Mortality Reduction In Relation To ICD Programming In MADIT-RIT

Running title: Ruwald et al.; Mortality and ICD Programming

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Abstract:

**Background** - The benefit of novel ICD programming in reducing inappropriate ICD therapy and mortality was demonstrated in MADIT-RIT. However, the cause of the 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 CRT-D were randomized to one of three different ICD programming arms: conventional programming (VT-zone ≥170 bpm); high-rate programming (VT-zone ≥200 bpm); and delayed programming (60 sec. delay before therapy ≥170 bpm). Multivariate Cox models were used to assess the influence of time-dependent appropriate and inappropriate ICD therapy (shock and/or antitachycardia pacing [ATP]) 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 %), non-cardiac in 23 patients (32.4%), and unknown in 8 patients (11.3%). Appropriate shocks (Hazard Ratio [HR] = 6.32 [95% CI: 3.13-12.75], p<0.001) and inappropriate therapy (HR=2.61 [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 ATP only (HR=1.02 [0.36-2.88], p=0.98). Randomization to conventional programming was identified as an independent predictor of death when compared to patients randomized to high-rate programming (HR=2.0 [1.06-3.71], p=0.03).

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

**Clinical Trial Registration** - clinicaltrials.gov; Unique Identifier: NCT00947310.

**Key words:** mortality, implanted cardioverter defibrillator, arrhythmia, MADIT-RIT, ICD therapy, inappropriate ATP, ICD programming
Introduction

An implantable cardioverter defibrillator (ICD) and cardiac resynchronization therapy defibrillator (CRT-D) have been shown to reduce mortality in patients at high risk for ventricular tachycardia or fibrillation (VT or VF). However, many patients experience inappropriate defibrillator therapy, defined as therapy delivered for a non-ventricular arrhythmia. Inappropriate shocks have been associated with reduced quality of life, myocardial injury, rare fatal proarrhythmia, 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). While ATP may reduce shocks, and improve quality of life, the effect of ATP on mortality, if any, remains unknown.

In the Multicenter Automatic Defibrillator Implantation Trial-Reduce Inappropriate Therapy (MADIT-RIT) study, we investigated the effect of two 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 (bpm) or to delayed programming (12-60 seconds before ATP or shock) was associated with reductions in inappropriate therapy when compared to conventional programming. Mortality was higher with conventional programming than in the other two programming arms. In the current MADIT-RIT sub-study, we investigated the factors associated with mortality in the three 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 due in part...
to the high frequency of inappropriate ICD therapies in this treatment arm when compared to the other two treatment arms.

**Methods**

**MADIT-RIT randomization, programming and interrogation**

MADIT-RIT\textsuperscript{22, 23} enrolled 1500 patients with guideline-indicated,\textsuperscript{24} primary prevention ICD or CRT-D devices at 98 centers in the United States, Canada, Europe, Israel, and Japan from September 15\textsuperscript{th} 2009 to October 10\textsuperscript{th} 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 one of three different programming arms. Arm A, conventional programming, used VT-detection 170-199 bpm with a 2.5 sec. delay before therapy (ATP or shock) and a faster VT and/or VF zone above 200 bpm with a 1 sec. delay before therapy. Arm B, high-rate programming, had a monitor-only zone from 170-199 bpm and a therapy zone at 200 bpm and above with a 2.5 sec. delay before therapy. Arm C, delayed therapy, consisted of 3 therapy zones; Zone 1 provided therapy from 170-199 bpm after a 60 sec. delay; Zone 2, 200-249 bpm, used a 12 sec. delay before therapy; and Zone 3 treated VT/VF above 250 bpm after a 2.5 sec. 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.\textsuperscript{25}

The protocol allowed reprogramming of the devices after an inappropriate ICD therapy. Device interrogations were conducted every three months the first year and every six months.
thereafter. Post-mortem device interrogation was encouraged.

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

The MADIT-RIT study 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.\(^{22,23}\) For the current analysis, all-cause mortality was utilized as the primary end point. An independent morbidity and mortality committee adjudicated and classified deaths as cardiac, non-cardiac 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/or hospital personnel, the physician’s determination of the cause of death, death records and when available post-mortem ICD interrogation.

