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Heart Rhythm Disorders

The Effect of Intermittent Atrial Tachyarrhythmia on Heart Failure or Death in Cardiac Resynchronization Therapy With Defibrillator Versus Implantable Cardioverter-Defibrillator Patients

A MADIT-CRT Substudy (Multicenter Automatic Defibrillator Implantation Trial With Cardiac Resynchronization Therapy)

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Objectives This study aimed to investigate the effect of both history of intermittent atrial tachyarrhythmias (IAT) and in-trial IAT on the risk of heart failure (HF) or death comparing cardiac resynchronization therapy with defibrillator (CRT-D) to implantable cardioverter-defibrillator (ICD) treatment in mildly symptomatic HF patients with left bundle branch block (LBBB).

Background Limited data exist regarding the benefit of CRT-D in patients with IAT.

Methods The benefit of CRT-D in reducing the risk of HF/death was evaluated using multivariate Cox models incorporating the presence of, respectively, a history of IAT at baseline and time-dependent development of in-trial IAT during follow-up in 1,264 patients with LBBB enrolled in the MADIT-CRT (Multicenter Automatic Defibrillator Implantation Trial With Cardiac Resynchronization Therapy) study.

Results The overall beneficial effect of CRT-D versus ICD on the risk of HF/death was not significantly different between LBBB patients with or without history of IAT (HR: 0.50, $p = 0.028$, and HR: 0.46, $p < 0.001$, respectively; p for interaction = 0.79). Among patients who had in-trial IAT, CRT-D was associated with a significant 57% reduction in the risk of HF/death compared with ICD-only therapy (HR: 0.43, $p = 0.047$), similar to the effect of the device among patients who did not have IAT (HR: 0.47, $p < 0.001$; p for interaction = 0.85). The percentage of patients with biventricular pacing ≥92% was similar in both groups ($p = 0.43$). Consistent results were shown for the benefit of CRT-D among patients who had in-trial atrial fibrillation/flutter (HR: 0.30, $p = 0.027$; p for interaction = 0.41).

Conclusions In the MADIT-CRT study, the clinical benefit of CRT-D in LBBB patients was not attenuated by prior history of IAT or by the development of in-trial atrial tachyarrhythmias. (MADIT-CRT: Multicenter Automatic Defibrillator Implantation Trial With Cardiac Resynchronization Therapy; NCT00180271) (J Am Coll Cardiol 2014;63:1190–7) © 2014 by the American College of Cardiology Foundation

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Major randomized studies have substantiated the beneficial effects of cardiac resynchronization therapy (CRT) in heart failure (HF) patients with depressed left ventricular ejection fraction and intraventricular conduction disturbances who are in sinus rhythm (1–4). Patients with left bundle branch block (LBBB) have been shown to derive a more pronounced benefit from CRT than non-LBBB patients (5,6). Atrial tachyarrhythmias (AT) are the most common arrhythmias in HF patients (7). However, guidelines on device implantation have only recently included a class IIa-IIb recommendation for patients in atrial fibrillation (7,8), although this recommendation does not distinguish between permanent or paroxysmal atrial fibrillation.

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In recent years it has been questioned whether patients with AT gain the same benefit from CRT as patients in sinus rhythm. However, relevant studies on the subject have primarily included patients with permanent atrial fibrillation and showed attenuated effect of CRT in this study group (9–12). Gasparini et al. (13) and others (10,14) have suggested that permanent or persistent atrial fibrillation reduces effective biventricular (BIV) pacing capture, resulting in diminished response to CRT, and that atrioventricular nodal ablation may improve survival and response to CRT (9,12,13,15,16).

Every day clinicians are faced with patients who otherwise fulfill recommended guideline criteria (7,8,17) for CRT but who have intermittent atrial tachyarrhythmia (IAT). This aspect is not considered in present guidelines (7,8,17), and only limited data reflect the efficacy of CRT in patients with IAT before implantation of the device. Therefore, the question remains whether patients with IAT who otherwise meet the recommended guideline criteria for CRT derive benefit from CRT, or if an implantable cardioverter-defibrillator (ICD) would suffice in these patients?

