

Effect of Cardiac Resynchronization Therapy on the Risk of First and Recurrent Ventricular Tachyarrhythmic Events in MADIT-CRT

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Objectives

This study aimed to evaluate the effect of cardiac resynchronization therapy with a defibrillator (CRT-D) on the risks of first and recurrent ventricular tachyarrhythmic events (VTEs) in the MADIT-CRT.

Background

Reverse remodeling associated with CRT-D therapy was suggested to reduce arrhythmic risk. However, the effect of the device on the risk of recurrent VTEs among patients who experience a first arrhythmic event has not been investigated.

Methods

The CRT-D versus defibrillator-only risks for first and subsequent fast VTEs (>180 beats/min) were assessed by Cox proportional hazards and Andersen-Gill proportional intensity regression modeling, respectively, in efficacy analyses recognizing active device-type during follow-up.

Results

Multivariate analysis showed that CRT-D was associated with a significant 29% ($p = 0.003$) reduction in the risk of a first VTE, with a pronounced effect among patients with left bundle branch block (LBBB) (hazard ratio [HR]: 0.58; $p < 0.001$) and no significant effect among non-LBBB patients (HR: 1.05; $p = 0.82$, p for the difference = 0.02). Patients with LBBB who experienced a first VTE had no change in the risk of subsequent VTEs with CRT-D (HR: 0.98; $p = 0.85$). In contrast, the risk of recurrent VTEs with CRT-D was significantly increased among non-LBBB patients (HR: 3.62; $p = 0.002$, p for the difference = 0.009). Recurrent VTEs increased the risk of subsequent heart failure or death.

Conclusions

In MADIT-CRT, active treatment with CRT-D was associated with a significant reduction in the risk of life-threatening VTEs. However, our findings suggest that CRT-D does not reduce the risk of subsequent VTEs in patients who experience a first arrhythmic event and may increase subsequent arrhythmic risk in non-LBBB patients. (Multicenter Automatic Defibrillator Implantation With Cardiac Resynchronization Therapy [MADIT-CRT]; NCT00180271) (J Am Coll Cardiol 2012;60:1809-16) © 2012 by the American College of Cardiology Foundation

Patients with congestive heart failure are at an increased risk of life-threatening ventricular arrhythmias due to ischemia or myocardial substrate changes (1). The incidence of sudden cardiac death approaches 20% in those with ejection

fractions <30% (1). Evidence-based consensus guidelines recommend treatment with implantable cardioverter-defibrillators (ICDs) in patients with New York Heart Association (NYHA) functional class I/III symptoms and reduced ejection fraction due to a previous myocardial infarction to reduce mortality (2). Similar results, albeit less robust, have also been reported in patients with heart failure of nonischemic etiology and resulted in guideline inclusions (3-5).

The MADIT-CRT (Multicenter Automatic Defibrillator Implantation Trial With Cardiac Resynchronization Therapy) showed that cardiac resynchronization therapy with a defibrillator (CRT-D) is associated with a significant reduction in the risk of heart failure hospitalizations or all-cause mortality in patients with prolonged QRS duration and mild heart failure symptoms (NYHA class I or II) of

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**Abbreviations
and Acronyms**

ATP = antitachycardia pacing
CRT = cardiac resynchronization therapy
CRT-D = cardiac resynchronization therapy with a defibrillator
HR = hazard ratio
ICD = implantable cardioverter-defibrillator
LBBB = left bundle branch block
NYHA = New York Heart Association
VTE = ventricular tachyarrhythmic event

ischemic and nonischemic etiologies (6). These results were subsequently confirmed in a population of patients with mild to moderate heart failure (NYHA class II or III) (7). The ventricular conduction pattern has been shown to be an important parameter to predict response to cardiac resynchronization therapy (CRT) because patients with left bundle branch block (LBBB) appear to derive greater benefit from CRT than those with other conduction abnormalities in terms of time to a first and recurrent heart failure events (8,9). In this MADIT-CRT substudy, we seek to: 1) elucidate the impact

of CRT on the occurrence of first and recurrent ventricular tachyarrhythmic events (VTEs) in mildly symptomatic heart failure patients; 2) relate recurrent arrhythmic risk in this population to QRS morphology; and 3) assess the prognostic implications of first and recurrent VTEs.