**ICD therapy and arrhythmia definitions**

All ICD therapies from in-clinic and available post-mortem interrogations (18 of 71 death, 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.\(^{22}\) 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 beta-blockers, statins, diuretics, digitalis,
angiotensin-II-receptor blocker (ARB), angiotensin converting enzyme inhibitor (ACE), 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 chi-square or Fisher’s 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: 1) ICD therapy throughout the study, 2) pharmacotherapy throughout the study, and 3) 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 two 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, in order to account for multiple comparisons. No significant interactions were found.

Hazard ratios (HR) with their 95% confidence intervals (CI) and two-sided p-values are reported. A two-tailed p-value below 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%), non-cardiac in 23 patients (32.4%) and unknown in 8 patients (11.3%) (Figure 1). The majority of the cardiac deaths were due to heart failure (HF), closely followed by SCD (Figure 1). The proportions of cardiac deaths were equally distributed among the programming arms, whereas the percentage of non-cardiac deaths were higher in the
conventional and delayed programming arms compared to the high-rate programming arm. Most of the non-cardiac death in the conventional programming arm were related to cancer (n=8).

**Baseline factors and all-cause mortality**

Patients who died were significantly older, had lower left ventricular ejection fraction (LVEF), lower diastolic blood pressure, and were more likely to have ischemic cardiomyopathy, diabetes, and to receive amiodarone and/or digitalis at baseline than patients who survived (Table 1). Similarly, in multivariate analysis, older age, lower diastolic blood pressure, NYHA class III (compared to lower NYHA class), lower LVEF, ischemic cardiomyopathy, diabetes, and implantation of an ICD (compared to 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 due to atrial tachyarrhythmia, occurred in 152 of 1500 patients (10.1%). Patients in the conventional programming arm received a higher frequency of both appropriate and inappropriate therapies than patients in the other two 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 3a). Increased risk of mortality was associated with the delivery of appropriate shock, inappropriate shock, and/or inappropriate ATP-only (Table 3a). No increased risk of mortality was found in the 112 patients who experienced appropriate ATP-only (Table 3a). The significant associations persisted after adjustment for programming arm and time-dependent pharmacotherapy (results not shown).
Over the course of the follow-up, a total of 7 inappropriate therapies (in 6 patients) induced VT/VF requiring appropriate device therapy. Three patients experienced such an induced VT/VF event in conventional arm, 3 in high-rate arm, and 1 in the delayed arm. None of these patients died during the trial.

Assessing the risk of mortality associated with ICD therapies by heart rate range revealed that inappropriate ICD therapy in the 170-199 bpm range was associated with a significantly increased risk of death, whereas appropriate ICD therapy in the same heart rate range had no associated mortality risk (Table 3b). The risk of mortality was increased in patients who experienced appropriate ICD therapy ≥200 bpm, although we were unable to show an increased risk of mortality with inappropriate ICD therapy ≥200 bpm (Table 3b).

Compared with first ICD events, multiple ICD therapies of the same type did not result in an additional increase in mortality risk considering either 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 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 4).

**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 (HR=2.52 [1.34-4.74], p=0.004) and the lack of ACE/ARB use (HR=2.59 [1.56-4.31], p<0.001) were associated with increased mortality risk. No other pharmacological treatment was significantly associated with mortality. No differential anti-
Arrhythmic 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-values: range=0.12-0.78). Importantly, the influence of ICD therapy on mortality was not altered when adjusting for time-dependent amiodarone and ACE/ARB 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 to 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 ACE/ARB (Table 5). A significant mortality risk was not present when comparing conventional programming to delayed programming (Table 5). The results were consistent when considering cardiac mortality (Table 5).

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 above mentioned parameters only 9 patients died, with equal distribution among the programming arms (3 events in each arm).

**Discussion**

In the MADIT-RIT trial, 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 to 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.\textsuperscript{23} 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/or life-threatening ventricular tachyarrhythmias, as previously suggested.\textsuperscript{9} However, inappropriate ATP and/or 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 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 non-cardiac deaths between the programming arms, and this was mostly due to cancer-related deaths as adjudicated by the Mortality Review Committee. Although an element of chance might be 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 170-199 bpm range potentially compromising their limited medical reserve.

