

Effectiveness of Cardiac Resynchronization Therapy by QRS Morphology in the Multicenter Automatic Defibrillator Implantation Trial–Cardiac Resynchronization Therapy (MADIT-CRT)

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Background—This study aimed to determine whether QRS morphology identifies patients who benefit from cardiac resynchronization therapy with a defibrillator (CRT-D) and whether it influences the risk of primary and secondary end points in patients enrolled in the Multicenter Automatic Defibrillator Implantation Trial–Cardiac Resynchronization Therapy (MADIT-CRT) trial.

Methods and Results—Baseline 12-lead ECGs were evaluated with regard to QRS morphology. Heart failure event or death was the primary end point of the trial. Death, heart failure event, ventricular tachycardia, and ventricular fibrillation were secondary end points. Among 1817 patients with available sinus rhythm ECGs at baseline, there were 1281 (70%) with left bundle-branch block (LBBB), 228 (13%) with right bundle-branch block, and 308 (17%) with nonspecific intraventricular conduction disturbances. The latter 2 groups were defined as non-LBBB groups. Hazard ratios for the primary end point for comparisons of CRT-D patients versus patients who only received an implantable cardioverter defibrillator (ICD) were significantly ($P<0.001$) lower in LBBB patients (0.47; $P<0.001$) than in non-LBBB patients (1.24; $P=0.257$). The risk of ventricular tachycardia, ventricular fibrillation, or death was decreased significantly in CRT-D patients with LBBB but not in non-LBBB patients. Echocardiographic parameters showed significantly ($P<0.001$) greater reduction in left ventricular volumes and increase in ejection fraction with CRT-D in LBBB than in non-LBBB patients.

Conclusions—Heart failure patients with New York Heart Association class I or II and ejection fraction $\leq 30\%$ and LBBB derive substantial clinical benefit from CRT-D: a reduction in heart failure progression and a reduction in the risk of ventricular tachyarrhythmias. No clinical benefit was observed in patients with a non-LBBB QRS pattern (right bundle-branch block or intraventricular conduction disturbances).

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Key Words: bundle-branch block ■ heart failure ■ prognosis ■ cardiac resynchronization therapy ■ implantable cardioverter-defibrillators

Current recommendations regarding clinical management of systolic heart failure include device therapy consisting of an implantable cardioverter defibrillator (ICD) or cardiac resynchronization therapy (CRT) with a defibrillator (CRT-D) combined with optimal pharmacological therapy

according to broadly approved guidelines that are based on results of major clinical trials.^{1–8} CRT is currently approved for patients with advanced heart failure (New York Heart Association [NYHA] class III and IV) and a wide QRS complex, and these patients derive significant benefit from

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this therapy, which results in a reduction of risk of heart failure hospitalizations and deaths, in addition to improvement in patients' functional status.^{4,7,8} Among patients treated with CRT, those with significant QRS prolongation (>150 ms) appear to derive the most benefit, although in most of the studies, there was not sufficient statistical power to document statistically significant interactions of CRT effectiveness with QRS >150ms.⁷⁻¹⁴

Clinical Perspective on p 1072

The benefits of CRT-D were investigated recently in NYHA class I and II heart failure patients with a wide QRS complex who were enrolled in the Multicenter Automatic Defibrillator Implantation Trial–Cardiac Resynchronization Therapy (MADIT-CRT).¹⁵ In this large trial of 1820 patients, CRT-D therapy was associated with a significant 34% reduction of risk of a heart failure event or death compared with ICD therapy.

Recent retrospective single-center studies evaluating the association of QRS morphology with outcome of CRT indicated that patients with left bundle-branch block (LBBB) pattern derived more benefit from CRT than patients with right bundle-branch block (RBBB) or those with nonspecific intraventricular conduction disturbances (IVCD).^{16,17} In the primary MADIT-CRT publication,¹⁵ a significant interaction between treatment arm (CRT-D versus ICD-only) and QRS duration was reported. The present study was undertaken to investigate this effect further and to determine whether specific QRS morphologies identify patients who do and do not benefit from CRT.

Methods

Study Design and Population

The details of the design and study population of MADIT-CRT have been reported previously.¹⁵ Briefly, MADIT-CRT enrolled 1820 patients with ischemic NYHA class I or II symptoms or nonischemic NYHA class II cardiomyopathy, an ejection fraction of 30% or less, and QRS duration of at least 130 ms. The majority (93%) of patients received implants for primary prevention indications, whereas the remaining 7% had evidence of documented tachyarrhythmias with secondary prevention indications. The patients were randomized in a 3:2 ratio to CRT-D or ICD therapy. Patients were required to be undergoing optimal medical therapy. The study was approved by an institutional review committee, and the subjects gave informed consent.

Study End Points

Patients were followed up for an average of 2.4 years, with heart failure event or death as the primary end point. The diagnosis of a heart failure event required signs and symptoms consistent with congestive heart failure that was responsive to intravenous decongestive therapy on an outpatient basis or an augmented decongestive regimen with oral or parenteral medications during an in-hospital stay (87% of heart failure events were inpatient admissions). Secondary end points included death, heart failure event, ventricular tachycardia (VT) or ventricular fibrillation (VF) that required ICD therapy, and VF that required ICD shocks. Secondary combined end points are reported as (1) VT or VF that required ICD therapy or death and (2) VF that required ICD shocks or death. All end points, including death, heart failure events, and VT and VF that required ICD therapy, were centrally adjudicated by respective end-point adjudication committees and core laboratories.

