Novel ICD Programming and Inappropriate ICD Therapy in CRT-D Versus ICD Patients
A MADIT-RIT Sub-Study

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Background—The Multicenter Automatic Defibrillator Implantation Trial–Reduce Inappropriate therapy (MADIT-RIT) trial showed a significant reduction in inappropriate implantable cardioverter defibrillator (ICD) therapy in patients programmed to high-rate cut-off (Arm B) or delayed ventricular tachycardia therapy (Arm C), compared with conventional programming (Arm A). There is limited data on the effect of cardiac resynchronization therapy with a cardioverter defibrillator (CRT-D) on the effect of ICD programming. We aimed to elucidate the effect of CRT-D on ICD programming to reduce inappropriate ICD therapy in patients implanted with CRT-D or an ICD, enrolled in MADIT-RIT.

Methods and Results—The primary end point of this study was the first inappropriate ICD therapy. Secondary end points were inappropriate anti-tachycardia pacing and inappropriate ICD shock. The study enrolled 742 (49%) patients with an ICD and 757 (51%) patients with a CRT-D. Patients implanted with a CRT-D had 62% lower risk of inappropriate ICD therapy than those with an ICD only (hazard ratio [HR] =0.38, 95% confidence interval: 0.25–0.57; P<0.001). High-rate cut-off or delayed ventricular tachycardia therapy programming significantly reduced the risk of inappropriate ICD therapy compared with conventional ICD programming in ICD (HR=0.14 [B versus A]; HR=0.21 [C versus A]) and CRT-D patients (HR=0.15 [B versus A]; HR=0.23 [C versus A]; P<0.001 for all). There was a significant reduction in inappropriate anti-tachycardia pacings in both group and a significant reduction in inappropriate ICD shock in CRT-D patients.

Conclusions—Patients implanted with a CRT-D have lower risk of inappropriate ICD therapy than those with an ICD. Innovative ICD programming significantly reduces the risk of inappropriate ICD therapy in both ICD and CRT-D patients.

Clinical Trial Registration—http://clinicaltrials.gov; Unique identifier: NCT00947310.

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Key Words: atrial fibrillation ■ cardiac resynchronization therapy ■ ICD Programming ■ implantable cardioverter–defibrillator ■ MADIT-RIT ■ supraventricular tachycardia

The Multicenter Automatic Defibrillator Implantation Trial–Reduce Inappropriate therapy (MADIT-RIT) was a randomized clinical trial investigating different implantable cardioverter defibrillator (ICD) programming strategies to reduce inappropriate ICD therapy in primary prevention ICD patients. The trial showed that ICDs programmed to a high-rate cut-off with ventricular tachycardia (VT) detection and therapies starting at rates ≥200 bpm or with 60 s delayed VT therapy for VTs in the 170–199 bpm range significantly reduced the risk of inappropriate ICD therapies, when compared with conventional ICD programming. Patients enrolled in MADIT-RIT received guideline that indicated dual chamber ICDs or cardiac resynchronization therapy devices with ICD (CRT-D). Previous studies have suggested that patients implanted with a CRT-D device have a lower risk of atrial tachyarrhythmias. However, there are limited data evaluating the effect of CRT-D on inappropriate ICD therapy in general. Furthermore, the effect of innovative ICD programming on inappropriate ICD therapy and on regular supraventricular tachycardia (SVT)/sinus tachycardia has not yet been thoroughly investigated in patients with an implanted ICD or a CRT-D.

Therefore, the aim of this study was (1) to evaluate the effect of CRT-D versus ICD on inappropriate ICD therapy, (2) to assess the impact of innovative ICD programming on inappropriate ICD therapy in patients implanted with a CRT-D versus an ICD, enrolled in MADIT-RIT.
WHAT IS KNOWN

- In the MADIT-RIT study there was a significant reduction in inappropriate ICD therapy with novel ICD programming in primary prevention ICD therapy patients.
- It is also known that CRT reduces appropriate ICD therapy rates.