Methods

Study population. The details of the MADIT-CRT have been described; specifically, the trial investigated the effect of CRT-D versus ICD alone in patients with early heart failure, either in NYHA class I or II due to ischemic etiologies or NYHA class II due to nonischemic cardiomyopathy, reduced ejection fraction ($\leq 30\%$), ventricular conduction delay as evidenced by QRS duration ≥ 130 ms (6). This current substudy comprises all 1,820 MADIT-CRT patients.

Data acquisition and follow-up. The MADIT-CRT began on December 22, 2004, and ended by recommendation of the data and safety monitoring board on June 22, 2009. However, additional data collection on heart failure events, mortality, and arrhythmia endpoints were collected through December 31, 2009. Data regarding VTEs were collected via device interrogation and evaluated by an independent committee. Device crossovers were recorded during follow-up. Thirty-seven percent of patients initially allocated to ICD-only therapy crossed over to CRT-D, whereas only 8% of those initially allocated to CRT-D crossed over to ICD-only therapy. Although devices were initially programmed in the same manner, individual physicians were permitted to change the device settings. Further information about the trial design and procedures was previously reported (6,10).

Device programming and interrogation. Commercially available transvenous devices (Boston Scientific, Natick, Massachusetts) were used in the trial. Standard techniques were used to implant the CRT-D and ICD-only devices.

Device testing and programming were performed as reported previously (10). Devices were programmed to monitor + therapy, with a protocol recommendation to a setting of the ventricular tachycardia zone at 180 beats/min, and the ventricular fibrillation zone at 250 beats/min. Sensitivity was programmed according to physician discretion. Detection was 2.5 s for the ventricular tachycardia zone and 1.0 s for the ventricular fibrillation zone. The protocol recommended programming the ventricular tachycardia zone first therapy to burst-type antitachycardia pacing (ATP) with 8 pulses at 88% of the measured cycle length with a 10-ms decrement between bursts, then shock therapy; second therapy should be shock at the defibrillation threshold plus at least 10 J (if possible). The remaining therapies should be maximal energy shocks. The ICDs were interrogated quarterly, after which ICD shocks and disks were sent to the core laboratory for categorization and final evaluation of detected arrhythmias. An arrhythmia episode was defined as any type of therapy that is rendered including ATP and shock. Only appropriate therapies delivered for fast VTEs (≥ 180 beats/min) were considered in the present study.

Echocardiographic methods and outcome measures.

Echocardiograms were obtained according to a study-specific protocol at baseline, which was before device implantation ($n = 1,809$), and at 1 year ($n = 626$ in the ICD group; $n = 752$ in the CRT-D group). Paired echocardiograms from baseline and at 12 months with the device turned on were available for 1,372 patients who composed the present study population. Echocardiographic parameters were measured in a core laboratory according to established American Society of Echocardiography protocols (11). Left ventricular volumes were measured by Simpson's method of discs in the apical 4- and 2-chamber views and averaged.

An echocardiographic response was defined as the percentage of reduction in left ventricular end-systolic volumes between enrollment and 1 year (calculated as the difference between 1-year cardiac volumes and baseline cardiac volumes, divided by baseline cardiac volumes). CRT-D patients were categorized into 2 groups based on their echocardiographic response: responders (defined as $\geq 25\%$ reduction [greater than the first quartile response] in left ventricular end-systolic volume at 1 year post-implantation) and nonresponders (defined as $< 25\%$ reduction [greater than the first quartile response] in left ventricular end-systolic volume at 1 year post-implantation).

Study design and endpoints. The primary outcome of this study was the occurrence of fast VTEs, herein defined as appropriate ICD therapy delivered for ventricular tachycardia/fibrillation with ventricular rates ≥ 180 beats/min. Device therapies included in the fast VTE endpoint comprised both ATP and shocks, with a detection threshold as defined above. All therapies were adjudicated by an independent committee that was blinded to treatment allocation. This rate was selected as nearly all devices were programmed to detect such arrhythmias. Only the first recorded VTE for

each patient in any 24-h period of follow-up was included to reduce the effect of ventricular tachycardia storms on the primary outcome. As previously reported, because the benefit of CRT-D appears to be restricted to patients with LBBB at baseline (8), we further stratified the treatment effects by QRS morphology.