Table 1. Baseline Clinical Characteristics of MADIT-CRT Patients by QRS Morphology

Clinical Characteristics	LBBB (n=1281)	Non-LBBB (n=536)	RBBB (n=228)	IVCD (n=308)
Age, y	64±11	65±10	66±10*	64±10
Females, n (%)	394 (31)	59 (11)†	18 (8)†	41 (13)†
Randomized to CRT-D, n (%)	761 (59)	327 (61)	136 (60)	191 (62)
Ischemic NYHA class I, n (%)	143 (11)	120 (22)†	47 (21)†	73 (24)†
Ischemic NYHA class II, n (%)	420 (33)	314 (58)†	150 (66)†	164 (53)†
Nonischemic NYHA class II, n (%)	718 (56)	102 (19)†	31 (14)†	71 (23)†
Diabetes, n (%)	386 (30)	165 (31)	73 (32)	92 (30)
Hypertension, n (%)	806 (63)	345 (64)	148 (65)	197 (64)
Prior myocardial infarction, n (%)	406 (32)	367 (70)†	167 (76)†	200 (66)†
Prior hospitalization, n (%)	563 (45)	274 (52)	112 (50)	162 (53)
Ejection fraction, %	23.5±5.3	24.5±5.0†	25.2±5.0†	23.9±5.2†
QRS, ms	163±19	146±15†	153±15†	142±14†
BUN, mg/dL	21±9	22±9	22±9	21±9
Creatinine, mg/dL	1.14±0.32	1.23±0.46†	1.28±0.53	1.18±0.40†
BNP, pg/dL (n=1196)	115±148	147±186†	149±193†	146±181†
Distance of 6-MWT, m	364±106	352±109*	344±109†	358±109*
LVEDV, mL	251±66	242±52*	231±45†	250±54*
LVESV, mL	180±53	171±41†	162±35†	177±43†
LAV, mL	94±22	93±21	92±22	94±20
Medication, n (%)				
ACE inhibitors	982 (77)	418 (78)	177 (78)	241 (78)
Angiotensin receptor blockers	278 (22)	98 (18)	42 (18)	56 (18)
β-Blockers	1204 (94)	490 (91)*	202 (89)†	288 (94)
Diuretics	873 (68)	353 (66)	147 (64)	206 (67)

MADIT-CRT indicates Multicenter Automatic Defibrillator Implantation Trial–Cardiac Resynchronization Therapy; LBBB, left bundle-branch block; RBBB, right bundle-branch block; IVCD, intraventricular conduction disturbances; CRT-D, cardiac resynchronization therapy with implanted defibrillator; NYHA, New York Heart Association; BUN, blood urea nitrogen; BNP, brain natriuretic peptide; 6-MWT, 6-minute walk test; LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume; LAV, left atrial volume; and ACE, angiotensin-converting enzyme.

* $P<0.05$.

† $P<0.01$ vs LBBB patients.

Electrocardiograms

Standard 12-lead ECGs were obtained at the time of patient enrollment and were analyzed centrally by the Rochester ECG Core Laboratory. Intraventricular conduction disturbances were defined according to criteria approved by the World Health Organization.^{18,19} LBBB was defined as QRS duration ≥ 130 ms; QS or rS in lead V₁; broad (frequently notched or slurred) R waves in leads I, aVL, V₅, or V₆; and absent q waves in leads V₅ and V₆. RBBB required QRS duration ≥ 130 ms; rsR', rsR', rSR', or qR in leads V₁ or V₂; and occasionally, a wide and notched R wave and wide S waves in leads I, V₅, and V₆. Nonspecific IVCD was defined as QRS ≥ 130 ms without typical features of LBBB or RBBB.