WHAT THE STUDY ADDS

- Our current sub-study from MADIT-RIT shows that patients implanted with a CRT-D have a lower risk of inappropriate ICD therapy than those with an ICD without CRT.
- Importantly, there was a significantly lower risk of inappropriate ICD therapy due to regular supraventricular tachycardia/sinus tachycardia as well as atrial fibrillation/flutter in CRT-D patients compared to those with an ICD only.
- Innovative ICD programming significantly reduces the risk of inappropriate ICD therapy in both ICD and CRT-D patients.

Methods

Study Population

The design and the primary results of the MADIT-RIT trial have been published previously.1,2 Briefly, the study enrolled 1500 patients in 98 centers from the United States, Canada, Europe, Israel, and Japan. All patients met current guideline criteria to receive either an ICD or a CRT-D for primary prevention of sudden cardiac death.3,7 Patients were excluded based on exclusion criteria published earlier.1 Patients were randomized to 1 of 3 ICD programming modes: conventional ICD programming, high-rate cut-off VT therapy, or delayed VT therapy initiation. The MADIT-RIT study was approved by an institutional review committee, and the subjects gave informed consent.

The current study included 742 patients (49.5%) who received a dual chamber ICD and 757 patients (50.5%) who were implanted a CRT-D device. One patient did not undergo any device implantation and was therefore excluded from this analysis.

Device Programming

The 3 programming arms, conventional therapy, high-rate therapy, or delayed VT therapy initiation, differed in the heart rate cutoff for treatment of VT and the delay of a VT episode being treated. Conventional programming, Arm A, had a VT detection zone \(\geq 170 \text{ bpm} \) (detection delay 2.5 s, treatment with anti-tachycardia pacing (ATP), and eventually shock) and a VF zone \(\geq 200 \text{ bpm} \) (detection delay 1 s, treatment with Quick Convert ATP, or shock). By contrast, devices programmed to a high-rate therapy configuration, Arm B, comprised a monitor-only zone between 170 and 199 bpm and a VT therapy zone starting at 200 bpm (VF zone, delay 2.5 s) with therapies, including ATP and shock. Devices programmed to the duration-delay therapy configuration, Arm C, started ATP or shock therapy after a 60 s delay of a detected VT rate of 170 to 199 bpm, followed by a second VT zone \(\geq 200 \text{ bpm} \) with a detection delay of 12 s and a third VF zone of >250 bpm (detection delay 2.5 s, Quick Convert ATP, or shock).

Interrogation and Follow-Up

Patients were followed every 3 months within the first year and then at 6-month intervals until the trial termination on July 10, 2012. During each visit, a brief interim history was recorded, and a physical examination and device interrogation was carried out.

Table 1. Baseline Clinical Characteristics of ICD and CRT-D Patients With or Without Inappropriate Therapy During the Follow-Up

