3-1-2021

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Reassessing the role of antitachycardia pacing in fast ventricular arrhythmias in primary prevention implantable cardioverter-defibrillator recipients: Results from MADIT-RIT

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BACKGROUND In Multicenter Automatic Defibrillator Implantation Trial – Reduce Inappropriate Therapy (MADIT-RIT), high-rate cutoff (arm B) and delayed therapy (arm C) reduced the risk of inappropriate implantable cardioverter-defibrillator (ICD) interventions when compared with conventional programming (arm A); however, appropriate but unnecessary therapies were not evaluated.

OBJECTIVE The purpose of this study was to assess the value of antitachycardia pacing (ATP) for fast ventricular arrhythmias (VAs) $\geq$ 200 beats/min in patients with primary prevention ICD.

METHODS We compared ATP only, ATP and shock, and shock only rates in patients in MADIT-RIT treated for VAs $\geq$ 200 beats/min. The only difference between these randomized groups was the *time delay* between ventricular tachycardia detection and therapy (3.4 seconds vs 4.9 seconds vs 14.4 seconds).

RESULTS In arm A, 11.5% patients had events, the initial therapy was ATP in 10.5% and shock in 1%, and the final therapy was ATP in 8% and shock in 3.5%. In arm B, 6.6% had events, 4.2% were initially treated with ATP and 2.4% with shock, and the final therapy was ATP in 2.8% and shock in 3.8%. In arm C, 4.7% had events, 2.5% were initially treated with ATP and 2.3% with shock, and the final therapy was ATP in 1.4% and shock in 3.3%. The final shock rate was similar in arm A vs arm B (3.5% vs 3.8%; $P = .800$) and in arm A vs arm C (3.5% vs 3.3%; $P = .855$) despite the marked discrepancy in initial ATP therapy utilization.

CONCLUSION In MADIT-RIT, there was a significant reduction in ATP interventions with therapy delays due to spontaneous termination, with no difference in shock therapies, suggesting that earlier interventions for VAs $\geq$ 200 beats/min are likely unnecessary, leading to an overestimation of the value of ATP in primary prevention ICD recipients.

KEYWORDS Antitachycardia pacing therapy; ICD; Ventricular arrhythmia; Ventricular fibrillation; Ventricular tachycardia

(Heart Rhythm 2021;18:399–403)

Introduction

Data from multiple randomized controlled clinical trials, registries, and observational studies indicate that patients at risk for sudden cardiac death with reduced left ventricular ejection fraction and heart failure derive a survival benefit from implantable cardioverter-defibrillators (ICDs), either alone or in conjunction with cardiac resynchronization therapy (CRT). However, the occurrence of supraventricular arrhythmias such as atrial fibrillation or flutter or non–life-threatening, nonsustained ventricular tachycardias (VTs) may result in either inappropriate therapy or prematurely applied, unnecessary therapy and is a direct consequence of specific device parameter programming.[1,2] Inappropriate or premature ICD interventions have previously been shown to be

Funding sources: The 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: Dr Schuger reports honoraria for advisory board and event committees from Boston Scientific and Medtronic. Dr Daubert reports honoraria for advisory boards, events committees, and lectures from Medtronic, Boston Scientific, Abbott, MicroPort, Biotronik, Biosense Webster, Farrapulse, and VytronUS. Dr Kutyifa reports research grants from Boston Scientific, ZOLL, and Biotronik and consultant fees from Boston Scientific and ZOLL. The rest of the authors report no conflicts of interest. **Address reprint requests and correspondence:** Dr Claudio Schuger, Department of Cardiac Electrophysiology, Henry Ford Heart & Vascular Institute, 2799 W Grand Blvd, Detroit, MI 48202. E-mail address: cschuge1@hfhs.org.

1547-5271/

https://doi.org/10.1016/j.hrthm.2020.11.019

associated with an impaired quality of life[3,4] and potentially an increased risk of all-cause mortality.[1,5]

The Multicenter Automatic Defibrillator Implantation Trial – Reduce Inappropriate Therapy (MADIT-RIT) trial is a large-scale randomized study designed to evaluate novel ICD programming to reduce *inappropriate* therapy in patients with primary prevention ICD or CRT-D. MADIT-RIT compared conventional ICD programming with either high-rate therapy or long delay before therapy delivery and showed that both high-rate cutoff programming and delayed therapy is associated with a significant reduction in inappropriate ICD therapy.[6,7]

In this secondary analysis of MADIT-RIT, we aimed to characterize the rates of different types of *appropriate* therapies (antitachycardia pacing [ATP], shock, or both) for adjudicated ventricular arrhythmias (VAs) at or above 200 beats/min by programming arm, rates at which the only difference between the therapy groups is the *time delay* between VT detection and therapy. We hypothesized that progressively longer delays will result in a reduction in the number of appropriate ICD therapies, whether ATP or shock, because of the self-terminating nature of many fast VAs, rendering early interventions premature and potentially unnecessary.