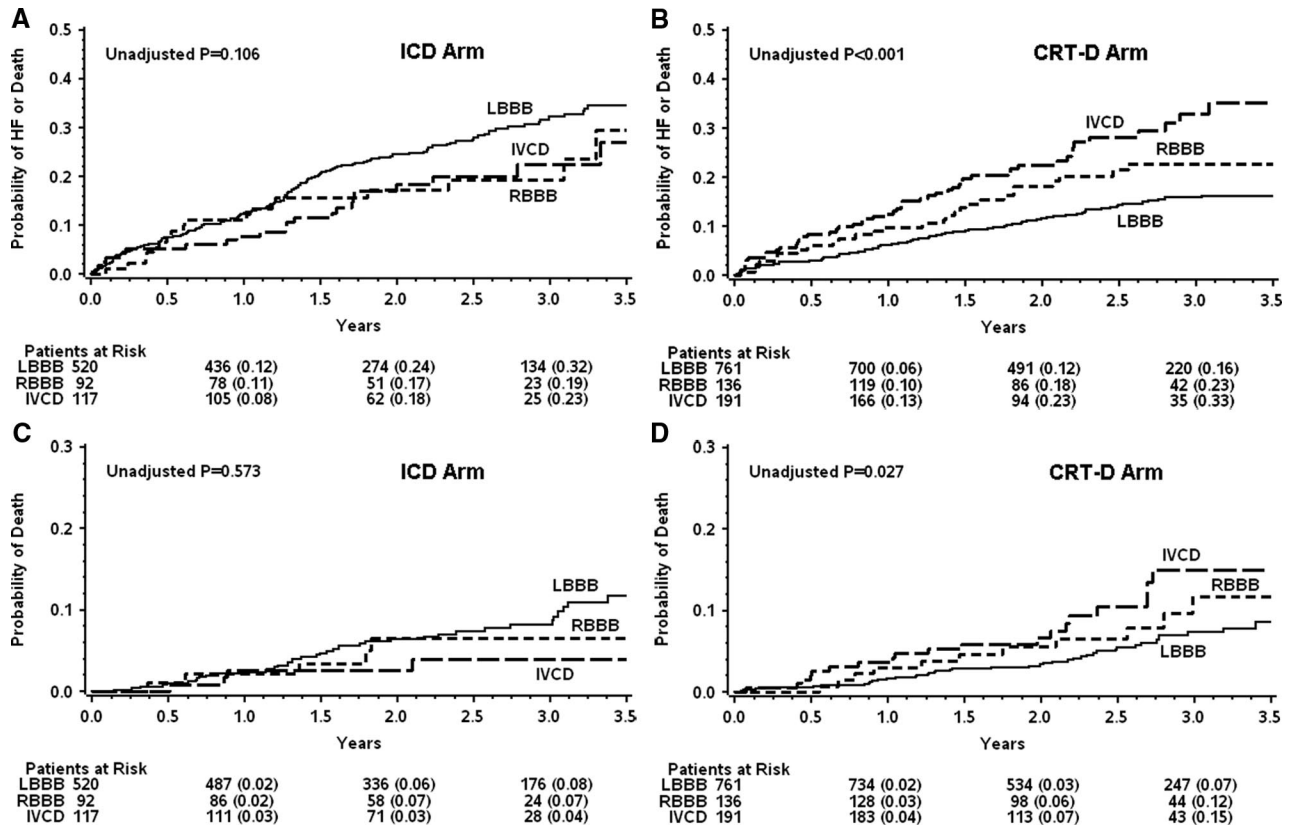


Figure 1. Cumulative probability of heart failure (HF) event or death (top) and of death (bottom) according to QRS morphology in the implantable cardioverter defibrillator (ICD) arm and cardiac resynchronization therapy with defibrillator (CRT-D) arm of the Multicenter Automatic Defibrillator Implantation Trial–Cardiac Resynchronization Therapy (MADIT-CRT). LBBB indicates left bundle-branch block; RBBB, right bundle-branch block; and IVCD, intraventricular conduction disturbances.

Clinical and Echocardiographic Data Collection

Baseline clinical information included patient demographics; data regarding the cause of the cardiomyopathy (ischemic or nonischemic); NYHA class; QRS duration; history of diabetes, hypertension, or revascularization; left ventricular (LV) ejection fraction; distance achieved in a 6-minute walk test; and laboratory variables, including blood urea nitrogen, creatinine, and brain natriuretic peptide.

Echocardiographic images were obtained both at enrollment and at 1-year follow-up in 748 patients randomized to CRT-D and 622 patients randomized to the ICD arm and were centrally interpreted by the Echo Core Laboratory at Brigham and Women's Hospital, Boston, MA. Follow-up echocardiographic images were obtained in the presence of LV pacing in CRT-D patients. Analyses of echocardiographic parameters were focused on LV end-diastolic volume, LV ejection fraction, and left atrial volume. LV volumes were also assessed as index values after adjustment for body surface area. Volumes were estimated by averaging those derived from the 2- and 4-chamber views according to Simpson's method.

Statistical Analysis

Clinical characteristic variables were compared with the Wilcoxon rank sum test for continuous variables and the χ^2 test for categorical variables. The Kaplan-Meier estimator of the survival function was used to evaluate the association between QRS morphologies and outcome, as well as between QRS morphologies and effects of CRT-D versus ICD-only therapy, with the log-rank test used to determine probability values. Cox proportional hazards regression analyses were performed to evaluate effects of CRT-D versus ICD-only therapy on prespecified primary and secondary outcomes.^{20,21} The main analyses were performed with stratification by ischemic status and with adjustment for clinical covariates.

Analyses evaluating the effects of CRT-D versus ICD-only in subgroups of LBBB and non-LBBB patients were performed without adjustment. All analyses were on an intention-to-treat basis, with end points collected by June 23, 2009. Interaction terms of QRS morphology with CRT-D treatment were also tested for the various end points. Changes in echocardiographic parameters from baseline to 1-year follow-up were tested with the Wilcoxon rank sum test of the paired differences. $P < 0.05$ was considered significant. Because these analyses were secondary to the original trial protocol and many statistical tests are performed, all probability values should be considered largely descriptive. Analyses were performed with version 4.0 of the MADIT-CRT database with SAS software (version 9.2).

Results

Clinical Characteristics of Studied Patients

Of the 1820 patients enrolled in MADIT-CRT, 2 had missing ECGs and 1 had an ECG with ventricular pacing; therefore, 1817 patients with available sinus rhythm ECGs were included in the present analysis. There were 1281 patients (70%) with LBBB, 228 (13%) with RBBB, and 308 (17%) with nonspecific IVCD. The latter 2 groups, defined as non-LBBB groups, comprised 536 patients (30%).