<table>
<thead>
<tr>
<th>Clinical Characteristics</th>
<th>ICD No Inappr Rx</th>
<th>ICD Inappr Rx</th>
<th>CRT-D No Inappr Rx</th>
<th>CRT-D Inappr Rx</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients (n)</td>
<td>639</td>
<td>103</td>
<td>708</td>
<td>49</td>
</tr>
<tr>
<td>Arm A (n, %)</td>
<td>188 (29)</td>
<td>70 (68)</td>
<td>221 (31)</td>
<td>35 (71)*†</td>
</tr>
<tr>
<td>Arm B (n, %)</td>
<td>232 (36)</td>
<td>16 (16)</td>
<td>246 (35)</td>
<td>5 (10)*†</td>
</tr>
<tr>
<td>Arm C (n, %)</td>
<td>219 (34)</td>
<td>17 (17)</td>
<td>241 (34)</td>
<td>9 (18)**†</td>
</tr>
<tr>
<td>Age at Enrollment (mean ± SD)</td>
<td>61±12</td>
<td>58±13</td>
<td>66±11</td>
<td>61±10*†‡</td>
</tr>
<tr>
<td>Female (n, %)</td>
<td>150 (23)</td>
<td>24 (23)</td>
<td>245 (35)</td>
<td>16 (33)‡</td>
</tr>
<tr>
<td>NYHA class III (n, %)</td>
<td>155 (25)</td>
<td>33 (33)</td>
<td>551 (78)</td>
<td>40 (82)‡</td>
</tr>
<tr>
<td>Ischemic etiology (n, %)</td>
<td>401 (63)</td>
<td>56 (54)</td>
<td>317 (45)</td>
<td>17 (35)‡</td>
</tr>
<tr>
<td>History of atrial fibrillation (n, %)</td>
<td>58 (9)</td>
<td>14 (14)</td>
<td>77 (11)</td>
<td>4 (8)</td>
</tr>
<tr>
<td>QRS duration (mean ± SD)</td>
<td>133±23</td>
<td>132±8</td>
<td>154±21</td>
<td>150±21</td>
</tr>
<tr>
<td>LV ejection fraction, %</td>
<td>27±6</td>
<td>25±6</td>
<td>26±7</td>
<td>26±7‡</td>
</tr>
<tr>
<td>Diabetes mellitus (n, %)</td>
<td>215 (34)</td>
<td>24 (24)</td>
<td>236 (34)</td>
<td>10 (20)*</td>
</tr>
<tr>
<td>DBP (n, %)</td>
<td>73.7±12.1</td>
<td>75.3±10.9</td>
<td>71.8±11.7</td>
<td>74.9±9.9†</td>
</tr>
<tr>
<td>Beta-blocker (n, %)</td>
<td>613 (96)</td>
<td>99 (96)</td>
<td>649 (92)</td>
<td>43 (88)‡</td>
</tr>
<tr>
<td>ACE/ARB (n, %)</td>
<td>554 (87)</td>
<td>95 (92)</td>
<td>619 (87)</td>
<td>44 (90)‡</td>
</tr>
<tr>
<td>Diuretics (n, %)</td>
<td>412 (64)</td>
<td>63 (61)</td>
<td>503 (71)</td>
<td>30 (61)‡</td>
</tr>
<tr>
<td>Amiodarone (n, %)</td>
<td>37 (6)</td>
<td>1 (1)</td>
<td>54 (8)</td>
<td>4 (8)†‡</td>
</tr>
</tbody>
</table>

Values are given as percent of patients or mean±SD. ACE inhibitors indicates angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockade; Arm A, conventional programming; Arm B, high-rate cut-off; Arm C, delayed therapy, as described in methods; DBP, diastolic blood pressure; LV, left ventricular; and NYHA, New York Heart Association class.
*P value <0.05 between CRT-D no inappr Rx. vs inappr Rx.
†P value <0.05 between CRT-D vs ICD-D.
‡P value <0.05 between ICD no inappr Rx. vs inappr Rx.
Clinical data and interrogation data from all devices 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 based on prespecified criteria.1

End Points and Definitions
Inappropriate therapy was defined as any ICD or CRT-D therapy delivered (ATP or shock) for sinus tachycardia, atrial fibrillation, atrial flutter, or regular SVT or for nonarrhythmic events, including detected noise, myopotentials, electromagnetic interference, and T-wave over-sensing. Regular SVT included regular atrial tachycardias, such as atrioventricular reentry tachycardia, and atrial tachycardia with 1:1 conduction.

Statistical Analysis
Continuous variables are expressed as mean±SD. Categorical data are summarized as frequencies and percentages. Baseline clinical characteristics were compared between patients with an implanted ICD or an implanted CRT-D stratified by the occurrence of inappropriate ICD therapy during the follow-up, using Wilcoxon ranked-sum test for continuous variables and Chi2 test for dichotomous variables.

Cumulative incidence rates were estimated for the end point of inappropriate therapy for patients with an implanted CRT-D versus an ICD. Gray’s test was used to test the differences in cumulative incidence between the groups. Furthermore, multivariate Cox proportional hazards regression analysis was used to assess the impact of CRT-D compared with ICD on the risk of inappropriate ICD therapy (ATP or shock only), as well as inappropriate ICD therapy for SVT/sinus tachycardia and for atrial fibrillation/flutter.