Statistical methods. FIRST AND SUBSEQUENT VTEs. Because the risk of VTEs increased after a first event, the risk of subsequent VTEs was analyzed separately from the first VTE endpoint. No distinctions were made among subsequent VTEs because there was little differential risk for second, third, and more VTEs.

EFFICACY ANALYSES. As previously mentioned, a large number of patients who were initially randomized to ICD-only treatment group crossed over to the CRT-D arm after a first heart failure exacerbation during trial follow-up. Given that many of the ventricular arrhythmias occurred after the first heart failure exacerbation, an efficacy analysis was applied for the present study, recognizing active device type during follow-up. We used the daily records of active device type to conduct an analysis of the primary outcome.

COVARIATE-ADJUSTED ANALYSES OF RISK. Cox proportional hazards modeling was used to perform multivariate analysis of time to first VTE as well as time to first heart failure event or death. In the models, the treatment arm was used as a time-dependent covariate (i.e., comparing risks of

events occurring while specific devices were active by incorporating data for each patient after crossover between devices). Several baseline characteristics were identified using best subsets for inclusion in the multivariate models including age older than 65 years at enrollment, left ventricular end-diastolic volume >240 ml/m² at enrollment (corresponding to the approximate median value), sex, etiology of heart failure (ischemic or nonischemic), history of myocardial infarction, and history of a ventricular tachyarrhythmia. In an additional analysis, the occurrence of heart failure during follow-up was accounted for by including this factor as a time-dependent covariate in the multivariate models. Anderson Gill proportional intensity regression was used to assess the same risk factors for recurrent VTEs among patients who experienced a first VTE. All models included a pre-specified treatment by QRS morphology (LBBB or non-LBBB) interaction.

SURVIVAL CURVES. Survival curves were constructed for the entire study population and stratified by QRS morphology from the date of initial implant to the first VTE or death, whichever occurred first. Among the patients who experienced and survived a first VTE, survival curves were created from the time of the first VTE to a second VTE or death, whichever occurred first, by the device type at the time of the first VTE. Patients were censored at the time of any device change or explantation.

Table 1 Baseline Patient Characteristics by the Number of VTEs During Follow-Up

	No. of VTEs Experienced During Follow-up				p Value*
	No VTE	1 VTE	2 VTEs	≥3 VTEs	
n	1,493	179	57	91	
Characteristic, %					
Randomized to CRT-D	61	56	54	56	0.40
Age ≥65 yrs	55	48	51	36	0.003
Female	27	15	14	14	<0.001
Ischemic NYHA functional class I	14	17	9	16	0.47
Ischemic NYHA functional class II	40	43	40	42	0.87
NYHA class III >3 months before enrollment	10	11	4	12	0.36
≥1 HF event during follow-up	15	27	32	38	<0.001
LBBB	72	64	65	68	0.11
Previous MI	42	52	46	55	0.007
QRS duration >150 ms	66	57	61	59	0.07
BUN >25 mg/dl	25	23	16	26	0.48
SCr ≥1.4 mg/dl	22	20	18	17	0.53
Baseline echocardiographic parameters, %†					
LVEF ≤25%	10	13	21	22	<0.001
LVEDV >240 ml/m ²	44	58	59	53	<0.001
Baseline medications, %					
Amiodarone	7	9	7	12	0.16
Beta-blockers	94	91	89	92	0.19

All entries are percentages with the characteristics among those who experienced the indicated number of VTEs during follow-up; p values are for the overall differences between the number of VTE groups. *The statistical significance of differences between the 4 VTE subgroups was assessed using a chi-square test comparing 4 percentages. †All echocardiographic parameters are based on core laboratory data, and volume measures were indexed to body mass index.

BUN = blood urea nitrogen; CRT-D = cardiac resynchronization therapy defibrillator; HF = heart failure; LBBB = left bundle branch block; LVEDV = left ventricular end-diastolic volume; LVEF = left ventricular ejection fraction; MI = myocardial infarction; NYHA = New York Heart Association; SCr = serum creatinine; VTE = ventricular tachyarrhythmic event.

SOFTWARE. All hypothesis tests were 2 sided with a pre-specified significance level of 0.05. Statistical analysis was performed using SAS version 9.2 (SAS Institute Inc., Cary, North Carolina).