Clinical characteristics of LBBB patients, non-LBBB patients, and those with RBBB and IVCD are presented in Table 1. The clinical profile of LBBB patients was significantly different from that of non-LBBB patients. LBBB patients were more frequently women and had more nonischemic cardiomyopathy, wider QRS duration, lower

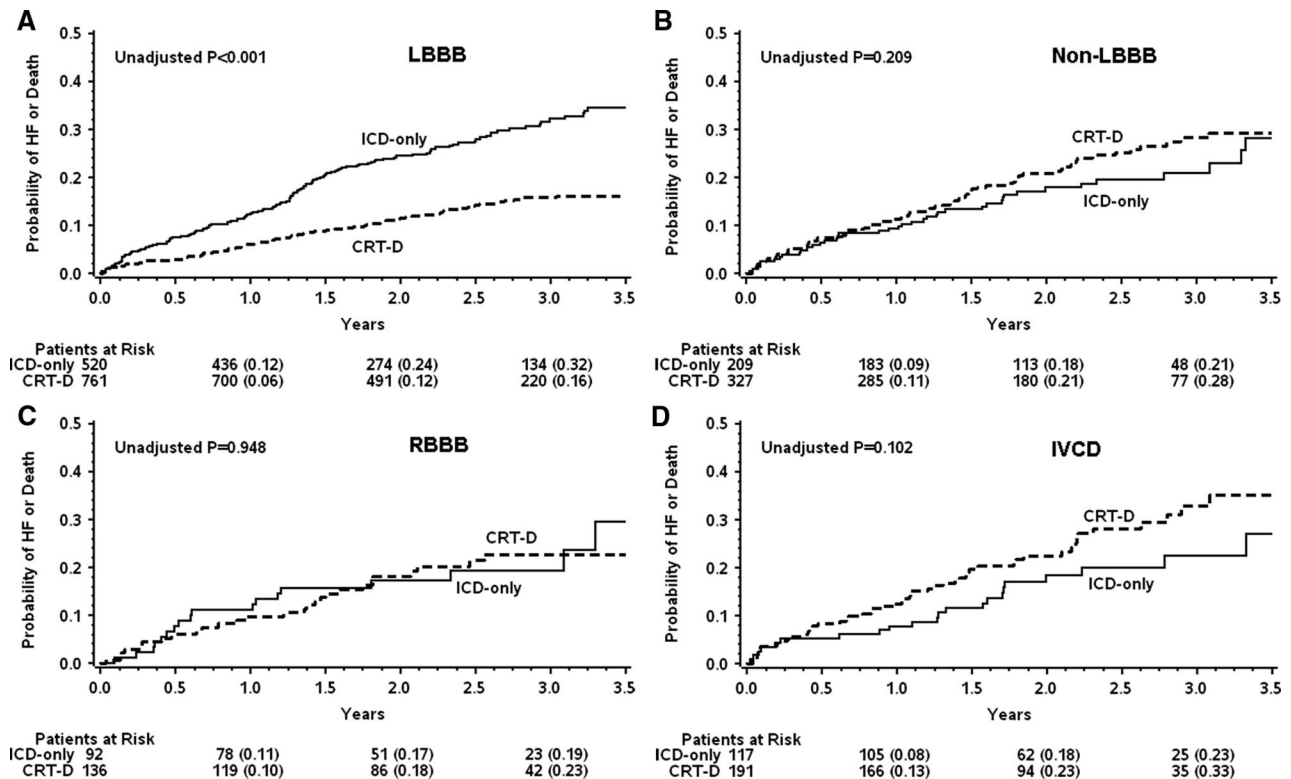


Figure 2. Cumulative probability of heart failure (HF) event or death according to treatment (cardiac resynchronization therapy with defibrillator [CRT-D] versus implantable cardioverter defibrillator [ICD] only) in patients with left bundle-branch block (LBBB), non-LBBB, right bundle-branch block (RBBB), and intraventricular conduction disturbances (IVCD) in Multicenter Automatic Defibrillator Implantation Trial-Cardiac Resynchronization Therapy (MADIT-CRT) patients.

ejection fraction, lower brain natriuretic peptide levels, and larger LV end-diastolic and end-systolic volumes than non-LBBB patients. Separate comparisons of RBBB versus LBBB patients and of IVCD versus LBBB patients revealed similar trends, although the IVCD group had LV ejection fractions and LV volumes similar to those of LBBB patients (Table 1).

Primary and Secondary End Points in Univariate Analyses

The cumulative probabilities of primary end points, consisting of heart failure event or death, and the secondary end point of death in each of the above-mentioned conduction groups are presented in Figure 1. In the ICD arm of the study, the LBBB patients had a nonsignificantly higher risk of primary end points at 3 years than the RBBB patients and IVCD patients (32% versus 19% versus 23%, respectively). Mortality was not different among the LBBB, RBBB, and IVCD groups (8% versus 7% versus 4% at 3 years). In the CRT-D arm, IVCD patients had a significantly higher risk of primary end points (33% versus 23% versus 16%) and a higher risk of mortality (15% versus 12% versus 7%) than RBBB and LBBB patients, respectively.

Regarding the effects of CRT-D versus ICD-only therapy in the studied QRS-based subgroups (Figure 2), only LBBB patients demonstrated a significant reduction in primary end points associated with CRT-D therapy compared with ICD-only therapy. The RBBB and IVCD patients and the overall

group of non-LBBB patients did not show clinical benefit, with a trend toward higher risk in the CRT-D group than in the ICD-only group.