Furthermore, even though it has been shown that CRT induces reverse remodeling of the left atrium, thus reducing subsequent risk of AT (18), a substantial number of patients still have atrial tachyarrhythmia (AT) after CRT implantation (19,20). To the best of our knowledge, no study has investigated whether development of AT after CRT implantation affects the clinical benefit of the device. Accordingly, the present study was carried out among 1,264 LBBB patients enrolled in the MADIT-CRT (Multicenter Automatic Defibrillator Implantation Trial With Cardiac Resynchronization Therapy) study and was designed to evaluate: 1) the effect of IAT before device implantation on the clinical benefit of CRT; and 2) the effect of IAT development after CRT implantation on the clinical benefit of the device.

Abbreviations and Acronyms

AT = atrial tachyarrhythmia
BIV = biventricular
CI = confidence interval
CRT = cardiac resynchronization therapy
CRT-D = cardiac resynchronization therapy-defibrillator
HF = heart failure
HR = hazard ratio
IAT = intermittent atrial tachyarrhythmias
ICD = implantable cardioverter-defibrillator
LAV = left atrial volume
LBBB = left bundle branch block
LVEF = left ventricular ejection fraction

Methods

The MADIT-CRT study. The study protocol and primary results of the MADIT-CRT study have been published previously (1,21). Briefly, the study randomized 1,820 patients with left ventricular ejection fraction ≤30%, ischemic or nonischemic cardiomyopathy and intraventricular conduction delay (QRS interval ≥130 ms) in a 3:2 fashion for implantation of a CRT-D or an ICD device. Patients were excluded if they were in New York Heart Association functional class III or IV, had a pre-existing indication for ICD/CRT-D/pacemaker implantation, had experienced a myocardial infarction within 90 days before enrollment, had atrial fibrillation within 1 month before enrollment, or presented with a rhythm other than sinus rhythm at enrollment. The trial was conducted in 110 centers in the United States, Canada, and Europe from December 22, 2004, through June 24, 2009, at which time the study was stopped by recommendation of the safety monitoring board. Extended follow-up was conducted until September 10, 2010.

After the primary publication of MADIT-CRT, subsequent analyses showed that the benefit of CRT in the trial was restricted to patients with LBBB (5,6). Accordingly, the present study group comprises 1,264 patients with LBBB who were enrolled in the trial and received a device.

Device programming and interrogation. Standard, commercially available Boston Scientific ICD/CRT-D devices were used and implanted by conventional transvenous implant procedures. All ICD/CRT-D devices were programmed according to a pre-specified study protocol (21), with a ventricular tachycardia zone set at 180 beats/min and a ventricular fibrillation zone set at 210 beats/min. All supraventricular tachycardia discriminators and antitachycardia pacing (ATP) were nominally programmed at "on" mode. Sensitivity was set at the discretion of the implanting physician. Patients were seen at scheduled visits 1 month after randomization and thereafter quarterly throughout the follow-up period. The devices were interrogated at each visit, and all interrogation disks were sent to an independent central core laboratory where an arrhythmia adjudication committee adjudicated all arrhythmias and therapies according to pre-defined definitions.

Endpoints and definitions. For the current study, the primary endpoint consisted of a combined endpoint of

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all-cause mortality or nonfatal HF events, whichever came first, as previously defined (1). Reverse remodeling measured by reduction in left atrial volume within a year was defined as a secondary endpoint. All primary endpoints were adjudicated centrally by an assigned HF and mortality committee according to pre-specified criteria. LBBB was defined as prolonged QRS duration (≥130 ms), QS or rS in lead V_1, wide R-wave in lead I, aVL, and absence of q-wave and presence of broad R-wave in lead V_5 and V_6, as previously reported (5).

Information on history of IAT was on the basis of medical history taken at enrollment. In-trial development of IAT was defined as any inappropriate therapy rendered for AT before the specific endpoint of HF or death (HF/death), whichever came first. A blinded arrhythmia adjudication committee evaluated all documented arrhythmias from device electrocardiograms and categorized them into pre-specified categories. The diagnosis of AT included atrial fibrillation, atrial flutter, and regular supraventricular tachycardia.

Echocardiography. According to the pre-specified protocol as described in the primary paper (1,21), a 2-dimensional echocardiographic study was performed at baseline and during the 1-year follow-up. In the present LBBB study group of 1,264 patients, paired echocardiograms at baseline and after 1 year were available for 977 patients. An independent echocardiographic core laboratory evaluated each echocardiography and measured left atrial and ventricular volumes according to the Simpson's method of disks in the apical 4-chamber and 2-chamber views (22).