Cumulative incidences of inappropriate therapy because of regular SVT/sinus tachycardia or atrial fibrillation/flutter at 2.5 years in ICD patients versus in CRT-D patients were displayed as bar graphs, and the overall difference during the follow-up was compared using Gray’s test P value. Percentage of patients treated inappropriately for each heart rate range was presented in Figure 3. Multivariate Cox proportional hazards regression analysis was used to evaluate the impact of CRT-D compared with ICD on the effect of novel ICD programming (Arms B and C) to reduce inappropriate ICD therapy. The Cox model was adjusted for relevant clinical covariates using best subset regression by forcing programming arm in the models. We then selected the model with the combination of covariates that yielded the highest value of the Score test chi-square statistic. Further, all the variables in the model needed to be statistically significant at P<0.05. All statistical tests were 2-sided, and a P value <0.05 was considered statistically significant. Interaction P values were computed and reported. For interaction testing, a P value of <0.10 was considered statistically significant. Analyses were carried out with SAS software (version 9.3; SAS institute, Cary, NC).

Results
Baseline Clinical Characteristics
Relevant baseline clinical characteristics of ICD and CRT-D patients with and without inappropriate ICD therapy during the follow-up are depicted in Table 1.

During the average follow-up of 17±7 months (median: 17 months, Q1: 12 months, Q3: 23 months), 103 of 742 ICD patients (14%) and 49 of 757 CRT-D patients (7%) experienced first inappropriate ICD therapy (ATP with or without shock). A total of 190 patients (13%) withdrew before the study ended. ICD patients with inappropriate ICD therapy were more often in programming Arm A compared with programming Arms B and C, they were younger than those without an inappropriate ICD therapy, they had less often diabetes mellitus, and they were less often treated with amiodarone. CRT-D patients with inappropriate ICD therapy were more

<table>
<thead>
<tr>
<th>End Point</th>
<th>Hazard Ratio</th>
<th>95% CI</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inappropriate therapy (ATP or shock)</td>
<td>CRT-D vs ICD</td>
<td>0.38</td>
<td>0.25–0.57</td>
</tr>
<tr>
<td>Inappropriate ATP</td>
<td>CRT-D vs ICD</td>
<td>0.37</td>
<td>0.25–0.57</td>
</tr>
<tr>
<td>Inappropriate shock only</td>
<td>CRT-D vs ICD</td>
<td>0.41</td>
<td>0.21–0.79</td>
</tr>
<tr>
<td>Inappropriate therapy for SVT/sinus tachycardia</td>
<td>CRT-D vs ICD</td>
<td>0.32</td>
<td>0.20–0.53</td>
</tr>
<tr>
<td>Inappropriate therapy for atrial fibrillation/flutter</td>
<td>CRT-D vs ICD</td>
<td>0.45</td>
<td>0.21–0.97</td>
</tr>
</tbody>
</table>

The models are adjusted for treatment arm B, treatment arm C, age at enrollment by decade, prior atrial arrhythmia before enrollment, diastolic blood pressure by 10 mm Hg, diabetes mellitus, and NYHA class at enrollment. ATP indicates anti-tachycardia pacing; CI, confidence interval; CRT-D, cardiac resynchronization therapy with a cardioverter defibrillator; ICD, implantable cardioverter defibrillator; and SV, supraventricular tachycardia.
often in programming Arm A compared with Arms B and C, they were younger, and they had a higher diastolic blood pressure at baseline.

Patients with an implanted CRT-D device were significantly older, more often females, had less often an ischemic cardiomyopathy, and they were more often in an advanced stage of NYHA functional class. CRT-D patients received more often diuretics or amiodarone, and they were less often treated with beta-blockers.

**Effects of CRT-D on the Risk of Inappropriate ICD Therapy**

Despite the fact that patients with an implanted CRT-D device had a more advanced stage of the disease, there was a significantly lower cumulative incidence of first inappropriate ICD therapy compared with those implanted with an ICD only (unadjusted $P<0.001$; Figure 1A). The cumulative incidence of inappropriate ICD shock in patients with a CRT-D was half of those with an ICD-only therapy (Figure 1B; unadjusted $P=0.023$).

The annual incidence of inappropriate shock was relatively low, 1.6%/year in the CRT-D group and 3.2%/year in the ICD group.

