Implantable cardioverter-defibrillator programming after first occurrence of ventricular tachycardia in the Multicenter Automatic Defibrillator Implantation Trial—Reduce Inappropriate Therapy (MADIT-RIT)

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BACKGROUND Implantable cardioverter-defibrillator (ICD) programming to novel settings can reduce the risk of inappropriate therapies.

OBJECTIVE The purpose of this study was to evaluate the impact of novel ICD programming after the first occurrence of ventricular tachycardia (VT).

METHODS In MADIT-RIT (Multicenter Automatic Defibrillator Implantation Trial—Reduce Inappropriate Therapy) patients who experienced a first occurrence of VT, the risk of subsequent inappropriate and appropriate ICD therapies and adverse cardiovascular events by ICD programming to Arm A (conventional: VT ≥170 bpm), Arm B (high rate: VT ≥200 bpm), or Arm C (duration delay: ≥60-second delay before therapy ≥170 bpm) was determined.

RESULTS Among 205 patients, ICD programming changes were made in 30 patients (15%) after they experienced a VT episode; 117 patients (57%) were programmed to Arm A settings and 88 patients (43%) to Arm B/C settings. At 15-month follow-up, the cumulative probability of inappropriate ICD therapy was significantly lower in Arm B/C compared to Arm A (9% vs 20%; log-rank P = .029 for overall difference). The rate of appropriate ICD therapy also was significantly lower in Arm B/C compared to Arm A (32% vs 64%; log-rank P = .001 for overall difference). Multivariate analysis showed that patients programmed to Arm B/C after the occurrence of VT had a 71% reduction (P = .02) in the risk of inappropriate ICD therapies and a 43% reduction (P = .02) in the risk of appropriate ICD therapies compared to Arm A.

CONCLUSION The benefit of high-rate cutoff or duration delay settings in patients with an ICD is maintained after the first occurrence of VT.

KEYWORDS Heart failure; Implantable cardioverter-defibrillator programming; Implantable cardioverter-defibrillator shock; Inappropriate implantable cardioverter-defibrillator shock; Ventricular tachycardia

Introduction

Placement of an implantable cardioverter-defibrillator (ICD) for primary prevention of fatal ventricular arrhythmias in patients having heart failure with reduced ejection fraction (HFrEF) is the standard of care.1,2 However, the benefits of primary prevention are balanced with the risk of inappropriate ICD therapy. Novel ICD programming schemes in MADIT-RIT (Multicenter Automatic Defibrillator Implantation Trial—Reduce Inappropriate Therapy) demonstrated a significant reduction in inappropriate therapies in patients programmed to high-rate cutoff or duration delay compared to conventional programming.3 Frequent ICD therapies, whether or not appropriate, are associated with worse outcomes, particularly in patients with HFrEF.4 Reduction in inappropriate therapies has been demonstrated to be associated with a reduction in major cardiac events, hospitalization, and death. As a result of the MADIT-RIT findings and other published data,5,6 recommendations for initial programming of primary prevention ICD have transitioned from low-rate,
short-duration cutoffs to high-rate, prolonged-duration cutoffs. However, data on optimal ICD settings after the first occurrence of ventricular tachycardia (VT) or ventricular fibrillation (VF) in patients implanted for a primary prevention indication are limited.

In this MADIT-RIT substudy, we aimed to determine the frequency and nature of ICD programming changes made after the first occurrence of VT and to identify the impact of ICD programming changes on the subsequent risk of appropriate ICD therapies, inappropriate ICD therapies, and adverse events.

Methods

Study population

The design and primary results of MADIT-RIT have been published previously. In brief, the study enrolled 1500 patients in 98 centers from the United States, Canada, Europe, Israel, and Japan. All patients met guideline criteria to receive an ICD or cardiac resynchronization therapy with defibrillator (CRT-D) device for primary prevention of sudden cardiac death. Patients were excluded if they were younger than 21 years, had recently experienced a myocardial infarction or undergone a revascularization procedure (within 3 months), had permanent atrial fibrillation, or had previously been implanted with a pacemaker or ICD. Patients were randomized to 1 of 3 ICD programming schemes—conventional therapy (Arm A: VT zone ≥170 bpm); high-rate therapy (Arm B: VT zone ≥200 bpm); or duration delay (Arm C: 60-second delay before therapy ≥170 bpm)—for the detection and initiation of therapy for VT or VF. The present study population comprised 205 (14%) of the 1500 MADIT-RIT patients who either had sustained VT ≥170 bpm for at least 30 seconds or had received their first ICD therapy for VT after enrollment in the trial. The study was approved by the institutional review board at each site before participation. All patients provided informed consent before enrollment.