Biventricular pacing. An independent interrogation core laboratory evaluated the final interrogation disks collected at the last follow-up. Data on the mean percent of BIV pacing, defined as left ventricular pacing percent throughout the follow-up, was acquired. According to results from previous studies, showing a decreased effect of CRT with <92% BIV pacing (14), we reported the percent of patients who received an average BIV pacing ≥92%, with or without prior history of IAT or in-trial IAT.

Statistics. The MADIT-CRT trial included 1,281 patients with LBBB. Of these, we excluded 17 patients who never received a device, leaving 1,264 LBBB patients for the analyses. Baseline characteristics between LBBB patients with or without a history of IAT were compared using nonparametric Wilcoxon or Kruskal-Wallis tests for continuous variables and the chi-square test or Fisher exact test for dichotomous variables. To assess changes in echocardiographic parameters from baseline to 1-year follow-up, within a specific group, we used paired *t* tests. Changes between groups were evaluated using the Wilcoxon rank sum test. To evaluate echocardiographic reverse remodeling in patients who had in-trial IAT, patients had to have had in-trial IAT within the first year; otherwise, they were considered as not having had in-trial IAT. For the endpoint of HF/death, in-trial IAT was defined as inappropriate therapy for AT that developed before the endpoint of HF/death.

The cumulative probability of HF/death was displayed by the method of Kaplan-Meier. Multivariate Cox interaction models were used to assess the efficacy of CRT-D versus ICD in LBBB patients with and without history of IAT and in-trial IAT. We adjusted for relevant variables found by stepwise selection and best subset, only including variables that entered the model at p values <0.05. The following variables were included for the endpoint of HF/death: glomerular filtration rate ≥60 $ml \cdot min^{-1} \cdot 1.73\ m^{-2}$, left atrial volume (LAV) indexed by body surface area (ml/m^2), diabetes mellitus, ischemic cardiomyopathy, prior all-cause hospital stays, and randomized treatment (CRT-D:ICD). In 2 different models, the effect of respectively prior IAT or in-trial IAT in CRT-D versus ICD patients was evaluated by forcing the interaction term between randomized treatment (CRT-D or ICD) and respectively prior IAT or in-trial IAT into the model along with the variables themselves.

Hazard ratios (HRs) with their 95% confidence intervals (CIs) and 2-sided p values were reported. A 2-tailed p value <0.05 was considered statistically significant. Interaction p values were computed according to standard methods. Analyses were performed using SAS statistical system 9.3 version (SAS Institute, Cary, North Carolina).

Results

In the MADIT-CRT study, 1,264 patients presented with LBBB and were implanted with a device. The ICD and CRT-D devices were implanted in 507 (40%) and 757 (60%) of the 1,264 patients, respectively. During a mean follow-up of 3.4 ± 1.1 years, 306 (24.2%) of 1,264 patients reached the primary endpoint of HF/death.

History of IAT. Information on history of IAT was not acquired in 23 patients, leaving 1,241 patients for this analysis, of whom 140 (11.3%) had a history of IAT. Table 1 depicts baseline characteristics for patients with or without a history of prior IAT. There were substantial differences between the 2 groups, generally emphasizing that patients with history of IAT had increased frequency of clinical risk factors. They were more often male, significantly older, and had more comorbidities (advanced renal disease, ischemic cardiomyopathy, prior myocardial infarction, past ventricular arrhythmias, and more prior hospital stays), compared to patients without a history of IAT. These differences also reflected significant differences in baseline use of medications (Table 1).

Efficacy of CRT-D in LBBB patients with history of IAT. In the total study group the 4-year cumulative incidence of HF/death in patients with a history of IAT was 33% as compared with 25% among patients without a history of IAT (Fig. 1). Although multivariate Cox regression models did not show increased risk of HF/death in patients with a history of IAT (HR: 1.04 [95% CI: 0.75 to 1.45], p = 0.82).