Results

A total of 327 patients experienced at least 1 VTE with a rate ≥ 180 beats/min, of whom 148 (45%) experienced at least 1 subsequent VTE. The baseline characteristics of study patients by the number of VTEs experienced during follow-up are shown in Table 1. Patients with fewer VTEs were more likely to be female, older than 65 years of age at enrollment, and with a lower left-ventricular end-diastolic volume on the baseline echocardiogram. In contrast, patients experiencing more VTEs were more likely to have a lower baseline ejection fraction, a previous myocardial infarction, and a heart failure event during follow-up. Notably, the groups did not differ in the proportion of patients with ischemic or nonischemic cardiomyopathy, LBBB conduction pattern, blood urea nitrogen, creatinine, and treatment with standard medications for heart failure (Table 1).

Effect of CRT-D on the risk of first VTEs. In the total study population, a Kaplan-Meier survival analysis showed that the cumulative probability for the occurrence of a first VTE or death was significantly lower among patients in the CRT-D group than in the ICD-only group ($p = 0.01$) (Fig. 1A). When assessed by QRS morphology, treatment with CRT-D was shown to be associated with a significantly lower rate of a first VTE or death among patients with LBBB ($p < 0.001$) (Fig. 1B), whereas among non-LBBB patients, event rates were nonsignificantly higher in the CRT-D group ($p = 0.15$) (Fig. 1C). Multivariate analysis consistently showed that in the total study population, active treatment with CRT-D was associated with a significant 29% ($p = 0.003$) reduction in the risk of a first VTE compared with ICD-only therapy (Table 2). When assessed by QRS morphology, CRT-D was shown to be associated with a 42% ($p < 0.001$) reduction in the risk of a first VTE among patients with baseline LBBB, whereas among non-LBBB patients, the risk of a first VTE was not significantly different between CRT-D and ICD-only patients (hazard ratio [HR]: 1.05, $p = 0.82$, p for QRS morphology-by-treatment interaction = 0.016) (Table 2).

Effect of CRT-D on the risk of recurrent VTEs. Among patients who experienced a first VTE, Kaplan-Meier survival analysis showed no statistically significant difference between the treatment groups with regard to the occurrence a second VTE or death ($p = 0.87$) (Fig. 2A). Similarly, when assessed by QRS morphology, the cumulative probability of a second VTE or death was not significantly different between the 2 treatment groups among both LBBB patients ($p = 0.42$) (Fig. 2B) and non-LBBB patients ($p = 0.086$) (Fig. 2C).