Programming during follow-up

For each patient, initial and all subsequent VT events and ICD programming were reviewed and adjudicated. After the detection or treatment of sustained of VT, all ICD programming changes were adjudicated by 2 study investigators (MA, AB) who were blinded to subsequent arrhythmic and clinical outcomes. Changes were classified as being “A-like,” “B-like,” or “C-like” based on the nature of the change in ICD programming. Changes to rhythm detection algorithms, antitachycardia pacing (ATP) attempts, ATP duration, and/or energy required for defibrillation were not considered substantial enough to reclassify programming. “A-like” programming was identified in 2 possible scenarios: (1) when programming initially assigned to Arm A remained substantially unchanged; and/or (2) when the post-VT changes made in baseline programming were made in a manner consistent with lower-rate cutoffs for VT zone detection and/or VT duration ≥2.5 seconds. Programming changes were identified as “B-like” in 2 possible scenarios: (1) when programming initially was assigned to Arm B and remained substantially unchanged; and/or (2) when post-VT changes made in baseline programming were consistent with the goal of high-rate cutoff for therapy (VT zone ≥200 bpm). “C-like” programming was identified in 2 possible scenarios: (1) when programming initially assigned to Arm C remained substantially unchanged; and/or (2) when post-VT changes made in baseline programming were consistent with the goal of similar or prolonged duration-delay cutoff for therapy with lower rate detection (VT zone ≥170 bpm and duration delay ≥60 seconds).

Given the known benefits of programming ICD to Arm B or C over Arm A, in the primary analysis of the study we combined Arms B and C and compared outcomes in the combined A/B group of novel ICD programming to conventional ICD programming in Arm A.

Interrogation and follow-up

Patients were followed every 3 months in the first year and every 6 months thereafter until trial termination on July 10, 2012. During each visit, a physical examination and device interrogation were carried out. Device reprogramming was left to the physician’s discretion after the first inappropriate or appropriate ICD therapy. Clinical and ICD interrogation data were sent to the study Coordination and Data Center at the University of Rochester, New York. Episodes from device interrogations were independently
reviewed by the interrogation adjudication committee blinded to the programming arm.

Endpoints and definitions
The diagnosis of detected arrhythmias after enrollment in the trial was determined by an adjudication committee that evaluated documented arrhythmias from device electrograms. Arrhythmia events detected by the ICD and CRT-D devices were categorized as appropriate and inappropriate. The first occurrence of VT was defined as sustained VT $\geq 170$ bpm or any ICD-treated VT.

The primary endpoint of the present study was the first occurrence of inappropriate ICD therapy, with follow-up beginning 1 day after the VT event. Secondary endpoints were (1) the risk for appropriate ICD therapy and (2) the risk for adverse cardiovascular events, defined as a composite of heart failure (HF) hospitalization, syncope, or death.

Statistical analysis
Continuous variables are expressed as mean $\pm$ SD. Categorical data are summarized as frequency and percentage. Baseline clinical characteristics were compared between patients in the conventional ICD programming arm vs those in the novel ICD programming arm using the Wilcoxon ranked sum test for continuous variables and the $\chi^2$ test for dichotomous variables, as appropriate.

Cumulative probability of inappropriate and appropriate ICD therapies as well as probability of adverse events are displayed according to the Kaplan-Meier method, with follow-up starting 1 day after the first detected or treated VT event in a landmark analysis, with comparisons of cumulative event rates by the log-rank test. Pointwise 95% confidence intervals based on log-log transformation were calculated and displayed on the Kaplan-Meier curves.

Multivariate Cox proportional hazards regression analysis was used to identify and evaluate the impact of ICD programming after the occurrence of a first VT episode on appropriate ICD therapies, inappropriate ICD therapies, and adverse cardiovascular events, with follow-up starting 1 day after the first detected or treated VT event. The Cox model was adjusted for relevant clinical covariates. A separate sensitivity analysis was performed with multivariate Fine and Gray regression analysis, accounting for the competing risk of death for the endpoints of inappropriate and appropriate therapy.

All statistical tests were 2-sided, and $P < .05$ was considered significant. Analyses were performed using SAS software (Version 9.4; SAS Institute, Cary, NC).

