrhythmias in the 170 to 199 beats per minute range was almost identical (21–22%) in the conventional and high-rate treatment arms. Inappropriate ATP can be proarrhythmic, but such episodes of direct and immediate harm were very infrequent, and no fatal ICD proarrhythmic events (from ATP or shock) were documented in MADIT-RIT. As compared with appropriate ATP, when inappropriate ATP was delivered approximately, twice as many pacing sequences resulted. Given that inappropriate therapy is rarely effective in terminating the atrial arrhythmias responsible for triggering the inappropriate response, it is possible that the larger number of sequences may have exerted an adverse influence on the myocardium. However, in summary, based on analysis of the available data, it is not currently possible to determine the mechanism by which inappropriate ATP was significantly associated with increased mortality.

Table 6. Impact of Randomized Programming Arm on Mortality

<table>
<thead>
<tr>
<th></th>
<th>All-Cause Mortality</th>
<th>Cardiac Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR 95% CI</td>
<td>P Value</td>
<td>HR 95% CI</td>
</tr>
<tr>
<td>Conventional vs high-rate programming</td>
<td>1.98</td>
<td>1.06–3.71</td>
</tr>
<tr>
<td>Conventional vs delayed programming</td>
<td>1.34</td>
<td>0.75–2.40</td>
</tr>
</tbody>
</table>

Two different Cox models were fitted, one for the end point of all-cause mortality and one for the end point of cardiac mortality. Time-dependent variables represent the risk time in on/off medication/implantable cardioverter defibrillator (ICD) therapy groups throughout the follow-up period. All interaction P values between programming arms and baseline characteristics or ICD therapies had P>0.01. CI indicates confidence interval; and HR, hazard ratio.

"Adjusted for age, left ventricular ejection fraction, diastolic blood pressure, diabetes mellitus, ischemic cardiomyopathy, New York Heart Association (NYHA) class III compared with lower NYHA classes, implanted device (ICD/cardiac resynchronization therapy with defibrillator), time-dependent appropriate and inappropriate ICD therapies, and time-dependent amiodarone usage and lack of angiotensin-converting enzyme inhibitor (ACE)/angiotensin II receptor blocker (ARB) usage.

Because MADIT-RIT was designed for analysis as 2 parallel trials, it is intriguing that both high-rate and delayed therapy intervention arms exhibited both a 75% to 80% lower incidence of first inappropriate therapy and also a 44% to 55% mortality reduction. Although the mortality difference was significant only for the conventional versus the high-rate programming arm, the results from the 2 arms are nevertheless mutually supportive. Moreover, the 2-fold higher cardiac mortality in the conventional programming arm compared with the other 2 arms supports the link between ICD therapy and mortality risk. We do, however, acknowledge the risk of confounding by the use of a common comparator group.

Recently, Gasparini et al reported the findings from ADVANCE III (Avoid Delivering Therapies for Nonsustained Arrhythmias in ICD Patients), a randomized trial involving 1902 primary and secondary prevention patients with ICD therapy. They evaluated the use of prolonged (30 of 40) versus standard (18 of 24) VT detection intervals and observed a 38% lower rate of delivered therapies including inappropriate shocks and appropriate ATP and shocks. However, no decreased risk of mortality was found. In MADIT-RIT, the total delivered therapies in the high-rate arm was 66% lower than the delivered therapies in the conventional therapy arm. This difference in delivered therapies between the control and interventional arm of the 2 studies, as well as both the higher detection limit in the control group and the shorter follow-up time in ADVANCE III as compared with MADIT-RIT, may explain the different findings regarding reduction in mortality between the 2 studies. Similar to MADIT-RIT, a trend toward mortality reduction was seen in the shock reduction programming study Primary Prevention Parameters Evaluation.

Study Limitations

Because MADIT-RIT was designed to evaluate the primary end point of first inappropriate therapy, we are limited in power for secondary analysis on the end point of mortality, with relatively
few mortality events in each of the programming arms during a comparatively short follow-up period (1.4±0.6 years). This is evident from the \( P \) value when comparing conventional programming with high-rate programming \((P=0.032)\). Given the number of statistical tests, the \( P \) values reported should be considered as nominal, and it is noted that the difference in all-cause mortality would not reach significance if we had corrected for the 2 comparisons A versus B and A versus C, although it would be very close to significant \((\text{significance limit accounting for 2 comparisons: } P<0.025, \text{ actual } P=0.032)\). Furthermore, by using the conventional programming arm as a common comparator, there is a risk of confounding. Second, the ICD device’s memory capacity might have led to unavailability of electrophysograms for some rare arrhythmia episodes because of overwriting. Third, although adjustments for multiple baseline variables were used to investigate the association of ICD therapy and mortality, there is a possibility that other unmeasured confounders, such as differential medical or surgical management, may have affected the results. Furthermore, postmortem interrogations were only available in 18 of 71 deaths \((25\%)\), which make it difficult to assess whether patients had ICD therapy before their death. This limitation might have impacted our results on an unknown level. Lastly, information regarding cancer at baseline was not reported, and cancer at baseline was not an exclusion criterion according to the protocol. Therefore, there is a chance that more patients randomized to conventional programming had cancer at enrollment, as compared with patients randomized to high-rate or delayed programming, which may have contributed to the mortality difference. As previously mentioned, patients with cancer may have less medical reserve because of their chronic illness and thus may be more vulnerable to the increased occurrence of adverse appropriate and inappropriate shocks in the conventional treatment arm.