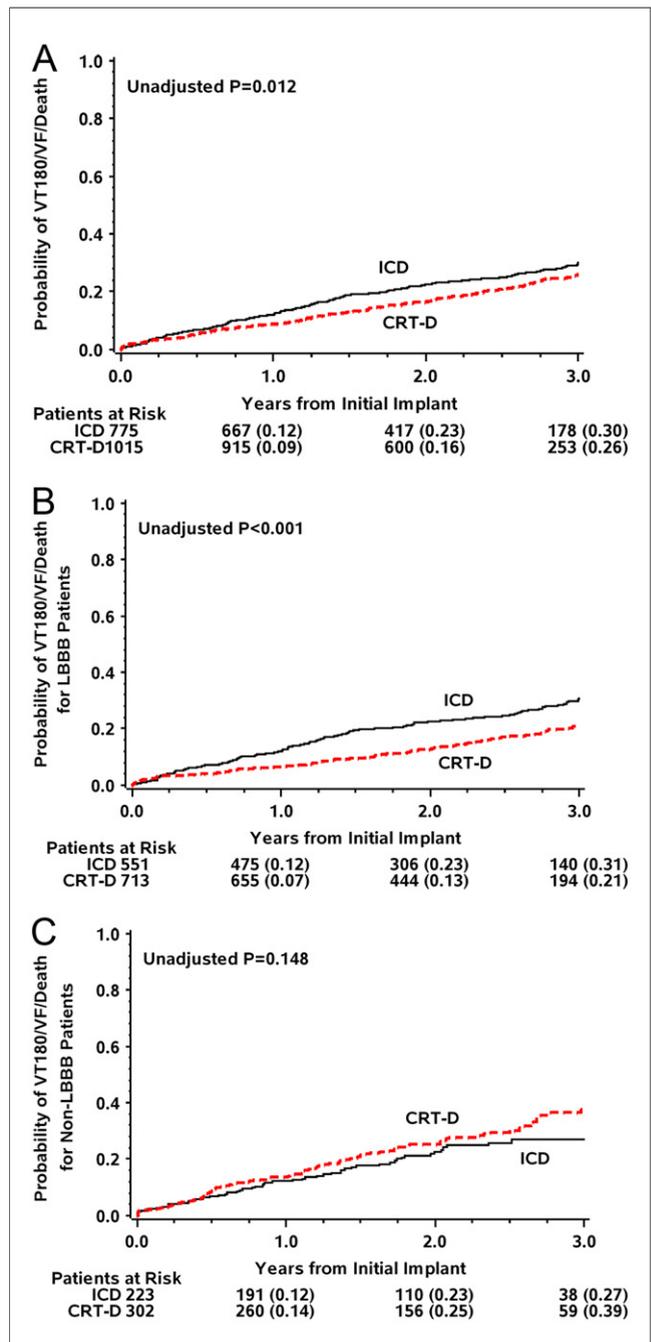


Figure 1 Rate of First VTE or Death by Treatment Arm in the Total Population and Stratified by Baseline LBBB Status

Cumulative probability of the occurrence of a first ventricular tachyarrhythmic event (>180 beats/min) or death by treatment arm in the total study population (A); study patients with left bundle branch block (B); and study patients without left bundle branch block (C). Survival curves were limited to time from implantation, with censoring at any device change or explantation. CRT-D = cardiac resynchronization therapy with a defibrillator; ICD = implantable cardioverter-defibrillator; VF = ventricular fibrillation; VT = ventricular tachycardia.

Consistent with the univariate findings, multivariate Anderson Gill modeling (Table 2) showed that the benefit of CRT-D for VTE reduction was not evident among those who experienced a first event. The treatment effect was

Table 2 **Multivariate Analysis: Impact of Active Device Treatment on the Occurrence of VTE in All Patients and by QRS Morphology***

Endpoint†	By QRS Morphology						
	All Patients		LBBB Patients		Non-LBBB Patients		p Value for difference‡
	HR (95% CI)	p Value	HR (95% CI)	p Value	HR (95% CI)	p Value	
First VTE (CRT-D vs. ICD)	0.71 (0.57–0.89)	0.003	0.58 (0.44–0.77)	<0.001	1.05 (0.71–1.54)	0.82	0.02
Subsequent VTEs (CRT-D vs. ICD)	1.58 (0.99–2.53)	0.05	0.98 (0.61–1.60)	0.95	3.62 (1.59–8.26)	0.002	0.009

*Efficacy analyses compare active CRT-D use relative to ICD use, using daily records; results for periods with no active device, having limited data, are omitted here. †The endpoint of a first VTE was assessed in 1,820 patients (310 events) using Cox proportional hazards regression modeling, and the endpoint of subsequent VTEs was assessed in the 310 patients with a first VTE (451 events) using Anderson-Gill regression modeling. All findings are further adjusted for age 65 years and older at enrollment, left ventricular end-diastolic volume ≤ 240 , sex, etiology of heart failure (ischemic or nonischemic), history of myocardial infarction, and history of a ventricular tachyarrhythmia before enrollment. For the subsequent VTE model, time to first VTE was estimated and found not to be a significant predictor; similar results were obtained in the models that included the occurrence of time-dependent heart failure as an additional covariate. ‡No other statistically significant interactions in the models for VTEs were identified once LBBB status was included in the model.

CI = confidence interval; HR = hazard ratio; ICD = implantable cardioverter-defibrillator; VTE = ventricular tachyarrhythmic event; other abbreviations as in Table 1.

again significantly different between the different conduction disturbance groups. Among patients with LBBB, there was a neutral treatment effect on the risk of recurrent VTEs after a first event (HR: 0.98, $p = 0.95$), whereas among non-LBBB patients who experienced a first VTE, active treatment with CRT-D was associated with >3-fold increase in the risk of subsequent VTEs (HR: 3.62; $p = 0.002$, p for QRS morphology-by-treatment interaction = 0.009) (Table 2).

VTEs and the risk of subsequent heart failure or death.

The occurrence of a first VTE did not significantly increase the risk of heart failure or death; however, second and third VTEs were significantly associated with this risk (HR: 2.44; $p = 0.010$ and HR: 3.26; $p < 0.001$, respectively [Table 3]). There were no significant VTEs by QRS morphology interactions, indicating a similar effect of cumulative VTEs on the endpoint of heart failure or death between the QRS morphology subgroups (not shown).