In the multivariate model after adjustments, the risk of first inappropriate therapy remained 62% lower in patients with CRT-D than in those with an ICD only (hazard ratio [HR]=0.38, 95% confidence interval=0.25–0.57; $P<0.001$). This lower risk in the CRT-D group was observed for both inappropriate ATP (HR=0.37; $P<0.001$) and for inappropriate ICD shock only (HR=0.41; $P=0.008$; Table 2).

The incidence of inappropriate ICD therapy because of regular SVT/sinus tachycardia and because of atrial fibrillation/flutter at 2.5 years is displayed in Figure 2. There was a significantly lower incidence of inappropriate ICD therapy both because of regular SVT/sinus tachycardia and atrial fibrillation/flutter in those with an implanted CRT-D versus an ICD only.

In the multivariate models, there was a significant 68% reduction in the risk of inappropriate ICD therapy because of sinus tachycardia and regular SVT in patients with CRT-D.

![Figure 3](http://example.com/figure3.png)

**Figure 3.** Percentage of patients treated with inappropriate implantable cardioverter defibrillator (ICD) therapy by heart rate ranges in ICD vs cardiac resynchronization therapy with a cardioverter defibrillator (CRT-D) patients.
(HR=0.32, 95% confidence interval: 0.20–0.53; \( P < 0.001 \)) than in those with an ICD only. This effect was slightly attenuated, but still present, with a 55% significant reduction of inappropriate ICD therapy because of atrial fibrillation or atrial flutter in CRT-D patients (HR=0.45, 95% confidence interval: 0.21–0.97; \( P = 0.045 \)) than in those with an implanted ICD.

Heart rate ranges of inappropriate ICD therapy in ICD versus CRT-D patients are displayed in Figure 3. Patients with an implanted ICD seemed to have more inappropriate ICD therapies in the 170 to 179, 180 to 189, 200 to 209, and 220 to 229 bpm heart rate ranges compared with CRT-D patients.

### Effects of Novel Programming on the Risk of Inappropriate ICD Therapy in CRT-D Versus ICD Patients

In ICD patients, there was a significant reduction in inappropriate therapy with the novel high-rate cut-off VT therapy programming (Arm B) or delayed therapy (Arm C) programming (Arm B versus Arm A, HR=0.15; Arm C versus Arm A, HR=0.23; \( P < 0.001 \) for both; Figure 4A and Table 3).

Despite the overall lower risk of inappropriate therapy in patients with a CRT-D compared with ICD-only patients, innovative ICD programming with high-rate cut-off VT therapy (Arm B) or delayed VT therapy (Arm C) was associated with a significant reduction in the risk of inappropriate ICD therapy in CRT-D patients comparable to those with an implanted ICD-only (Arm B versus Arm A, HR=0.14; Arm C versus Arm A, HR=0.21; \( P < 0.001 \) for both, interaction \( P \) values >0.10 for all arms; Figure 4B and Table 3). Results for inappropriate ATP for both ICD and CRT-D patients and programming Arm B or C were consistent (Table 3).

Furthermore, there was a significant reduction in inappropriate ICD shocks in CRT-D patients programmed to high-rate cut-off VT therapy, Arm B (Arm B versus Arm A, HR=0.23; \( P = 0.02 \)), and to delayed VT therapy, Arm C (Arm C versus Arm A, HR=0.19; \( P = 0.01 \); Table 3). However, the reduction in the risk of inappropriate ICD shocks in ICD patients with novel ICD programming was more modest, if at all discernible (HR=0.54 in Arms B versus Arm A, and HR=0.79 in Arm C versus Arm A, respectively), with significant interaction between ICD and CRT-D treatment for programming Arm C versus A (HR 0.79 versus 0.19; interaction \( P = 0.06 \)).

### Sensitivity Analyses
We have performed sensitivity analysis to test the robustness of our findings, including all relevant covariates in the multivariate model. This model included adjustment for treatment arm B versus A, treatment arm C versus A, age at enrollment by decade, prior atrial arrhythmia before enrollment, diastolic blood pressure by 10 mm Hg, diabetes mellitus, NYHA class at enrollment, female sex, ischemic origin of cardiomyopathy, LV ejection fraction, beta-blocker treatment, angiotensin-converting enzyme/angiotensin receptor blockade treatment, diuretics use, and amiodarone treatment at baseline. Even after full adjustment for these covariates, hazard ratios for CRT-D versus ICD (original model HR=0.38, new model HR=0.37) and for programming arms remained similar.