Methods

Study population

MADIT-RIT was a multicenter, randomized, prospective, controlled clinical trial evaluating patients with approved indications for primary prevention ICD or CRT.[8,9] The trial design and results had been published previously.[6,7] MADIT-RIT was approved by the institutional review boards at the participating centers in accordance with the guidelines of the Declaration of Helsinki. Briefly, patients were randomized to standard ICD programming $\geq$ 170 beats/min ("arm A"), a high-rate therapy cutoff $\geq$ 200 beats/min programming strategy ("arm B"), or a prolonged detection duration (60 seconds $\geq$170 beats/min and 12 seconds $\geq$200 beats/min) strategy ("arm C") after a successful implantation of a dual-chamber ICD or CRT-D device (Table 1). The primary end point of the study was time to *first inappropriate* ICD therapy (either ATP and/or shock). MADIT-RIT enrolled 1500 patients, 21 years or older, with ischemic or nonischemic systolic heart failure. All patients met the guideline criteria for implantation of primary prevention of ICD or CRT-D.[8,9]

MADIT-RIT was not prospectively designed to assess the role of high-rate cutoff programming or therapy delay programming in the frequency of *appropriate* ICD therapies only; however, because of an extensive adjudication process of all device interventions, we were able to retrospectively analyze the behavior of all therapy modalities in VAs above 200 beats/min that received a therapeutic intervention.

Definitions and study end points

During the total study duration, *first appropriate* ICD therapy event information was collected from device interrogations and adjudicated by an independent panel according to prespecified criteria.[7] *Appropriate therapy* was defined as any therapy (ATP, shock, or both) delivered for any VAs. Only episodes with available intracardiac electrograms were included for appropriate adjudication. Given the memory limitations of all ICDs, the arrhythmic events are stored chronologically in such a way that the electrograms of prior events may sometimes be erased from the device memory to allow the display of the most recent events.

In this analysis, we evaluated the rates of *first appropriate therapy* $\geq$ 200 beats/min treated with an ATP only, ATP and shock, and shock only, stratified by ICD programming arm. Because we eliminated all VAs events $<$ 200 beats/min, the only programming difference across the 3 ICD programming arms was therapy delay (Table 1).

Statistical analysis

First appropriate ICD therapy events $\geq$ 200 beats/min treated with ATP only, ATP and shock, and shock only are reported as frequencies and percentages. The rates of first appropriate ATP only and ATP and shock for VAs events $\geq$ 200 beats/min were displayed by programming arm A (conventional) vs arm B (high-rate cutoff) vs arm C (delayed therapy programming).

Comparisons of first appropriate ATP only and ATP and shock for VAs events $\geq$ 200 beats/min were performed between conventional arm A vs high-rate arm B and between conventional arm A vs delayed therapy arm C by using the χ^2 test for dichotomous variables. Dichotomous variables, as two separate tests, since the original study design aimed to compare these 2 ICD programming arms separately.

All statistical tests were 2-sided, and a P value of $<$.05 was considered statistically significant. Analyses were performed with SAS version 9.4 (SAS institute, Cary, NC).

Results

MADIT-RIT was a large-scale and well-balanced randomized clinical trial with no significant differences between

Table 1 Programming arms in MADIT-RIT for ventricular arrhythmias $>$ 200 beats/min

Arm A (conventional)	Arm B (high-rate cutoff)	Arm C (therapy delay)
VF zone $\geq$200 beats/min, 1 s delay	VF zone $\geq$200 beats/min, 2.5 s delay	VF zone $\geq$200 beats/min, 12 s delay $\geq$250 beats/min, 2.5 s delay
Quick convert ATP Shock	Quick convert ATP Shock	Quick convert ATP Shock

ATP = antitachycardia pacing; MADIT-RIT = Multicenter Automatic Defibrillator Implantation Trial – Reduce Inappropriate Therapy; VF = ventricular fibrillation.