Inappropriate ATP-only was very frequent in the conventional programming arm.\textsuperscript{23}
consistent with the increased risk of mortality associated with inappropriate therapy in the 170-199 bpm range. This association between inappropriate ATP and increased mortality risk was also reported in a recent sub-study of the MADIT-CRT trial. However, the mechanism by which inappropriate ATP, by itself, contributed to increased mortality risk is still unclear, since in both the current study and in MADIT-CRT trial, appropriate 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, since device interrogations revealed that the cumulative frequency of these arrhythmias in the 170-199 bpm 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.

Since MADIT-RIT was designed for analysis as two parallel trials, it is intriguing that both high-rate and delayed therapy intervention arms exhibited both a 75-80% lower incidence of first inappropriate therapy and also a 44-55% mortality reduction. Although the mortality difference was significant only for the conventional versus the high-rate programming arm, the results from the two arms are nevertheless mutually supportive. Moreover, the two-fold higher
cardiac mortality in the conventional programming arm compared to the other two 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, a randomized trial involving 1902 primary and secondary prevention patients with ICD therapy. They evaluated the use of prolonged (30 of 40) vs. 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 the MADIT-RIT trial, 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 two studies, as well as both the higher detection limit in the control group, and the shorter follow-up time in ADVANCE III as compared to MADIT-RIT, may explain the different findings regarding reduction in mortality between the two studies. Similar to MADIT-RIT, a trend toward mortality reduction was seen in the shock-reduction programming study PREPARE.

Study Limitations
Since 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 over a comparatively short follow-up period (1.4±0.6 years). This is evident from the p-value when comparing conventional programming to 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 two comparisons A vs. B and A vs. C, although
it would be very close to significant (significance limit accounting for two comparisons: p<0.025, actual p-value: p=0.032). Furthermore, by utilizing the conventional programming arm as common comparator there is a risk of confounding. Secondly, the ICD device memory capacity might have led to unavailability of electrograms for some repeat arrhythmia episodes due to overwriting.22 Third, even though 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, post-mortem interrogations were only available in 18 of 71 deaths (25%), which make it difficult to assess whether patients had ICD therapy prior to 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 to patients randomized to high-rate or delayed programming, which may have contributed to the mortality difference. As previously mentioned, the cancer patients may have less medical reserve due to their chronic illness and thus may be more vulnerable to the increased occurrence of adverse appropriate and inappropriate shocks in the conventional treatment arm.

**Conclusion**

In the MADIT-RIT study, 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 bpm, was associated with an increased risk of all-cause mortality as compared to ICD programming with a cut-off above 200 bpm, 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 to high-rate programming appears to be multifactorial with contributing risk factors including the higher frequency of inappropriate ATP-only therapies and inappropriate and unnecessary shock therapies in the 170-199 bpm range. In addition, there could be one or more 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.

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References:


Table 1: Clinical characteristics at baseline in patients who died compared to those who survived

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<thead>
<tr>
<th>Clinical Characteristics</th>
<th>Death  N=71</th>
<th>No Death  N=1429</th>
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<tbody>
<tr>
<td>Age at Time of Consent (years)</td>
<td>66±14</td>
<td>63±12*</td>
</tr>
<tr>
<td>Female</td>
<td>17(24)</td>
<td>419(29)</td>
</tr>
<tr>
<td>NYHA class III vs. class I-II</td>
<td>46(65)</td>
<td>734(52)*</td>
</tr>
<tr>
<td>Left ventricular ejection Fraction ≤ 25 %</td>
<td>43(61)</td>
<td>683(48)*</td>
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<tr>
<td>Body Mass Index (kg/m²)</td>
<td>29.5±9.0</td>
<td>29.3±6.7</td>
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<tr>
<td>Systolic Blood Pressure (mmHg)</td>
<td>120.8±21.5</td>
<td>123.7±19.1</td>
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<tr>
<td>Diastolic Blood Pressure (mmHg)</td>
<td>69.5±13.3</td>
<td>73.1±11.7*</td>
</tr>
<tr>
<td>Resting Heart Rate (beats per min.)</td>
<td>72.1±12.0</td>
<td>72.1±12.5</td>
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<tr>
<td>Conventional programming arm</td>
<td>34(48)</td>
<td>480(34)*</td>
</tr>
<tr>
<td>High-rate programming arm</td>
<td>16(23)</td>
<td>484(34)*</td>
</tr>
<tr>
<td>Delayed programming arm</td>
<td>21(30)</td>
<td>465(33)</td>
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<tr>
<td>Implanted Device Type: CRT-D (vs. ICD)</td>
<td>29(41)</td>
<td>728(51)</td>
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**Comorbidities at baseline**