### Discussion
Our study showed that novel ICD programming using either a high-rate VT cut-off (≥200 bpm) or delayed VT therapy initiation (60 s) in the 170–199 bpm range VT zone significantly reduces the risk of inappropriate ICD therapy in both ICD and CRT-D patients. The risk of inappropriate ICD therapy is lower in patients with an implanted CRT-D device than in ICD-only patients. Furthermore, there was a significant reduction in the risk of inappropriate ICD shocks in patients with an implanted CRT-D device programmed to high-rate cut-off or delayed VT therapy. CRT-D therapy was associated with a significant reduction in inappropriate ICD therapy induced by SVT, sinus tachycardia, and atrial fibrillation or atrial flutter.

Our study has significant clinical implications. It suggests that in HF patients who are in need for CRT, CRT-D therapy is associated with less frequent inappropriate ICD therapy. Novel programming with either high-rate cut-off or delayed therapy initiation provided further reduction in unwanted ICD shock delivery in CRT-D patients. The underlying pathophysiologic mechanism explaining the significant reduction in inappropriate ICD therapy may be related to improvement in
functional capacity and HF, leading to less sinus tachycardia and a reduced incidence of atrial fibrillation or atrial flutter, possibly linked to a reduction in the left atrial size. CRT is thought to induce reverse remodeling of the left atrium.8–11 Brenyo et al have shown that a reduction in left atrial volumes after implantation of a CRT-D device was associated with a significant decrease of atrial tachyarrhythmias in patients with mild heart failure.6 Furthermore, the significant reduction in regular supra-ventricular tachyarrhythmias implies that there is another important contribution of the beneficial CRT effect, namely reduction of abnormal sympathetic activity, especially in CRT responders.12–14 Cha et al investigated 16 consecutive CRT patients and 10 controls and found that the delayed heart/mediastinum 123I-MIBG ratio increased significantly, and the heart/mediastinum 123I-MIBG washout rate decreased significantly, suggestive of a rebalanced cardiac autonomic control.12 Another study from the same group suggested that these beneficial changes are only seen in CRT responders, but not in nonresponders.13 Another group suggested that dyssynchrony is associated with an imbalanced sympathetic activity, but can be improved by CRT.14

Several studies evaluated the predictors of inappropriate ICD therapy in the past15–17; however, most of these studies did not assess the role of CRT-D on inappropriate ICD therapies. Recently, Chen et al reported in a smaller retrospective cohort analysis with prospectively collected data that CRT-D reduces inappropriate ICD shocks as compared with ICD only.18 They suggested that this finding might be likely because of the reduction in atrial fibrillation in patients with CRT-D. In our study, we confirmed these findings in a larger patient cohort from a randomized clinical trial and extended it with reporting that the reduction in inappropriate ICD therapies are both as a result of reduction in atrial fibrillation/flutter and in SVT/sinus tachycardia. In addition, we also demonstrated that novel programming in both ICD and CRT-D patients reduces inappropriate ATP and shock delivery. It is important to note that despite the lower incidence of inappropriate ICD therapy in patients with CRT-D devices as compared with ICD only, CRT-D patients still had 9% inappropriate ICD therapy over 2.5 years, irrespective of the programming arm. This might be the reason that novel ICD programming was similarly beneficial in reducing inappropriate ICD therapy in both ICD and CRT-D patients. Therefore, novel ICD programming to reduce inappropriate ICD therapy is recommended in primary prevention ICD and CRT-D patients.