Table 2 First appropriate ICD therapy delivered by MADIT-RIT ICD programming arm for ventricular arrhythmias ≥ 200 beats/min

Randomized arm	Conventional therapy (n = 514)	High-rate therapy (n = 500)	Delayed therapy (n = 486)	*P*
Delay before ATP delivery after detection	1 s	2.5 s	12 s	
First episode—*shock* (ATP + shock, shock alone)	18 (3.5%)	19 (3.8%)	16 (3.3%)	.910
Shock for rate ≥ 250 beats/min	5 (1.0%)	12 (2.4%)	11 (2.3%)	.178
Shock for failed appropriate ATP	13 (2.5%)	7 (1.4%)	5 (1.0%)	=.153
First episode—*ATP* alone	54 (10.5%)	21 (4.2%)	12 (2.5%)	<.0001
Total first episode	*59 (11.5%)*	*33 (6.6%)*	*23 (4.7%)*	*.0002*

ATP = antitachycardia pacing; ICD = implantable cardioverter-defibrillator; MADIT-RIT = Multicenter Automatic Defibrillator Implantation Trial – Reduce Inappropriate Therapy.

patient clinical characteristics across the different ICD programming arms.[6] In this analysis, we evaluated only VAs events ≥ 200 beats/min for which the only programming difference across the 3 ICD programming arms was therapy delay (Table 1).

Rates of ATP only, ATP and shock, and shock only appropriate therapy events ≥ 200 beats/min

In MADIT-RIT *arm A* with conventional ICD programming, 59 patients (11.5%) had VAs ≥ 200 beats/min; 54 of them (10.5%) were initially treated with ATP and 5 of them (1%) with shock (VAs ≥ 250 beats/min at onset). The *final therapy*, defined as the therapy modality preceding the return to normal rhythm, was ATP in 41 patients (8%) and shock in 18 patients (3.5%). In *arm B*, 33 patients (6.6%) had VAs ≥ 200 beats/min; 21 (4.2%) were initially treated with ATP and 12 (2.4%) with shock (VAs ≥ 250 beats/min at onset). The final therapy was ATP in 14 patients (2.8%) and shock in 19 patients (3.8%). In *arm C*, 23 patients (4.7%) had VAs ≥ 200 beats/min; 12 (2.5%) were initially treated with ATP and 11 (2.3%) with shock (VAs ≥ 250 beats/min at onset). The final therapy was ATP in 7 patients (1.4%) and shock in 16 patients (3.3%). The final shock event rate was similar, 3.5%, 3.8%, and 3.3%, in arms A, B, and C, while ATP therapy was significantly reduced between therapy arms, revealing the influence of incrementally delayed therapy on the incidence of ATP delivery (Table 2 and Figure 1).

The proportion of patients who received an appropriate ICD therapy for VAs ≥ 200 beats/min in MADIT-RIT was reduced by up to 62% when comparing the conventional ICD programming arm (arm A) with the delayed therapy ICD programming arm (arm C). When analyzed by the 2 types of ICD therapy, we find that this decrease was driven almost entirely by a 78% reduction in the delivery of ATP. Because MADIT-RIT was a large and well-balanced randomized study, this outcome is likely the result of longer therapy delays across study arms, allowing even longer "non-sustained" VAs to self-terminate before therapy delivery as illustrated in Figure 2.

Moreover, it is interesting to note that the apparent ATP efficacy across ICD programming arms in MADIT-RIT appears to decrease (Figure 2). In arm A, the ATP success rate is 75.9% (41 of 54 events); in arm B, it is 66.7% (14 of 21 events); and in arm C, it is 58.3% (7 of 12 events). Since ATP was applied in some VAs that were destined to self-terminate as mentioned above, the perceived efficacy of ATP in patients with primary prevention ICD may be overstated as well when applied prematurely.

Discussion

In this retrospective analysis of the MADIT-RIT cohort with appropriate therapies at or above 200 beats/min, we clearly demonstrated that increasing therapy delays resulted in marked reductions in the utilization of ATP therapies as the time to therapy was increased from 3.4 seconds (arm A) to 4.9 seconds (arm B) to 14.4 seconds (arm C). Furthermore, the 2 types of ICD therapies (ATP or shock) revealed that the incidence of appropriate shocks delivered for VAs ≥ 200 beats/min was similar across all 3 arms with no significant differences. The incidence of appropriate ATP in the conventional ICD programming arm was 18% compared with 5% in those with high-rate therapy programming and 2% in those with delayed therapy programming. These findings altogether suggest a limited value of ATP for treating fast VAs ≥ 200 beats/min with longer detection delays in a population with primary prevention ICD as opposed to high ATP efficacy in populations with secondary prevention.[4]

The only plausible explanation for the above observations is that as therapy delay is increased, many of the VAs self-terminate. The importance of this observation is 2-fold: (1) The value of ATP effectiveness in a *population with primary prevention* could be overestimated in light that with long therapy delays, many VAs are in fact self-terminating without an ATP intervention. (2) Relatively long therapy delays are well tolerated without an increase in cardiovascular morbidity while enormously reducing the frequency of unnecessary interventions, mainly ATP.