Table 1 Baseline Characteristics Comparing LBBB Patients With or Without History of IAT

Clinical Characteristics	No History of IAT (n = 1,101)	History of IAT (n = 140)
CRT-D implanted	668 (61)	72 (51)*
Female	355 (32)	27 (19)*
Age at enrollment, yrs	63.7 ± 10.9	67.3 ± 9.7*
Heart rate, beats/min	68.5 ± 10.9	66.8 ± 11.2
Creatinine ≥1.4, mg/dl	209 (19)	41 (29)*
GFR, ml/min/1.73 m^2	70.2 ± 20.2	64.2 ± 18.3*
Systolic blood pressure (mm Hg)	122.7 ± 16.9	122.4 ± 18.4
Diastolic blood pressure (mm Hg)	71.6 ± 10.3	70.7 ± 9.8
Nonischemic NYHA class II	646 (59)	52 (37)*
Worst NYHA functional class >2 (>3 months prior)	102 (10)	29 (22)*
Electrocardiographic characteristics		
PR interval, ms	196 ± 32	205 ± 35*
QRS, ms	162.4 ± 19.2	167.8 ± 19.8*
Echocardiography characteristics at baseline		
Left ventricular ejection fraction	28.8 ± 3.4	28.3 ± 3.7
LVEDV index, ml/BSA	126.3 ± 30.0	125.4 ± 31.1
LVESV index, ml/BSA	90.4 ± 24.4	90.4 ± 25.3
LAV index, ml/BSA	46.9 ± 10.0	48.8 ± 10.6*
Medical history		
Hospital stays in prior year	467 (43)	85 (61)*
Prior HF hospital stays	408 (38)	68 (49)*
Diabetes mellitus	329 (30)	42 (30)
Hypertension	688 (63)	88 (63)
Prior myocardial infarction	325 (30)	68 (51)*
Past ventricular arrhythmias	58 (5)	20 (15)*
Pharmacotherapy at baseline		
Antiarrhythmic add agent	29 (3)	55 (39)*
ACE inhibitor or ARB	1058 (96)	137 (98)
Beta-blocker excluding sotalol	1042 (95)	123 (88)*
Digitalis	305 (28)	40 (29)
Diuretic agent	751 (68)	99 (71)
Statins	685 (62)	103 (77)*

Values are n (%) or mean ± SD. *p ≤ 0.05.

ACE = angiotensin-converting enzyme; ARB = angiotensin-receptor blocker; BSA = body surface area; CRT-D = cardiac resynchronization therapy with defibrillator; GFR = glomerular filtration rate; HF = heart failure; LAV = left atrial volume; LVEDV = left ventricular end-diastolic volume; LVESV = left ventricular end-systolic volume; NYHA = New York Heart Association.

CRT was associated with a significant reduction in the rate of HF/death compared with ICD-only therapy among both patients with a history of IAT (Fig. 2A) and patients without such a history (Fig. 2B). Consistently, multivariate analysis showed that the overall beneficial effect of CRT-D versus ICD on the risk of HF/death was similar in LBBB patients with or without a history of IAT (HR: 0.50 and 0.46, respectively; p for interaction = 0.79) (Table 2). This effect was primarily driven by a benefit on HF events that was seen both in LBBB patients with a history of IAT (HR: 0.36 [95% CI: 0.18 to 0.75], p = 0.006) and in LBBB patients without a history of IAT (HR: 0.40 [95% CI: 0.30 to 0.53], p < 0.001; p for interaction = 0.80).

History of IAT and change in left atrial volume. As shown in Table 1, baseline LAV was significantly higher in LBBB patients with than without a history of IAT.

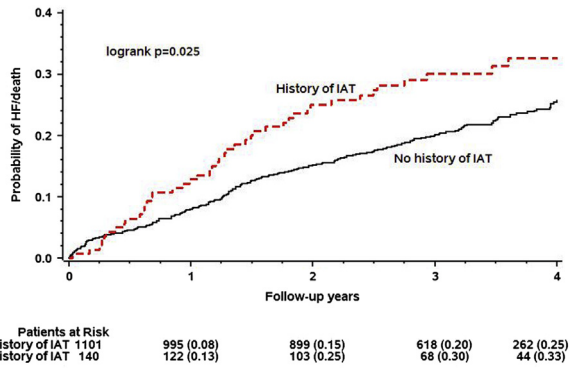

Figure 1 Risk of HF/Death in LBBB Patients Stratified by History of IAT

CRT-D = cardiac resynchronization therapy with defibrillator; HF = heart failure; IAT = intermittent atrial tachyarrhythmia; ICD = implantable cardioverter-defibrillator; LBBB = left bundle branch block.