Notably, the effect of a first VTE on subsequent outcomes was not significantly different between first events associated with shock therapy versus those associated with ATP (first shock vs. ATP risk of subsequent VTEs: HR: 0.86 [95% confidence interval: 0.62 to 1.19]; first shock versus ATP risk of subsequent heart failure/death: HR: 0.86 [95% confidence interval: 0.52 to 1.43]).

Relation between change in cardiac volumes at 1 year and the risk of subsequent VTEs.

We carried out an additional exploratory analysis in an attempt to identify a mechanistic link between the effect of CRT-D on the risk of recurrent VTEs and its relation to QRS morphology. Patients with non-LBBB conduction pattern were twice as likely to have experienced a lack of response to CRT as measured by echocardiographic parameters (48% in patients with non-LBBB vs. 24% in patients with LBBB) (Fig. 3). Multivariate analysis showed that among echocardiographic responders at 1-year treatment with CRT-D was associated with a significant 46% ($p < 0.001$) reduction in the risk of subsequent VTEs, whereas among echocardiographic nonresponders, CRT-D was associated with a significant 45% ($p < 0.001$) increase in the risk of subsequent VTEs (Table 4).

Discussion

To our knowledge, the present study is the first to assess the effect of treatment with CRT-D on the risk of recurrent VTEs. Our findings show that in the MADIT-CRT population: 1) active treatment with CRT-D was associated with a significant reduction in the risk of a VTE (>180 beats/min); 2) the beneficial effects of CRT-D therapy on the risk of a first VTE were related to a pronounced effect on arrhythmic risk among patients with LBBB at enrollment; 3) despite the beneficial effects of CRT-D on the risk of a first VTE in LBBB patients, once a patient experiences an arrhythmic event with the device, the effects of this therapy on subsequent VTEs are neutral compared with ICD alone; 4) patients with a non-LBBB morphology before device implantation experienced an increased risk of subsequent VTEs with CRT-D; and 5) the occurrence of recurrent VTEs increases the subsequent risk of death or heart failure exacerbations.

CRT-D reduces the risk of heart failure exacerbations for patients at both early and late stages of congestive heart failure (6,12–14). However, mounting evidence suggests that the benefit derived from CRT-D varies significantly by baseline conduction disturbances. The risks of initial heart failure and initial ventricular arrhythmia were reduced by CRT-D to a greater extent in patients with LBBB than in those without LBBB (8,12,15–19). Patients with LBBB experience greater reverse remodeling than those without due to correction of greater underlying mechanical dyssynchrony (20–24), and greater reverse remodeling predicts greater reductions in the risk of a heart failure exacerbation (25). We recently showed that the reduction in the risk of ventricular tachyarrhythmic events in MADIT-CRT is related to the degree of echocardiographic response to the device (26). Furthermore, in the present study, we show that the frequency of echocardiographic nonresponse to CRT was 2-fold higher among non-LBBB patients compared with LBBB patients and that echocardiographic response to CRT-D was related to the risk of subsequent VTEs. Thus, the present findings among non-LBBB patients regarding the lack of CRT reduction in the risk of a first VTE and