<table>
<thead>
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<th>Comorbidities at baseline</th>
<th>Death  N=71</th>
<th>No Death  N=1429</th>
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</thead>
<tbody>
<tr>
<td>Ischemic cardiomyopathy</td>
<td>48(68)</td>
<td>743(52)*</td>
</tr>
<tr>
<td>Diabetes Mellitus</td>
<td>34(48)</td>
<td>451(32)*</td>
</tr>
<tr>
<td>Hypertension</td>
<td>51(73)</td>
<td>978(69)</td>
</tr>
<tr>
<td>Myocardial Infarction</td>
<td>35(50)</td>
<td>603(44)</td>
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<td>Currently Smoking</td>
<td>10(15)</td>
<td>237(18)</td>
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<td>History of Ventricular Arrhythmias</td>
<td>1(1)</td>
<td>47(3)</td>
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<tr>
<td>History of Atrial Arrhythmias</td>
<td>12(17)</td>
<td>191(13)</td>
</tr>
<tr>
<td>Non-CABG Revascularization</td>
<td>27(40)</td>
<td>428(30)</td>
</tr>
<tr>
<td>CABG Surgery</td>
<td>24(34)</td>
<td>344(24)</td>
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**Medication at baseline**

<table>
<thead>
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<th>Medication at baseline</th>
<th>Death  N=71</th>
<th>No Death  N=1429</th>
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<tbody>
<tr>
<td>Amiodarone</td>
<td>13(18)</td>
<td>83(6)*</td>
</tr>
<tr>
<td>ACE Inhibitor/ Angiotensin Receptor Blocker</td>
<td>58(82)</td>
<td>1254(88)</td>
</tr>
<tr>
<td>Beta-blocker</td>
<td>64(90)</td>
<td>1340(94)</td>
</tr>
<tr>
<td>Digitalis</td>
<td>15(21)</td>
<td>178(12)*</td>
</tr>
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<td>Aldosterone antagonist</td>
<td>30(42)</td>
<td>514(36)</td>
</tr>
<tr>
<td>Diuretic</td>
<td>55(77)</td>
<td>953(67)</td>
</tr>
<tr>
<td>Calcium Channel Blocker</td>
<td>4(6)</td>
<td>118(8)</td>
</tr>
<tr>
<td>Statins</td>
<td>41(58)</td>
<td>838(59)</td>
</tr>
</tbody>
</table>

Values are presented as mean ± SD or frequencies with percentages in parenthesis.  
* p<0.05  
CABG = coronary artery bypass graft surgery, CRT-D = Cardiac Resynchronization Therapy Defibrillator, ICD = Implantable Cardioverter Defibrillator
Table 2. Baseline clinical characteristics associated with mortality*

<table>
<thead>
<tr>
<th></th>
<th>Hazard ratios</th>
<th>95 % confidence interval</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Implanted device (ICD:CRT-D)</td>
<td>2.66</td>
<td>1.53-4.62</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>NYHA class III vs. Class I-II</td>
<td>2.50</td>
<td>1.42-4.37</td>
<td>0.001</td>
</tr>
<tr>
<td>Ischemic cardiomyopathy</td>
<td>1.76</td>
<td>1.04-3.00</td>
<td>0.036</td>
</tr>
<tr>
<td>Lower ejection fraction (per 10 % reduction)</td>
<td>1.74</td>
<td>1.25-2.43</td>
<td>0.001</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1.64</td>
<td>1.02-2.65</td>
<td>0.043</td>
</tr>
<tr>
<td>Increasing age (per decade)</td>
<td>1.36</td>
<td>1.08-1.72</td>
<td>0.009</td>
</tr>
<tr>
<td>Lower diastolic blood pressure (per 10 mmHg decrease)</td>
<td>1.28</td>
<td>1.03-1.60</td>
<td>0.029</td>
</tr>
</tbody>
</table>

* Based on a multivariate Cox model, with these seven covariates identified by best subset regression, setting the limit for entry into the model at p<0.05.
ICD = Implantable Cardioverter Defibrillator, CRT-D = Cardiac Resynchronization Therapy with Defibrillator, NYHA= New York Heart Association.
**Table 3a:** Influence of ICD therapy on the risk of mortality