However, both patients with or without a history of IAT had significant reduction in LAV within 1 year (% reduction 14.9 ± 11.3, p < 0.001, and 19.1 ± 13.0, p < 0.001, respectively). This reduction was significant in all 4 subgroups of ICD and CRT-D with or without history of IAT (p < 0.001 in all 4 groups). As shown in Figure 3, LAV was reduced to a significantly greater degree in CRT-D compared to ICD patients both with a history of IAT (% reduction CRT-D 25.9 ± 10.7 vs. ICD 8.2 ± 6.5, p < 0.001) and without a history of IAT (% reduction CRT-D 29.9 ± 12.0 versus ICD 10.3 ± 7.6, p < 0.001), affirming that LBBB patients with a history of IAT also derive a benefit of CRT-D measured by echocardiographic parameters. Similar results were found for left ventricular volumes (data not shown).

Development of IAT after device implantation and effect of CRT-D benefit. The cumulative probability of in-trial development of IAT with ventricular rate above the ICD detection criteria and resulting in inappropriate therapy was 4% at 1 year, 6% at 2 years, 8% at 3 years, and 10% at 4 years, without any difference between CRT-D and ICD patients (p = 0.67). The LBBB patients who experienced in-trial IAT had a higher frequency of past ventricular arrhythmias and a slightly shorter QRS duration at baseline compared to patients who did not experience in-trial IAT. No other significant difference was seen between the groups (Online Table).

In the total study group, multivariate analysis showed that the development of in-trial IAT was associated with an increased risk of subsequent HF/death (HR: 1.63 [95% CI: 1.06 to 2.50], p = 0.027). The pattern was similar for in-trial development of atrial fibrillation/flutter in the overall LBBB study group (HR: 2.09 [95% CI: 1.21 to 3.59], p = 0.008). Multivariate analysis, employing development of in-trial IAT as a time-dependent covariate, showed that the implantation of a CRT-D device in LBBB patients,

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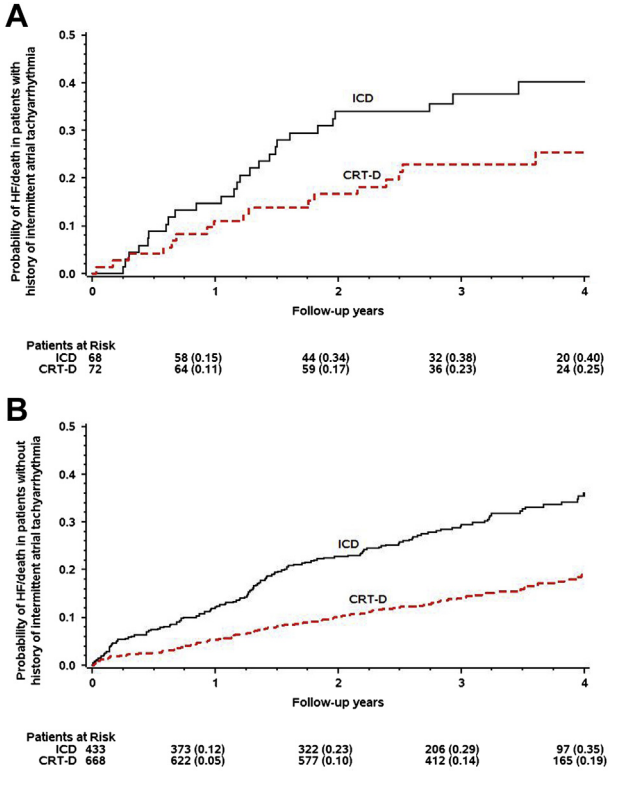

Figure 2 Risk of HF/Death Comparing CRT-D to ICD in LBBB Patients With and Without History of IAT

(A) Risk of heart failure (HF)/death comparing cardiac resynchronization therapy with defibrillator (CRT-D) to implantable cardioverter-defibrillator (ICD) in patients with left bundle branch block (LBBB) and a history of intermittent atrial tachyarrhythmia (IAT). **(B)** Risk of HF/death comparing CRT-D to ICD in patients with LBBB without a history of intermittent atrial tachyarrhythmia.

was associated with significant reductions in the risk of HF/death when compared to implantation of an ICD device, irrespective of in-trial development of IAT (p for interaction = 0.85) (Table 3, Fig. 4). The main effect was seen in HF events with equal efficacy of CRT-D in LBBB patients who had in-trial IAT and patients who did not (HR: 0.47 and HR: 0.39; p for interaction = 0.67). Similar results were found for in-trial development of atrial fibrillation or flutter (Table 3), suggesting that the development of atrial fibrillation or flutter after CRT-D implantation did not attenuate the clinical benefit of the device.