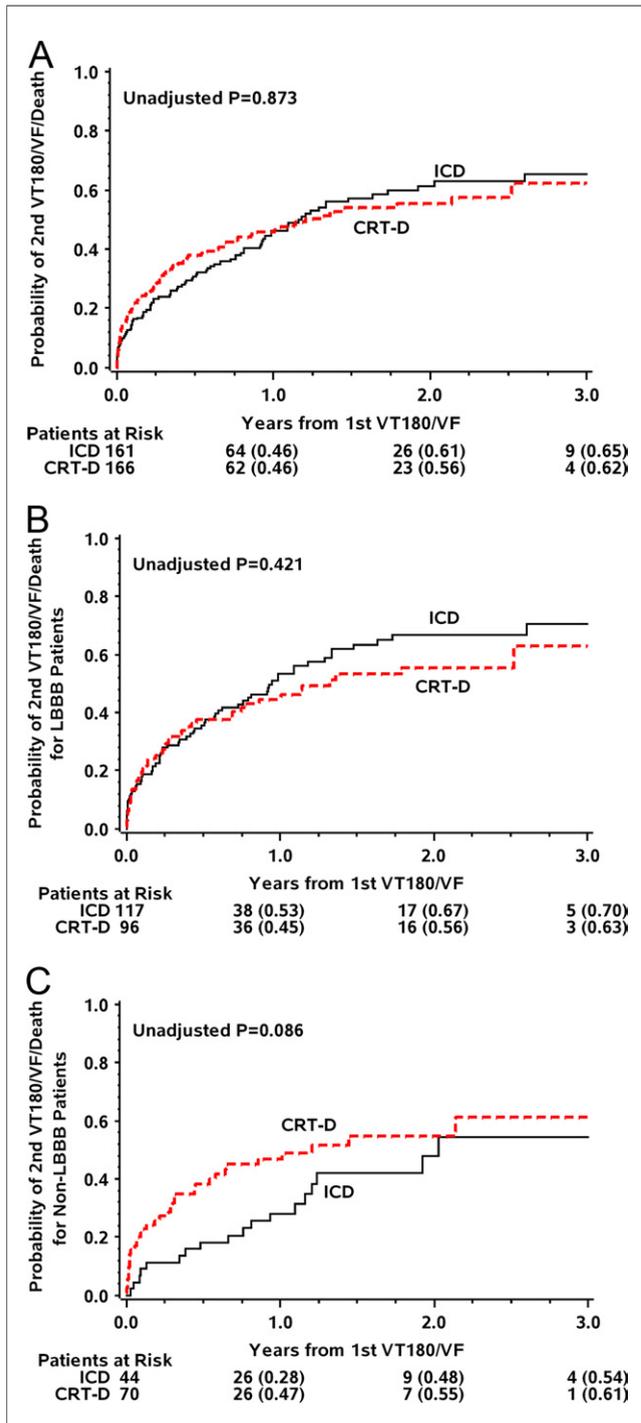


Figure 2 Rate of Second VTE or Death Following a First Event by Treatment Arm in the Total Population and Stratified by Baseline LBBB Status

Cumulative probability of a second ventricular tachyarrhythmic event (VTE) (>180 beats/min) or death after the occurrence of a first event in the total study population (A); study patients with LBBB (B); and study patients without LBBB (C). Survival curves were limited to time after the occurrence of a first VTE, with censoring at any device change or explantation. LBBB = left bundle branch block; abbreviations as in Figure 1.

Table 3 Multivariate Analysis: Impact of Time-Dependent VTEs on the Occurrence of a First Heart Failure Event or Death in the Total Study Population

Risk Factor	HR	95% CI	p Value
First VTE vs. no VTE	1.33	0.90–1.96	0.15
Second VTE vs. no VTE	2.44	1.23–4.82	0.01
Third VTE vs. no VTE	3.26	1.79–5.93	<0.001

Adjusted for 65 years of age and older at enrollment, assigned treatment at randomization, diabetes mellitus, heart rate ≥ 80 , QRS duration ≥ 150 ms, ejection fraction $\leq 25\%$, left atrial volume (treated as a continuous variable), estimated glomerular filtration rate ≥ 60 ; results were similar in LBBB and non-LBBB patients (all p values for VTE-by-QRS morphology interactions >0.20).

Abbreviations as in Tables 1 and 2.

increased risk of subsequent VTEs may be related to the higher frequency of nonresponders in this patient subset. Lending biological plausibility to this explanation is evidence that reverse remodeling involves the restoration of myocardial ion channel homeostasis (27), dysregulation of which is likely involved in the pathogenesis of arrhythmias in the setting of heart failure (28–30). In addition, a potential mechanism for the proarrhythmic role of CRT-D in non-LBBB patients is the reversal of left ventricular activation and increased transmural dispersion of repolarization with epicardial pacing, thus allowing for the development of early after depolarizations and re-entrant circuits (31,32).