Interestingly, an analysis of mortality in MADIT-RIT[10] revealed a statistically significant association between inappropriate ATP and all-cause mortality while no association was found between appropriate ATP and all-cause mortality. However, an association does not necessarily imply causality, and further investigation into ATP and its value in a population with primary prevention ICD is warranted.

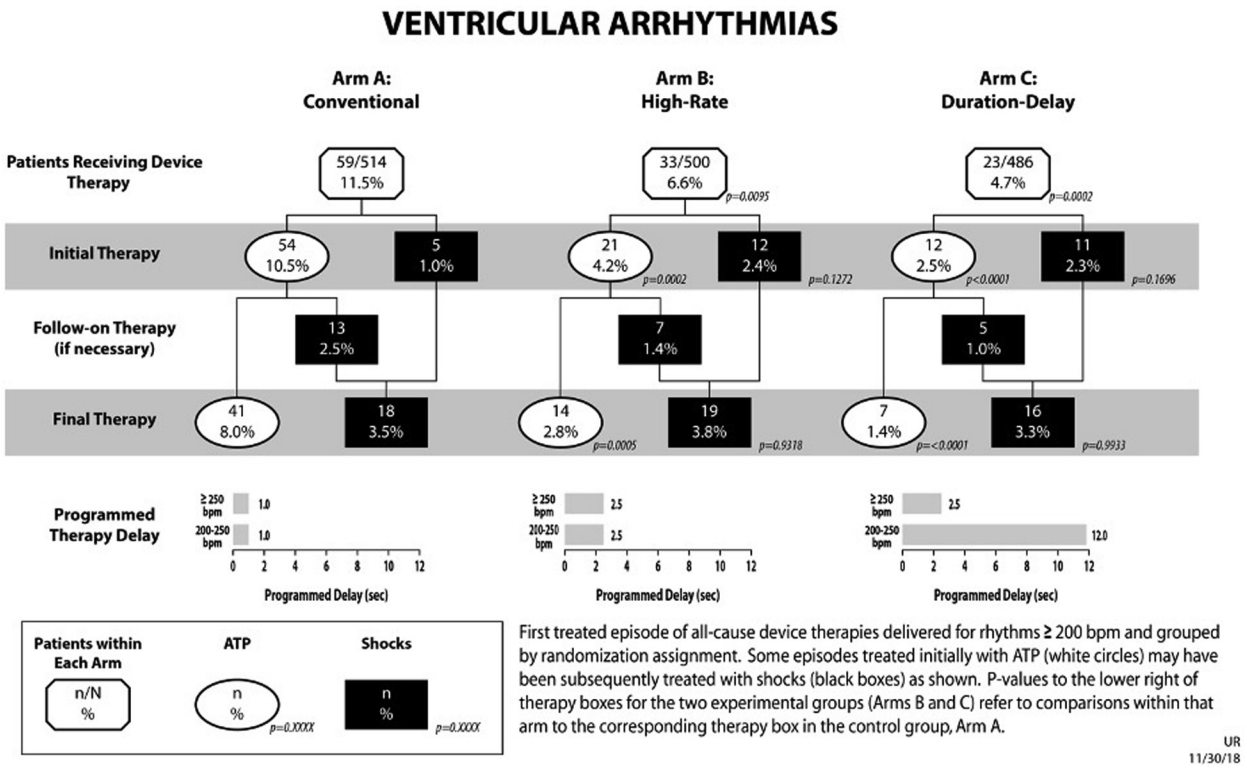

Figure 1 The rate of first appropriate implantable cardioverter-defibrillator therapies (antitachycardia pacing [ATP] only, ATP and shock, and shock only) for ventricular arrhythmias ≥ 200 beats/min in Multicenter Automatic Defibrillator Implantation Trial – Reduce Inappropriate Therapy by programming arms.