<table>
<thead>
<tr>
<th></th>
<th>Deaths/Total patients with the specific ICD therapy</th>
<th>Hazard ratios</th>
<th>95% confidence interval</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Overall inappropriate</strong></td>
<td>10/152</td>
<td>2.61</td>
<td>1.28-5.31</td>
<td>0.008</td>
</tr>
<tr>
<td>therapy</td>
<td></td>
<td></td>
<td></td>
<td></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><strong>Overall appropriate</strong></td>
<td>15/186</td>
<td>2.66</td>
<td>1.45-4.88</td>
<td>0.002</td>
</tr>
<tr>
<td>therapy</td>
<td></td>
<td></td>
<td></td>
<td></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, ischemic cardiomyopathy, NYHA class III compared to lower NYHA class and implanted device (ICD/CRT-D)

**Table 3b:** Influence of ICD therapy by different heart rate ranges on mortality

<table>
<thead>
<tr>
<th></th>
<th>Deaths/Total patients with the specific ICD therapy</th>
<th>Hazard ratio</th>
<th>95% confidence interval</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inappropriate therapy 170-199 bpm</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 bpm</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 bpm</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 bpm</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, ischemic cardiomyopathy, NYHA class III compared to lower NYHA class and implanted device (ICD/CRT-D)
Table 4: Frequency of different ICD Therapies per Treated Episode

<table>
<thead>
<tr>
<th>Variable</th>
<th>Total episodes</th>
<th>Mean therapies±standard deviation</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>

IQR= inter-quartile range, ATP=anti-tachycardia pacing

Table 5: 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></td>
<td>Hazard ratios</td>
<td>95% confidence interval</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.

All-Cause mortality: adjusted for age, left ventricular ejection fraction, diastolic blood pressure, diabetes, ischemic cardiomyopathy, NYHA class III compared to lower NYHA classes, implanted device (ICD/CRT-D), time-dependent appropriate and inappropriate ICD therapies, and time-dependent amiodarone usage and lack of ACE/ARB usage.

Cardiac mortality: adjusted for left ventricular ejection fraction, diastolic blood pressure, ischemic cardiomyopathy, time-dependent appropriate and inappropriate ICD therapies, and time-dependent amiodarone usage and lack of ACE/ARB usage.

Time-dependent variables represent the risk-time in on/off medication/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.
Figure Legends:

**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 sub-division into cardiac, non-cardiac and unknown cause of death.

**Figure 2:** Deaths in different programming arms according to prior ICD therapy. Bar-chart showing the number of patients who died with or without antecedent ICD therapies by programming arm.
The bar chart shows the distribution of cause-specific deaths across different treatment groups:

- **All-cause death**:
  - Conventional therapy: 34
  - High-Rate therapy: 16
  - Delayed therapy: 21

- **Cardiac death**:
  - Conventional therapy: 20
  - High-Rate therapy: 10
  - Delayed therapy: 10

- **Non-cardiac death**:
  - Conventional therapy: 7
  - High-Rate therapy: 4
  - Delayed therapy: 3

- **Unknown death**:
  - Conventional therapy: 3
  - High-Rate therapy: 6
  - Delayed therapy: 6

- **All Non-Cardiac death**
  - Conventional therapy: 13
  - High-Rate therapy: 2
  - Delayed therapy: 8

Categories for non-cardiac deaths include:

- Cancer
- Vascular
- Infection
- Other

**Other**

- Conventional therapy: 4
- High-Rate therapy: 0
- Delayed therapy: 2

**Unknown Cause**

- Conventional therapy: 1
- High-Rate therapy: 4
- Delayed therapy: 3
Mortality Reduction In Relation To ICD Programming In MADIT-RIT
Anne-Christine Ruwald, Claudio Schuger, Arthur J. Moss, Valentina Kutyifa, Brian Olshansky, Henry Greenberg, David S. Cannom, N.A. Mark Estes III, Martin H. Ruwald, David T. Huang, Helmut Klein, Scott McNitt, Christopher A. Beck, Robert Goldstein, Mary W. Brown, Josef Kautzner, Morio Shoda, David Wilber, Wojciech Zareba and James P. Daubert

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