### Results
After the development of either monitored or treated sustained VT, ICD programming changes were made in 30 of the 205 study patients (15%) (Table 1). With these changes to ICD programming, 117 patients (57%) in the study cohort had Arm A settings, 54 (26%) had Arm B settings, and 34 (17%) had Arm C ICD settings. Table 2 lists the baseline characteristics of patients programmed to Arm A ICD settings compared to those programmed to Arm B/C settings. Patients in Arm B/C had a significantly higher number of VT episodes that were monitored compared to patients in Arm A. No significant differences in baseline clinical characteristics were noted between the 2 groups, except for current smoking, which was more frequent in patients programmed to Arm A (Table 2).

#### Inappropriate defibrillator therapy (ATP or shock)
During mean follow-up of $12 \pm 7$ months after ICD reprogramming due to treated or monitored VT, 26 patients (13%) had inappropriate ICD therapy subsequent to the index VT event. At 15-month follow-up, the cumulative probability of inappropriate ICD therapy was 9% in Arm B/C and was...
appropriate implantable cardioverter-defibrillator therapy with 95% pointwise confidence intervals among patients programmed to Arm A compared to Arm B/C.

significantly higher in Arm A (20%; log-rank \( P = .029 \) for overall comparison) (Figure 1).

Consistently, Cox proportional hazards regression analysis showed that patients programmed to Arm B/C experienced a significant 71% reduction (\( P = .02 \)) in the subsequent risk of inappropriate ICD therapies compared to patients programmed to Arm A (Table 3).

Appropriate defibrillator therapy (ATP or shock)
During the study period, 87 patients (42%) experienced a ventricular tachyarrhythmia event requiring ICD therapy subsequent to the index VT event. At 15 months, the cumulative probability of first appropriate ICD therapy was significantly lower in patients programmed to Arm B/C settings (32%) compared to those programmed to Arm A settings (64%; log-rank \( P = .001 \) for overall difference during follow-up) (Figure 2).

Multivariate Cox proportional hazards regression analysis confirmed that patients programmed to Arm B/C settings experienced a significant 43% reduction (\( P = .021 \)) in the subsequent risk of appropriate ICD therapies compared to patients programmed to Arm A settings (Table 3).

| Endpoint                        | Hazard ratio | 95% Confidence interval | \( P \) value |
|---------------------------------|--------------|--------------------------|---------------|
| Inappropriate therapy           | 0.29         | 0.09–0.845               | .02*          |
| Appropriate therapy             | 0.57         | 0.36–0.92                | .02*          |
| Adverse cardiovascular events   | 1.13         | 0.75–1.72                | .57           |

Variables included in the model were gender, New York Heart Association functional class, and ischemic etiology of heart failure.

ICD = implantable cardioverter-defibrillator.

*\( P < .05 \) statistically significant.

When multivariate Fine and Gray analysis was used to account for the competing risk of death, consistent results were obtained, most likely due to the very low death rate observed in both treatment groups.

Adverse cardiovascular events
Figure 3 shows the cumulative probability of adverse cardiovascular events between the 2 ICD programming groups. No significant differences in the rate of adverse events were observed in patients during 15-month follow-up.

Consistently, no difference in the risk of adverse cardiovascular events was observed between the programming groups after adjusting for multiple clinical covariates (Table 3).

Discussion
The present study has important clinical implications regarding device programming after the first occurrence of VT among patients implanted with an ICD for primary prevention of sudden cardiac death. First, patients programmed to high-rate cutoff or duration delay settings had a significantly lower risk for inappropriate ICD therapies compared to patients whose ICD was programmed to conventional settings. Second, patients programmed to high-rate cutoff or duration delay settings also were at a significantly lower risk for subsequent appropriate ICD therapies compared to patients in the conventional ICD programming arm. Finally, the risk of adverse cardiovascular events consisting of HF hospitalization, syncope, or death was similar between patients programmed to novel ICD settings and those programmed to conventional ICD settings. These findings suggest that the benefit of high-rate cutoff or duration delay settings in patients with an ICD implanted for primary prevention may apply after the first occurrence of VT.