Reverse remodeling in LBBB patients with or without development of in-trial IAT within the first year. Overall, LBBB patients with and without development of in-trial IAT in the first year had significant reverse remodeling of LAV at 1-year follow-up (% reduction 20.4 ± 13.0, $p < 0.001$, and 18.6 ± 13.0, $p < 0.001$, respectively), which was also highly significant in all 4 subgroups of ICD and CRT-D with and without in-trial development of IAT ($p < 0.01$).

As shown in Figure 3, LAV was reduced to a greater degree in CRT-D patients compared to ICD patients who had in-trial IAT (% reduction 27.2 ± 12.4 vs. 10.2 ± 8.7, $p < 0.001$) and in patients who did not have in-trial IAT (% reduction 29.6 ± 12.0 vs. 9.9 ± 7.4, $p < 0.001$), affirming that patients who had in-trial IAT still derived a benefit of CRT-D. Interestingly, no significant difference was seen in reverse remodeling between CRT-D patients with or without in-trial IAT ($p = 0.34$). Similar results were found for reductions in left ventricular volumes (data not shown).

Biventricular pacing. Data on the mean percent of BIV pacing at the end of follow-up was available for 632 of 757 (83.4%) of all CRT-D patients with LBBB. The percent of patients who received BIV pacing ≥92% was not different between patients with prior history of IAT (95.0%) and patients without prior history of IAT (89.6%; $p = 0.13$). This was consistent for patients with in-trial IAT (87.5%) and patients without in-trial IAT (90.2%; $p = 0.43$), suggesting that there was an efficient resynchronization effect in both groups, corresponding to the lack of difference seen in the effect of CRT-D between the groups.

Discussion

In the current study, we show a beneficial effect of CRT-D when compared to ICD in patients with LBBB and mild HF, irrespective of both a history of IAT as well as in-trial development of IAT. The benefit of CRT-D versus ICD on the endpoint of HF/death in LBBB patients with a history of IAT persisted even though these patients presented with more comorbidities, which even further strengthens these findings. Furthermore, we have shown that the development of in-trial IAT or only atrial fibrillation or flutter after CRT-D implantation did not attenuate the clinical benefit of the device, and that the BIV pacing percentage remained high even if patients had a history of IAT or had in-trial IAT.

Table 2 Effects of History of IAT on HF/Death in Comparing CRT-D to ICD Treatment in Patients With LBBB

	Number of Events/Patients	Hazard Ratio CRT-D:ICD	95% Confidence Interval	p Value	p Value for Interaction
No history of IAT	252/1,101	0.46	0.36–0.59	<0.001	0.79
History of IAT	45/140	0.50	0.27–0.93	0.028	

The table shows that patients benefit from CRT-D independently of prior history of intermittent atrial tachyarrhythmias, and that there is no difference in the beneficial effect of CRT on HF/Death depending on history of intermittent atrial tachyarrhythmias. Adjusted for glomerular filtration rate ≥60 (ml·min^{-1}·1.73 m^{-2}), left ventricular atrial volume at baseline indexed by body surface area (ml/m^2), prior hospital stay, diabetes, ischemic cardiomyopathy, and the interaction variable between implanted device and history of IAT.

ICD = implantable cardioverter-defibrillator.