The Pacing Fast Ventricular Tachycardia Reduces Shock Therapies (PainFREE Rx II) study[11] is the only multicenter prospective randomized study that has previously evaluated the efficacy of ATP for rapid VAs. Patients were randomized to receive ATP or shocks only, with both arms programmed to detection of 18 of 24 fast intervals at a rate cutoff of 188 beats/min. This study enrolled patients from January 2001 to March 2002 and included a mix of patients with mainly secondary indications but ceased enrollment before the era of primary prevention ICD indications. More than one-third of episodes in the shock arm self-terminated during a median capacitor charge time of 3.3 seconds, leading to the possibility that a longer detection time could have further reduced the rate of ATP or shocks for VTs. Other studies that examined the role of therapy delays, such as the Primary Prevention Parameters Evaluation study[11] and the Avoid Delivering Therapies for Nonsustained Arrhythmias in ICD Patients III (ADVANCE-III) study,[12] had considerably shorter therapy

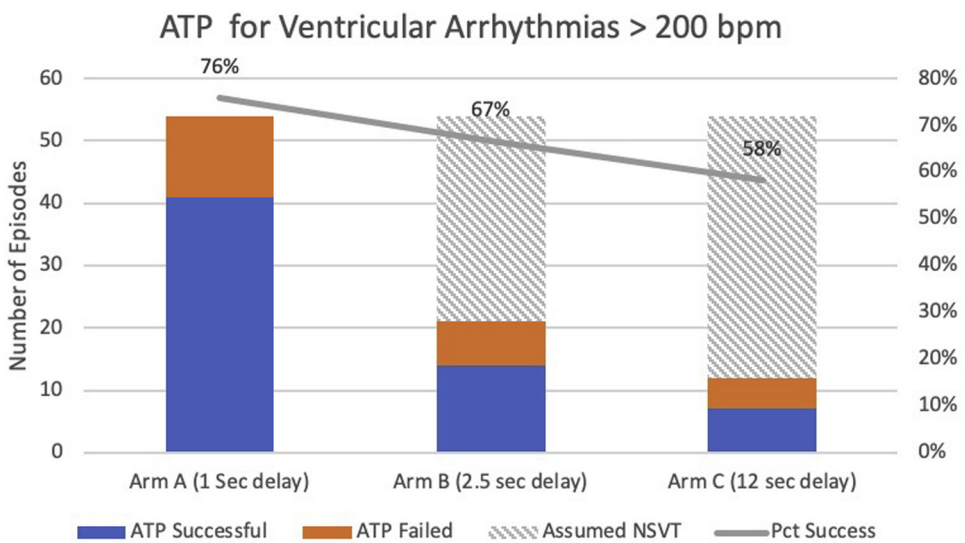

Figure 2 The rate of successful and failed antitachycardia pacing (ATP) across Multicenter Automatic Defibrillator Implantation Trial – Reduce Inappropriate Therapy programming arms for ventricular arrhythmias ≥ 200 beats/min. NSVT = non-sustained ventricular tachycardia; Pct = percent.

delays (an effective delay of ~9 seconds) and included patients with both primary and secondary prevention indications. In a subanalysis of ADVANCE-III[13] that specifically tried to look at the value of ATP over a long detection interval, the authors find an efficacy of only 52% in the long detection arm, similar to our finding when compared to the standard detection interval arm. However, the authors ascribed an additive value of ATP over long detections on the basis of a hypothetical scenario that all tachycardias that terminated during charging did so because of ATP at the time of charging without considering the possibility of self-termination. Moreover, the authors acknowledge that ATP was less effective in patients with primary prevention as opposed to patients with secondary prevention. As is the case with our study, there was not statistically significant difference in the number of shocks delivered for VAs between both arms of ADVANCE III.

The studies previously mentioned evaluated ATP interventions with the implicit assumption that termination of those events was the result of the intervention. However, application of longer delays in this study rendered up to 78% of ATP episodes unnecessary. This appropriately highlights that the risk/profile benefit of ATP in primary prevention ICD recipients should be reexamined in a prospective randomized trial given that the presumption of efficacy in a pure primary prevention cohort remains unproven.

It is also worth mentioning that the number of patients needing shock therapy was not statistically different across ICD programming arms despite a massive reduction in ATP events, suggesting that ATP-induced accelerations leading to sustained rapid VAs requiring shocks are uncommon, a finding also reported in the ADVANCE III subanalysis.

Limitations

This analysis from MADIT-RIT is retrospective, and the usual caveats about hypothesis-generating data analysis apply. Moreover, given the small number of patients in MADIT-RIT with delayed therapy who had ATP events, a substantially larger prospective randomized controlled trial will be necessary to confirm this hypothesis.

Conclusion

We conclude from the data of this secondary analysis of MADIT-RIT that the value of ATP in patients with primary prevention ICD may have been overestimated. ATP success as previously reported in other studies potentially includes a large proportion of patients who receive unnecessary ATP for nonsustained VT destined to terminate spontaneously anyway.

The ultimate value of ATP in a pure primary prevention population remains speculative.

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