The risk of death did not differ between LBBB patients with CRT-D versus ICD only (Figure 3). However, there was a trend toward reduction in mortality in LBBB patients, whereas the non-LBBB patients demonstrated a trend toward a higher mortality when treated with CRT-D, and this increase was observed primarily in patients with IVCD. The risk of the combined end point that consisted of either VT or VF that required appropriate therapy or death was decreased significantly in LBBB patients treated with CRT-D versus ICD only (Figure 4), but there was a nonsignificant increase in this combined end point in CRT-D patients compared with ICD patients among the non-LBBB patients. A similar trend was observed when we analyzed the combined end point that consisted of VF that required appropriate ICD shocks or death (data not shown).

Primary and Secondary End Points in Multivariate Analyses

Table 2 shows hazard ratios and interaction probability values for primary and secondary end points after adjustment for clinical covariates. The LBBB patients treated with CRT-D experienced a 53% reduction (hazard ratio 0.47; $P<0.001$) in the risk of the primary end point (heart failure event or death) compared with LBBB patients treated with ICD only. The non-LBBB patients did not derive clinical benefit from CRT-D therapy (hazard ratio 1.24, $P=0.257$). The probability

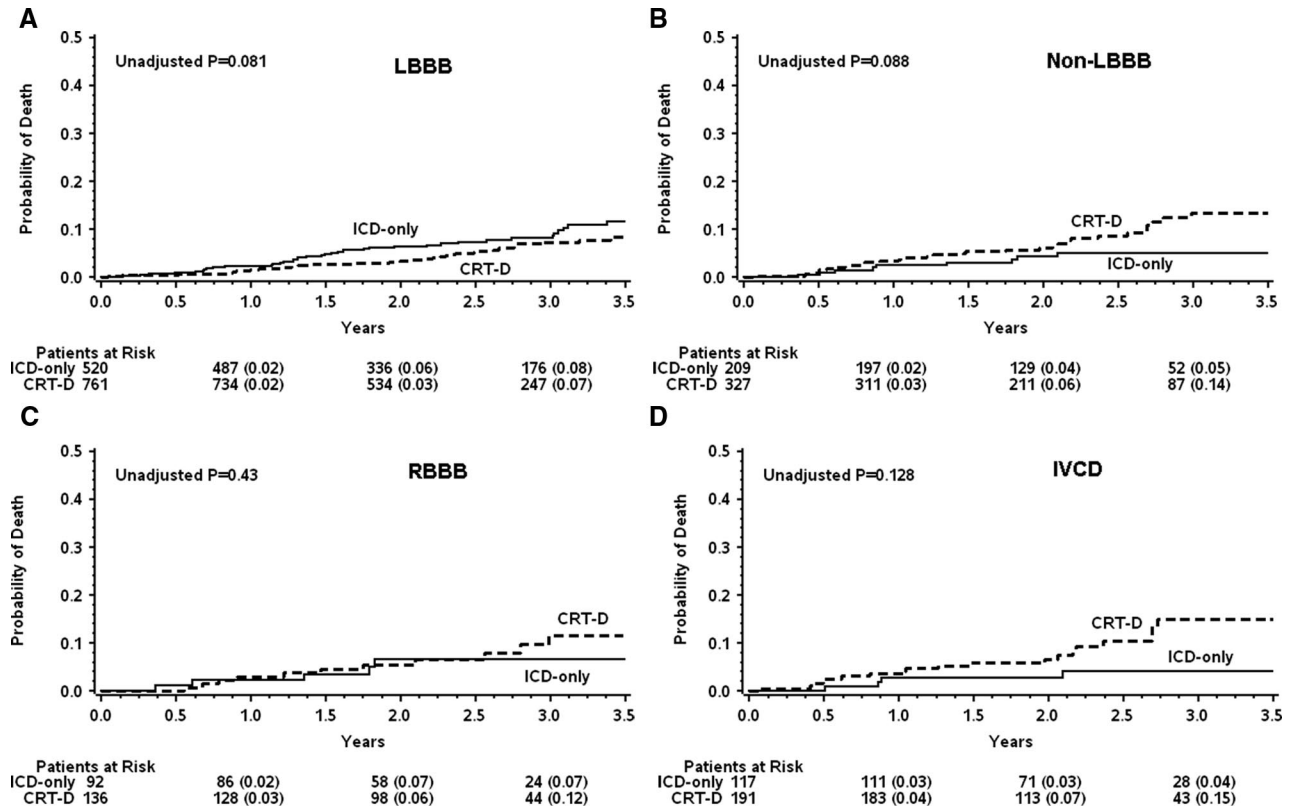


Figure 3. Cumulative probability of death according to treatment (cardiac resynchronization therapy with defibrillator [CRT-D] versus implantable cardioverter-defibrillator [ICD] only) in Multicenter Automatic Defibrillator Implantation Trial–Cardiac Resynchronization Therapy (MADIT-CRT) patients with left bundle-branch block (LBBB), non-LBBB, right bundle-branch block (RBBB), and intraventricular conduction disturbances (IVCD).

value for interaction was <0.001 . The respective hazard ratios for comparisons of CRT-D versus ICD-only therapy were 0.99 ($P=0.969$) in RBBB patients and 1.44 ($P=0.143$) in IVCD patients. Analyses performed with stratification for the enrolling center and for ischemic origin but without adjustment for clinical covariates yielded similar results (not shown).