Other factors beyond mechanical dyssynchrony may also contribute to the differential response to CRT-D illustrated in this study. For example, the non-LBBB group has a greater percentage of male patients and ischemic etiology, both of which have been shown to predict less response to CRT, although these factors were adjusted for in multivariate analysis (33,34). In addition, data from the InSync Italian ICD Registry also suggest that VTEs differ in rate and frequency of self-termination between ischemic and nonischemic patients (35). Thus, it is possible that CRT-D

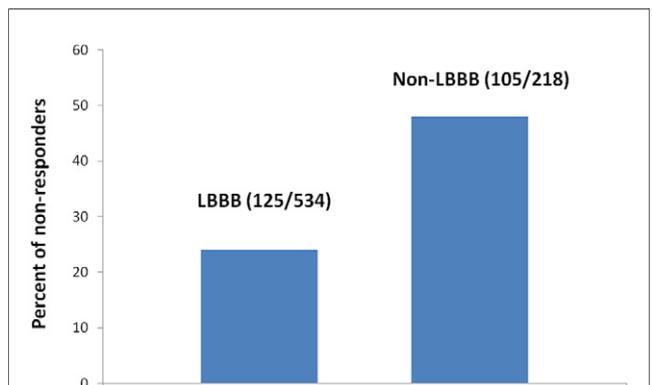


Figure 3 Percentage of Echocardiographic Nonresponders to CRT-D at 1 Year of Follow-Up by QRS Morphology

Fractions listed above columns represent the number of nonresponders among CRT-D patients with and without left bundle branch block, respectively. Echocardiographic nonresponse was defined as a $<25\%$ reduction in left ventricular end-systolic volume (LVESV) at 12 months of follow-up, corresponding to less than the first quartile of percentage of reduction in LVESV. CRT-D = cardiac resynchronization therapy with a defibrillator.

Table 4

Multivariate Analysis: Impact of Nonresponder Status at 12 Months of Follow-Up on the Occurrence of Recurrent VTEs

Treatment Effect	HR	95% CI	p Value
CRT-D responder* vs. ICD	0.54	0.42–0.68	<0.001
CRT-D nonresponder† vs. ICD	1.45	1.17–1.80	<0.001

Follow-up for the occurrence of recurrent VTEs was started after the 12-month echocardiographic assessment. The endpoint of recurrent VTEs (≥ 1 event) was assessed using Anderson-Gill regression modeling. All findings are further adjusted for age 65 years and older at enrollment, left ventricular end-diastolic volume ≤ 240 , sex, etiology of heart failure (ischemic or nonischemic), history of myocardial infarction, and history of a ventricular tachyarrhythmia before enrollment.

*An echocardiographic response to CRT-D was defined as $\geq 25\%$ reduction in left ventricular end-systolic volumes (first quartile) at 1 year of follow-up.

Abbreviations as in Tables 1 and 2.

is less effective in preventing certain types of VTEs that are more common in non-LBBB patients.

This study provides the first evidence that CRT-D does not reduce the risk of subsequent VTEs in LBBB patients and appears to be deleterious in patients with other conduction disturbances. Progression of patients' myocardial disease with further electrical and mechanical changes may have also contributed to subsequent VTEs. It appears that this progression is also accompanied by a higher incidence of heart failure events or death, as shown by our data here. This lends support for close clinical follow-up of patients with recurrent VTEs and may call for more aggressive medical therapy and/or ablation.

Study limitations. The MADIT-CRT was initially designed to identify a treatment effect of CRT-D versus ICD in terms of first heart failure event or death. As such, this study may not be adequately powered to detect potential reductions in the risk of subsequent VTEs in patients with LBBB. Furthermore, adjustment for any imbalances between LBBB and non-LBBB groups was accomplished through the use of covariates in a multivariate model rather than through randomization.

The primary outcome of the present study included the occurrence of appropriate ICD therapies (both ATPs and shocks) delivered for fast VTEs. Thus, endpoint events may have included therapies delivered for nonlife-threatening events such as nonsustained VTEs. These events, however, occurred only in 36 study patients.

Finally, the follow-up duration may have been insufficient to capture a benefit several years after device implantation.

Conclusions

Although CRT-D does reduce the risk of a first VTE in LBBB patients, it does not reduce the risk of subsequent recurrent VTEs. In addition, CRT-D may increase the risk of subsequent VTEs in patients without LBBB. Data here demonstrate that baseline QRS morphology may predict a patient's risk of future VTEs after implantation of CRT-D. Our results also suggest that recurrent VTEs have prognostic implications for heart failure patients, increasing the risk of subsequent heart failure or death. These findings demonstrate the importance of identifying effective interventions to reduce

the risk of subsequent arrhythmic events among patients who experience a first VTE after device implantation.

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Key Words: cardiac resynchronization therapy ■ heart failure ■ implantable cardioverter-defibrillator ■ ventricular tachyarrhythmias.