**Table 3. Multivariate Models Assessing the Effect of Programming in ICD vs CRT-D**

<table>
<thead>
<tr>
<th>End Point</th>
<th>HR</th>
<th>95% CI</th>
<th>P Value</th>
<th>Interaction P Value for trt x Programming Arm</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Inappropriate therapy (ATP or shock)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ICD patients (103 events in 742 patients)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arm B: Arm A</td>
<td>0.15</td>
<td>0.08–0.27</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Arm C: Arm A</td>
<td>0.23</td>
<td>0.14–0.40</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>CRT-D patients (49 events in 757 patients)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arm B: Arm A</td>
<td>0.14</td>
<td>0.05–0.35</td>
<td>&lt;0.001</td>
<td>0.878</td>
</tr>
<tr>
<td>Arm C: Arm A</td>
<td>0.21</td>
<td>0.10–0.43</td>
<td>&lt;0.001</td>
<td>0.802</td>
</tr>
<tr>
<td><strong>Inappropriate ATP</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ICD patients (94 events in 742 patients)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arm B: Arm A</td>
<td>0.14</td>
<td>0.07–0.25</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Arm C: Arm A</td>
<td>0.22</td>
<td>0.13–0.38</td>
<td>&lt;0.001</td>
<td></td>
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<tr>
<td>CRT-D patients (47 events in 757 patients)</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arm B: Arm A</td>
<td>0.14</td>
<td>0.05–0.36</td>
<td>&lt;0.001</td>
<td>0.958</td>
</tr>
<tr>
<td>Arm C: Arm A</td>
<td>0.21</td>
<td>0.10–0.45</td>
<td>&lt;0.001</td>
<td>0.960</td>
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<tr>
<td><strong>Inappropriate shock</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ICD patients (40 events in 742 patients)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arm B: Arm A</td>
<td>0.54</td>
<td>0.24–1.22</td>
<td>0.136</td>
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</tr>
<tr>
<td>Arm C: Arm A</td>
<td>0.79</td>
<td>0.37–1.70</td>
<td>0.547</td>
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</tr>
<tr>
<td>CRT-D patients (20 events in 757 patients)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arm B: Arm A</td>
<td>0.23</td>
<td>0.07–0.80</td>
<td>0.02</td>
<td>0.264</td>
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<tr>
<td>Arm C: Arm A</td>
<td>0.19</td>
<td>0.06–0.68</td>
<td>0.01</td>
<td>0.060</td>
</tr>
</tbody>
</table>

ATP indicates anti-tachycardia pacing; CI, confidence interval; CRT-D, cardiac resynchronization therapy with a cardioverter defibrillator; and ICD, implantable cardioverter defibrillator.

*The models are adjusted for treatment arm B, treatment arm C, age at enrollment by decade, prior atrial arrhythmia before enrollment, diastolic blood pressure by 10 mm Hg, diabetes mellitus, and NYHA class at enrollment.

ATP indicates anti-tachycardia pacing; CI, confidence interval; CRT-D, cardiac resynchronization therapy with a cardioverter defibrillator; and ICD, implantable cardioverter defibrillator.
or IV heart failure may be an independent predictor of inappropriate ICD firing. They mentioned that inappropriate ICD shocks were mainly because of atrial fibrillation. In the light of their findings, we may speculate that reduced inappropriate ICD therapy in our analysis indirectly indicates that our CRT patients had significant benefit from cardiac resynchronization. Furthermore, in our study, there was a significantly lower incidence in the risk of not only atrial fibrillation and atrial flutter but also regular supraventricular arrhythmias and sinus tachycardia in patients with CRT-D compared with ICD only.

Our analysis has certain limitations. ICD and CRT-D patients in our study had different clinical characteristics at baseline, and ICD or CRT-D treatment was not randomized. Furthermore, unmeasured confounders could not be taken into consideration that might have influenced our results. The incidence of inappropriate ICD shocks was relatively low, especially in the CRT-D group, which may limit our power to assess the effects of programming modes on inappropriate ICD shock delivery. In this study, we did not particularly assess the risk of recurrent ATP or shock deliveries or patients with electrical storm.

Conclusions

In our study, implantation of a CRT-D device in heart failure patients was associated with significantly lower incidence of inappropriate ICD therapy and inappropriate ICD shock than in ICD patients. In CRT-D patients, both atrial fibrillation/flutter and regular SVT/sinus tachycardia occur less often than in ICD patients. Furthermore, there is a beneficial effect of novel ICD programming using VT high-rate cut-off or delayed initiation of VT therapy delivery to reduce the risk of inappropriate ICD therapy in both ICD and CRT-D patients. In CRT-D patients, novel ICD programming was associated with a significant reduction in inappropriate ICD shocks.

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