Among 308 IVCD patients, 191 (62%) had LBBB-like QRS morphology that was characterized by predominantly negative QRS morphology in V_1 through V_3/V_4 and presence of Q waves in V_5/V_6 or lack of significant conduction delay in V_5 and V_6 . When we combined LBBB patients with LBBB-like patients from the IVCD group, the hazard ratios for CRT-D versus ICD only changed from 0.47 to 0.55 ($P<0.001$, 95% confidence interval 0.44 to 0.70), which indicates there was still a highly significant reduction in risk of the primary end point.

Hazard ratios for the individual end points of death, heart failure event, VT/VF, or VF, as well as combined arrhythmia end points without censoring death, are shown in Table 2. Consistently, LBBB patients treated with CRT-D had significant reductions in these end points, apart from death, for which the probability value did not reach significance. No clinical benefit of CRT-D regarding these secondary end points was observed in non-LBBB patients. There was a nonsignificant trend toward a higher risk of these events in patients with IVCD.

LBBB Versus Non-LBBB Patients in Subgroup Analyses

When we analyzed the effect of CRT-D versus ICD-only therapy by QRS duration for each sex, women showed consistently low (unadjusted) hazard ratios in all QRS duration categories (Table 3); however, men with QRS <160 ms showed limited or no benefit from CRT-D. When the analyses were focused on QRS morphology, both men and women with LBBB derived significant benefit from CRT-D, with the risk reduction more pronounced in women than in men ($P=0.006$ for interaction). Men and women with the non-LBBB pattern of QRS complex did not show clinical benefit from CRT-D, with a trend toward harm in the IVCD subgroup.

Apart from sex, additional analyses in subgroups pre-specified in the primary report according to age, NYHA class, QRS duration ≥ 150 ms, LV volumes, and LV ejection fraction showed consistent results that indicated a clinical benefit of CRT-D compared with ICD-only therapy in all subgroups of LBBB patients (Figure 5). In the non-LBBB patients, there was no evidence of clinical benefit from CRT-D regardless of the evaluated subgroup (Figure 5).

Remodeling Effects of CRT-D in LBBB and Non-LBBB Patients

Table 4 shows changes in echocardiographic parameters at 1 year compared with the baseline preimplantation evaluation