Conclusions
In MADIT-RIT, appropriate shock, inappropriate shock, and inappropriate ATP were all independent predictors of all-cause mortality, whereas appropriate ATP was not. Conventional ICD programming, beginning therapies at 170 beats per minute, was associated with an increased risk of all-cause mortality as compared with ICD programming with a cutoff \(>200\) beats per minute, even when taking into account ICD therapies delivered. The explanation of the increased mortality seen in MADIT-RIT patients randomized to conventional programming as compared with high-rate programming seems to be multifactorial with contributing risk factors including the higher frequency of inappropriate ATP-only therapies and inappropriate and unnecessary shock therapies in the 170 to 199 beats per minute range. In addition, there could be 21 unknown confounding factors as well as a chance effect in the distribution of deaths that may also contribute to a higher mortality in the conventional programming arm.

Acknowledgments
We acknowledge Bronislava Polonsky, MS; Claire Zhang; Suneet Mittal, MD; Ilan Goldenberg, MD; Poul Erik Block Thomsen, MD, PhD; Christian Jons, MD, PhD; Mark Haigney, MD; Emad Aziz, MD, RN; Ted Dwyer, MD; Jackson Hall, PhD; and all the Multicenter Automatic Defibrillator Implantation Trial-Reduce Inappropriate Therapy investigators and enrolling centers. We thank them for their contributions. This research was performed while A.-C. Ruwald was a Mirowski-Moss Awardee; she has further received unrestricted travel grants from the Denmark-America Foundation, Falck Denmark, the Lundbeck-Foundation, Bønnelykkefonden, Carl and Ellen Hertz, and Torben and Alice Frimods Foundation.

Sources of Funding
Multicenter Automatic Defibrillator Implantation Trial-Reduce Inappropriate Therapy was supported by a research grant from Boston Scientific to the University of Rochester, with funds distributed to the coordination and data center, enrolling centers, core laboratories, committees, and boards under subcontracts from the University of Rochester.

Disclosures
This research was performed while A.-C. Ruwald was a Mirowski-Moss Awardee. Dr Ruwald has received travel grants from the Denmark-America Foundation, Falck Denmark, the Lundbeck-Foundatio, Bønnelykkefonden, Carl and Ellen Hertz, and Torben and Alice Frimods Foundation. Dr Moss reports receiving grant support from Boston Scientific and lecture fees from Boston Scientific, Medtronic, and St Jude Medical. Dr Olshansky reports receiving consulting and speaking fee from Medtronic, Boston Scientific, Boehringer Ingelheim, Biocontrol, and Amarin. Dr Schuger reports receiving research grants from Boston Scientific. Dr Estes reports receiving grant support from Boston Scientific and consulting fees from Boston Scientific, Medtronic, St Jude Medical. Dr Kautzner reports receiving payment for board membership and lecture fees from Boston Scientific; payment for board membership and lecture fees from St Jude Medical; lecture fees as well as grant support through his institution, from Biotronik; and lecture fees as well as grant support through his institution, from Medtronic. Dr Shoda reports receiving consultant honoraria from Boston Scientific. Dr Wilber reports receiving honoraria for lectures from Medtronic, St Jude, and Boston Scientific. Dr Zareba reports receiving grant support from Boston Scientific. Dr Klein reports receiving grant support from Boston Scientific and speaker honoraria from Boston Scientific. Dr Beck reports receiving grant support from Boston Scientific. Dr Cannom reports receiving speakers bureau from Medtronic, Boston Scientific, and Pfizer. Dr Huang reports receiving consulting fees/honoraria from St Jude Medical, speakers bureau from Biotronik, research grants and fellowship support from Medtronic Inc, Boston Scientific, St Jude Medical, and Biotronik. Dr Daubert reports receiving grant support from Boston Scientific, Biosense-Webster, Medtronic, and Gilead, and honoraria for lectures or consultation from Boston Scientific, Medtronic, Biosense-Webster, St Jude Medical, Biotronik, Premier, and Sorin. The other authors report no conflicts.

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Anne-Christine Ruwald, Claudio Schuger, Arthur J. Moss, Valentina Kutyifa, Brian Olshansky, Henry Greenberg, David S. Cannom, N.A. Mark Estes, Martin H. Ruwald, David T. Huang, Helmut Klein, Scott McNitt, Christopher A. Beck, Robert Goldstein, Mary W. Brown, Jose Kautzner, Morio Shoda, David Wilber, Wojciech Zareba and James P. Daubert

Circ Arrhythm Electrophysiol. 2014;7:785-792; originally published online August 18, 2014; doi: 10.1161/CIRCEP.114.001623

Circulation: Arrhythmia and Electrophysiology is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 1941-3149. Online ISSN: 1941-3084

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