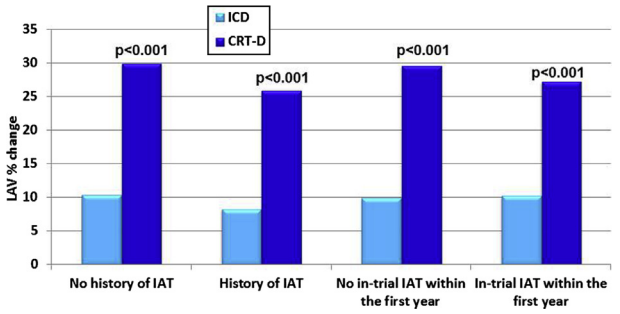

Figure 3 **Left Atrial Reverse Remodeling at 1-Year Follow-Up in LBBB Patients Comparing CRT to ICD in Patients With or Without Either History of IAT or Interim Occurrence of IAT Within the First Year**

Light blue = ICD; **dark blue bars** = CRT-D. LAV = left atrial volume; other abbreviations as in Figure 1.

We showed significant reverse remodeling in CRT-D patients with a history of IAT and in patients with in-trial IAT measured by reductions in LAV and left ventricular volumes. These findings highlight that LBBB patients with a history of IAT and/or in-trial IAT derive benefit of CRT-D versus ICD, not only on the endpoint of HF/death but also on echocardiographic parameters. This finding is in accordance with a previous MADIT-CRT substudy (18) that showed that resynchronization therapy induces reduction in LAV, resulting in less AT. Of note, Gasparini et al. (9) failed to show improvement in echocardiographic remodeling parameters in patients with permanent atrial fibrillation. We believe that the nature of IAT allows the myocardium to gain benefit from the CRT-D device between episodes of AT that would not be present in patients with permanent AT. Furthermore, with the positive remodeling of the left atrium we showed in this study, it might have other beneficial effects including shortening the paroxysms, diminishing the frequency of IAT episodes and possibly delaying the natural course of IAT into permanent AT. These factors might all contribute to a long-term beneficial effect on mortality.

We cannot eliminate the possibility of physician-initiated pharmacological therapy and/or ICD programming changes as a consequence of IAT, which could have contributed to the overall benefit of the CRT-D device. However, we believe that these interventions should have occurred equally in ICD and CRT-D patients, and thus, the potential beneficial effect should thereby not impact the overall results of this study.

Studies investigating the effect of CRT-D in patients with permanent atrial fibrillation have shown that the percent of BIV pacing has an important impact on CRT efficacy. Some studies have suggested that atrial fibrillation reduces effective BIV pacing capture, resulting in diminished response to resynchronization therapy (10,13,14) and that the percentage of BIV pacing should exceed 92% for the patient to respond to CRT-D treatment (14,23). In this study, we found that the BIV pacing percentage was still high, both in patients with prior IAT and in patients who experienced in-trial IAT. This may very well be due to the fact that episodes of IAT only cause short periods of reduced biventricular pacing capture that would not diminish the overall efficacy of CRT-D in these patients, which might explain why we do not find an attenuated effect of CRT-D in patients with IAT.

When analyzing both history of IAT as well as in-trial development of IAT, we believe that we are able to make an overall evaluation of the impact of IAT on CRT-D efficacy. We investigated the effect of IAT on subsequent CRT-D efficacy in patients who otherwise met the guideline criteria for CRT-D implantation (7,8). Previous studies have focused on permanent or persistent AT and showed a reduced effect of CRT-D in these patients (9–12). RAFT (Resynchronization for Ambulatory Heart Failure Trial) (10) compared the efficacy of CRT-D versus ICD in patients with permanent atrial fibrillation <90 beats/min and found no significant improvement in HF/death; however, the results were not statistically different from those for patients without permanent atrial fibrillation, who had a significant reduction in HF/death. In the RAFT study, the lack of CRT-D effect in patients with permanent atrial fibrillation with a ventricular rate <90 beats/min might be explained by a lower mean QRS

Table 3 **Effects of In-Trial Development of IAT Comparing CRT-D to ICD in Patients With LBBB on the Endpoint of HF/Death**

	Number of Events/Patients	Hazard Ratio CRT-D:ICD	95% Confidence Interval	p Value	p Value for Interaction
In-trial development of IAT					
No in-trial IAT*	283/1,175	0.47	0.37–0.60	<0.001	0.85
In-trial IAT*	23/89	0.43	0.19–0.99	0.047	
In-trial development of intermittent atrial fibrillation/flutter					
No in-trial intermittent atrial fibrillation/flutter*	292/1,217	0.48	0.38–0.61	<0.001	0.41
In-trial intermittent atrial fibrillation/flutter*	14/47	0.30	0.10–0.87	0.027	