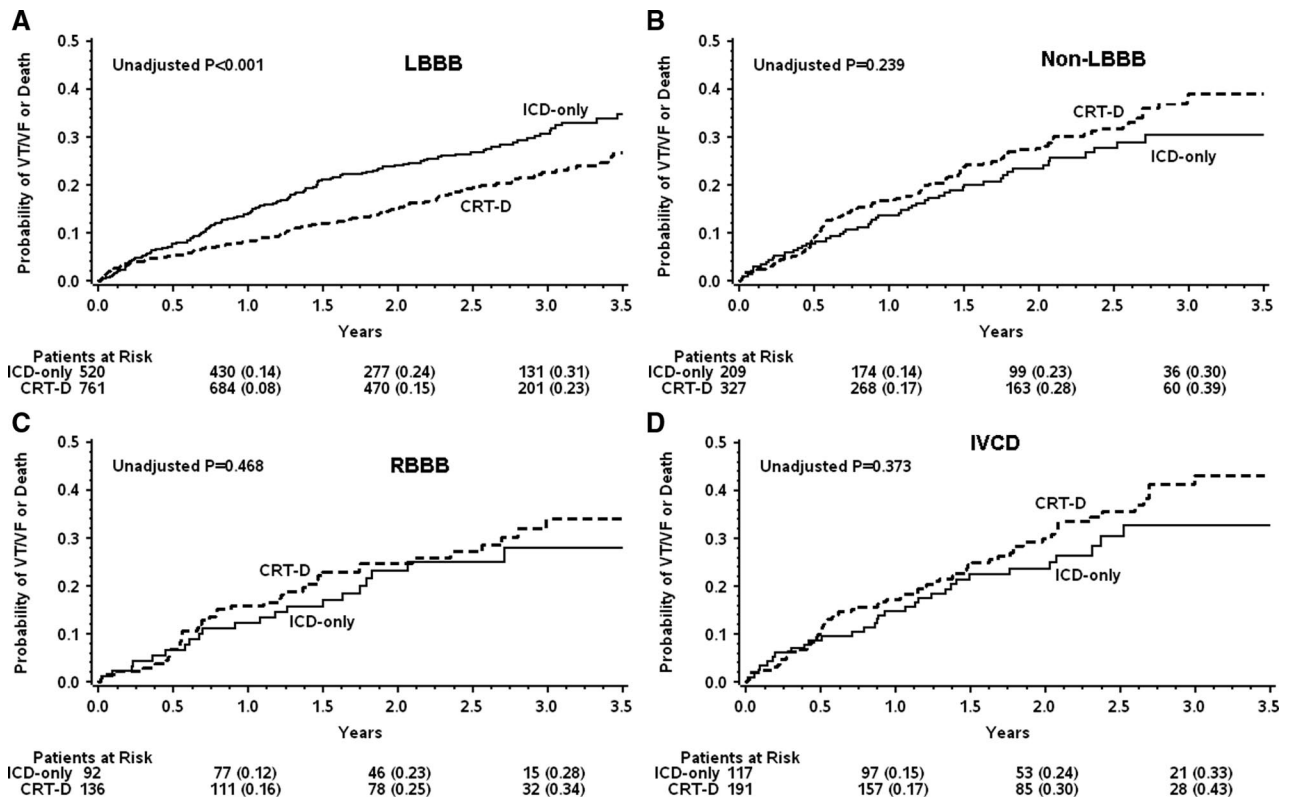


Figure 4. Cumulative probability of combined end point of ventricular tachycardia (VT) or ventricular fibrillation (VF) requiring implantable cardioverter defibrillator (ICD) therapy or death, according to treatment (cardiac resynchronization therapy with defibrillator [CRT-D] versus implantable cardioverter defibrillator [ICD] only) in Multicenter Automatic Defibrillator Implantation Trial-Cardiac Resynchronization Therapy (MADIT-CRT) patients with left bundle-branch block (LBBB), non-LBBB, right bundle-branch block (RBBB), and intraventricular conduction disturbances (IVCD).

in the studied patients with LBBB and non-LBBB QRS patterns. There was a significantly higher reduction in LV volumes (considered as continuous variables) in LBBB than in non-LBBB patients treated with CRT-D. The average reductions in LV end-systolic volume in the CRT-D arm were 35% in LBBB patients and 26% in non-LBBB patients, and average reductions in LV end-diastolic volume were 23% versus 16%, respectively ($P<0.001$ for both comparisons). Similarly, a significantly greater increase in the absolute value of ejection fraction was observed in LBBB than in non-LBBB patients (12% versus 9%, respectively; $P<0.001$). Left atrial volume also showed a significant reduction. Non-LBBB patients treated with CRT-D had significant improvement in volumes compared with non-LBBB patients treated with ICD only ($P<0.001$) for all parameters. These reductions were present in both RBBB and IVCD patients (data not shown).

Comparisons of dichotomized values representing CRT-induced changes in echocardiographic variables are also presented in Table 4. This dichotomized analysis of echocardiographic responders was performed with adjustment for key clinical covariates. After adjustment for sex, ischemic status, and prior hospitalizations for heart failure, CRT-induced changes in dichotomized LV end-diastolic volume and ejection fraction were significantly different in LBBB than in non-LBBB patients. Although dichotomized LV end-systolic volume and left atrial volume showed similar

trends, they did not reach significance after adjustment for these clinical variables.

We also evaluated the relationship between hemodynamic responders, defined as those with a >15% reduction in LV end-systolic volume and primary end points among non-LBBB patients. There was only 1 superresponder, with a reduction >30%. The hazard ratio for non-LBBB nonresponders was 1.81 for CRT-D versus ICD ($P=0.189$, 95% confidence interval 0.75 to 4.39), whereas for non-LBBB responders, it was 2.43 for CRT-D versus ICD ($P=0.156$, 95% confidence interval 0.71 to 8.27). Therefore, among non-LBBB patients, neither hemodynamic responders or nonresponders showed any clinical benefit from CRT-D therapy.

Discussion

The primary finding of the present study is that heart failure patients with a wide QRS complex (≥ 130 ms) and with an LBBB pattern of QRS complex derive significantly more benefit from CRT than patients with non-LBBB QRS morphologies (RBBB and IVCD). This benefit of CRT-D therapy in LBBB patients is associated with a significant 53% reduction in risk of heart failure event or death compared with ICD-only therapy. There also was a significant reduction in the secondary end points of heart failure event, combined end point of VT/VF requiring ICD therapy or death, and combined end point of VF requiring ICD therapy or death, as well

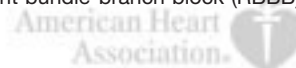


Table 2. Hazard Ratios for CRT-D vs ICD-Only Therapy in Predicting Clinical End Points by QRS Morphology*

End Points	LBBB (n=1281)	Non-LBBB (n=536)	<i>P</i> for Interaction	RBBB (n=228)	<i>P</i> for Interaction	IVCD (n=308)	<i>P</i> for Interaction
Heart failure event or death (n=377)							
HR	0.47	1.24		0.99		1.44	
95% CI	0.37–0.61	0.85–1.81		0.55–1.79		0.88–2.36	
<i>P</i>	<0.001	0.257	<0.001	0.969	0.025	0.143	<0.001
Heart failure event (n=323)							
HR	0.41	1.23		0.88		1.31	
95% CI	0.31–0.54	0.76–1.68		0.46–1.67		0.78–2.18	
<i>P</i>	<0.001	0.559	<0.001	0.690	0.035	0.306	<0.001
Death (n=127)							
HR	0.75	1.79		1.53		2.00	
95% CI	0.49–1.16	0.90–3.57		0.54–4.37		0.80–5.02	
<i>P</i>	0.196	0.097	0.037	0.423	0.219	0.139	0.060
VT/VF (n=365)							
HR	0.67	1.11		1.13		1.09	
95% CI	0.52–0.87	0.77–1.60		0.62–2.08		0.69–1.71	
<i>P</i>	0.002	0.574	0.028	0.685	0.121	0.723	0.073
VF (n=98)							
HR	0.54	1.24		0.94		1.32	
95% CI	0.33–0.87	0.58–2.66		0.21–4.19		0.54–3.25	
<i>P</i>	0.011	0.585	0.070	0.932	0.488	0.544	0.084
VT/VF/death (n=452)							
HR	0.69	1.21		1.26		1.18	
95% CI	0.55–0.87	0.87–1.69		0.74–2.15		0.77–1.79	
<i>P</i>	0.002	0.254	0.006	0.393	0.041	0.453	0.029
VF/death (n=211)							
HR	0.63	1.41		1.35		1.43	
95% CI	0.45–0.88	0.84–2.36		0.58–3.17		0.74–2.74	
<i>P</i>	0.007	0.192	0.011	0.486	0.103	0.284	0.029