Most ICDs implanted today are for primary prevention of sudden cardiac death. Once such patients experience an appropriate ICD therapy for VT, clinicians often choose to maintain the ICD programming settings given that successful therapy was delivered. To date, optimal ICD programming in this clinical circumstance has not been studied or defined. Our study demonstrates that a significant reduction in appropriate as well as inappropriate ICD therapies can be achieved with novel ICD programming, that is, when ICDs are programmed to either high-rate cutoff or duration delay settings. The findings are consistent with the primary results from MADIT-RIT\(^3\) that novel ICD programming is preferable to conventional programming even in a high-risk cohort of patients who experienced a ventricular tachyarrhythmic event.

A common concern is that delay in appropriate ICD therapy may lead to untoward symptoms, including syncope, HF decompensation, and increased mortality. Nearly 40% of patients in Arm B/C of our study had VT lasting \( \geq 30 \) seconds. Clinicians treating such patients
may be inclined to reprogram detection zones in order to provide ICD therapies to treat such sustained VT episodes. However, our study shows that maintaining high-rate cutoff or duration delay settings does not lead to an excess risk of syncope, HF hospitalization, or all-cause mortality. The practice of tailoring and programming of secondary prevention ICD settings varies widely, and several methods may be used as guidance for reprogramming after VT. Ideal ICD programming settings should follow several key tenants: minimization of patient symptoms, enhanced appropriate intervention, and minimization of inappropriate therapies without compromising morbidity or mortality. In a substudy of the PainFree SST (Pacing Fast Ventricular Tachycardia Reduces Shock Therapies—SmartShock Technology) trial, the impact of prolonged detection (30/40 intervals) was compared to standard detection (18/24 intervals) in patients receiving a secondary prevention ICD. Freedom from all-cause syncope was 96% in both detection arms, and a trend toward lower mortality was observed in the prolonged detection arm. These findings along with the observations from our study support the safe use of novel ICD programming parameters that allow for lenient detection of VT.

The 2015 HRS/EHRA/APHRS/SOLAECE (Heart Rhythm Society/European Heart Rhythm Association/Asian Pacific Heart Rhythm Society/Sociedad Latinoamericana de Estimulacion Cardiaca y Electrofisiologia) expert consensus statement on optimal implantable cardioverter-defibrillator programming and testing offers recommendations for settings for patients with primary and secondary prevention ICDs. However, the specific case of patients initially implanted with a primary prevention ICD who subsequently experience VT is not addressed in that document. In a substudy of the Avoid Delivering Therapies for Nonsustained Arrhythmias in ICD Patients III (ADVANCE-III) trial, 477 patients with a secondary prevention ICD were randomized to either nominal VT detection consisting of 18–24 intervals or long detection consisting of 30–40 intervals. During a 12-month follow-up period, a significant 25% reduction in overall ICD therapies was observed in the long detection arm. Although ADVANCE-III included patients with secondary prevention ICDs, when combined with our findings, our study lends additional support to the recommendation of programming ICDs that allow for delay in therapy even after detection of an initial VT event.

**Study limitations**

First, the analysis performed was a post hoc secondary analysis of the data obtained to evaluate the primary endpoint of the main trial; therefore, our study has inherent bias related to post hoc analysis. Second, ICD programming changes after the first occurrence of VT were not made in a randomized fashion but instead were left to the discretion of the treating physician; therefore, it is possible that unmeasured factors may have influenced the observed results. Third, the population of patients enrolled in the trial consisted of HF patients who were treated with optimal medical therapy and who had mean left ventricular ejection fraction of 25%; therefore, the results of our study may not apply to patients with more advanced HF and more severe left ventricular dysfunction. Fourth, given that the primary results of MADIT-RIT showed similar results for patients in Arms B and C, we combined these 2 arms and compared Arm B/C to Arm A in order to facilitate analysis in this study. Subgroup analysis on the impact of high-rate cutoff (Arm B) vs duration delay (Arm C) separately showed consistent results (15-month rates of inappropriate ICD therapies in Arms A, B, and C of 27%, 13%, and 0%, respectively) but is limited by sample size and therefore should be interpreted with caution. Fifth, the observed wide confidence interval in the multivariate analysis for the endpoint of adverse cardiovascular events...
suggests uncertainty regarding the potential risk associated with ICD programming in Arm B/C compared to Arm A. Finally, we adjusted our multivariate models for relevant covariates; however, unmeasured confounders may have not been taken into consideration.

**Conclusion**

This study showed that in HFrEF patients who undergo implant of a primary prevention ICD or CRT-D and develop sustained VT, a significant reduction in the risk of subsequent appropriate and inappropriate ICD therapies is seen when ICDs are reprogrammed to high-rate cutoff or duration delay settings.

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