There is a beneficial effect of CRT-D independently of in-trial intermittent atrial tachyarrhythmias or intermittent atrial fibrillation/flutter, and that there is no difference in the beneficial effect of CRT on HF/death depending on the occurrence of in-trial intermittent atrial tachyarrhythmias or intermittent atrial fibrillation/flutter. *Adjusted for glomerular filtration rate ≥60 ($ml \cdot min^{-1} \cdot 1.73\ m^{-2}$), left ventricular atrial volume at baseline indexed by body surface area (ml/m^2), prior hospital stays, diabetes mellitus, ischemic cardiomyopathy and the interaction variable between implanted device and in-trial IAT or in-trial intermittent atrial fibrillation/flutter.

Abbreviations as in Tables 1 and 2.

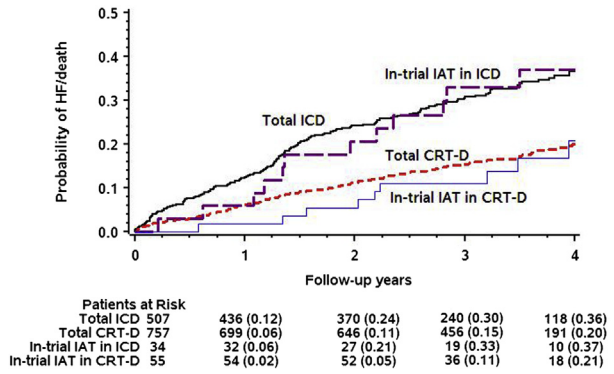

Figure 4 **Effect of In-Trial IAT on Probability of HF/Death in Patients With LBBB Comparing CRT-D to ICD Patients**

Abbreviations as in Figure 1.

duration at baseline, the failure to stratify by LBBB QRS morphology, and lower BIV pacing percentage.

In a recent study by Santini et al. (24), in-trial AT was associated with an increased risk of HF/death in CRT-D patients. However, this study included a high number of patients with permanent AT, and it did not compare CRT-D to ICD, but rather investigated CRT-D patients with in-trial AT compared to patients without in-trial AT. It is not surprising that AT, whether before or after CRT-D implantation, is associated with worse outcome. Several large studies on HF populations have previously shown this (25–27). What is important is to investigate, whether patients with IAT who otherwise meet the recommended criteria for CRT-D implantation, derive similar beneficial effects from a CRT-D device as patients without IAT, or whether an ICD would suffice. Our study indicates that patients with LBBB and IAT benefit equally from CRT-D as do patients without IAT.

Study limitations. We used device interrogations of inappropriate therapy as a marker for in-trial IAT, since we only have limited data on mode-switch time in the MADIT-CRT trial. As a result, only arrhythmias above the detection limit of 180 beats/min are included, and it is therefore possible that we are underestimating the actual "real-life" risk of IAT. Furthermore, given the limited data on mode-switch, we cannot provide any data on arrhythmia burden, which is known to influence CRT-D efficacy. We do not have information on the number of patients who had permanent or persistent AT with a ventricular rate below the device detection limit. However, we suspect the number is small, since only 41 of 678 (6%) CRT patients had a mode-switch time >0.5%, and approximately 90% of the patients, regardless of history of IAT and in-trial IAT, received BIV pacing ≥92%, indicating that merely a limited number of patients had permanent or persistent AT. The BIV pacing percentage was, unfortunately, not available in 16.6% of the patients, and that might have caused some degree of selection bias. Finally, although we adjusted for several possible confounding covariates in the multivariate models, unmeasured confounding may have affected our results to some degree.

Conclusions

Our findings from the MADIT-CRT study group demonstrate that in patients with mild HF and LBBB, the overall echocardiographic and clinical benefits of CRT-D are not attenuated among patients who have a prior history of IAT or among patients who develop IAT after device implantation. These findings further stress the pronounced beneficial effects of CRT-D for patients with mild HF symptoms regardless of associated IAT.

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Key Words: atrial arrhythmia ■ cardiac resynchronization therapy ■ death ■ efficacy ■ heart failure ■ implantable cardioverter-defibrillator ■ left atrial volume ■ left bundle branch block ■ reverse remodeling.

APPENDIX

For a supplemental table, please see the online version of this article.