CRT-D indicates cardiac resynchronization therapy with implanted defibrillator; ICD, implantable cardioverter-defibrillator; LBBB, left bundle-branch block; RBBB, right bundle-branch block; IVCD, intraventricular conduction disturbances; HR, hazard ratio; 95% CI, 95% confidence interval; VT, ventricular tachycardia; and VF, ventricular fibrillation.

P for interaction between LBBB and non-LBBB, LBBB and RBBB, and LBBB and IVCD, respectively. Number of patients with events is presented for each end point.

*The model adjusted for sex, ischemic or nonischemic cardiomyopathy, prior hospitalizations for heart failure, QRS>150 ms, left ventricular ejection fraction, and left ventricular end-systolic volume.

as a significant decrease in the occurrence of VT/VF and VF alone.

Non-LBBB patients did not benefit clinically from CRT-D therapy, with some trends toward a nonsignificant increase in primary and secondary end points. The findings regarding the clinical benefit of CRT-D in LBBB but not in non-LBBB patients were consistent throughout the MADIT-CRT population evaluated by age, sex, NYHA class, ischemic or nonischemic origin, QRS duration, and baseline hemodynamic status.

The present findings also showed that the echocardiographically measured remodeling effect of CRT in LBBB patients was significantly more pronounced than in non-LBBB patients. Interestingly, CRT in non-LBBB patients also contributed to a significant reduction in the measured volumes and an increase in ejection fraction despite the lack of clinical benefit measured by cardiac end points.

Reduction in volumes and improvement in ejection fraction in non-LBBB patients did not translate to a reduction in heart failure events.

Regarding prior studies on QRS morphology and outcome of CRT, Bristow et al,⁷ in the Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure (COMPANION) trial involving advanced heart failure patients, reported no significant difference in the risk of primary or secondary end points between the 70% of patients with LBBB and the remaining patients (representing both RBBB and IVCD); however, there was a trend toward lower mortality in LBBB patients treated with CRT than in those receiving only pharmacological therapy. A few single-center studies have been conducted. Iler et al²² evaluated 337 patients who received CRT and were followed up for 27 months on average, with death or heart transplantation as the primary end point. An LBBB pattern was observed in 45% of

Table 3. Hazard Ratios for CRT-D vs ICD-Only for Primary End Point by QRS Morphology and Duration for Each Sex

	Males			Females		
	n	HR (95% CI)	P	n	HR (95% CI)	P
QRS duration						
<140 ms	240	1.69 (0.97–2.95)	0.063	61	0.20 (0.06–0.66)	0.008
140–159 ms	465	0.77 (0.52–1.12)	0.164	178	0.31 (0.15–0.63)	0.001
160–179 ms	417	0.51 (0.33–0.79)	0.003	153	0.42 (0.19–0.94)	0.036
≥180 ms	242	0.50 (0.28–0.89)	0.019	61	0.33 (0.09–1.23)	0.100
QRS morphology						
LBBB*	887	0.56 (0.42–0.75)	<0.001	394	0.25 (0.15–0.41)	<0.001
Non-LBBB	477	1.25 (0.84–1.85)	0.273	59	1.55 (0.41–5.88)	0.516
RBBB	210	0.94 (0.52–1.72)	0.841	18	NA	
IVCD	267	1.49 (0.89–2.52)	0.133	41	1.31 (0.33–5.26)	0.701

CRT-D indicates cardiac resynchronization therapy with implanted defibrillator; ICD, implantable cardioverter-defibrillator; HR, hazard ratio; 95% CI, 95% confidence interval; LBBB, left bundle-branch block; RBBB, right bundle-branch block; IVCD, intraventricular conduction disturbances; and NA, not available.

Unadjusted hazard ratios are presented.

* $P=0.006$ for interaction comparing HR=0.56 in males vs HR=0.25 in females (differences in hazard ratios of other QRS categories by sex were not significant).

patients, but the LBBB pattern was not predictive for death. Adelstein and Saba¹⁶ evaluated a retrospective cohort of 636 patients who had LBBB (65%), paced QRS (26%), or RBBB (10%) and found that 3-year average survival was significantly better in LBBB than in RBBB patients, and there was a trend toward better survival in LBBB versus paced QRS patients. A similar series of 338 de novo CRT patients was described by Wokhlu et al¹⁷; 67% of patients had LBBB, 11% had RBBB, 13% had IVCD, and 9% had narrow QRS. Survival over a median 2.6 years of follow-up was significantly lower in RBBB than in LBBB patients, and there was a trend toward lower survival in IVCD than in LBBB patients. Gervais et al²³ reported a subanalysis of the CARE-HF (Cardiac Resynchronization in Heart Failure) trial and found that RBBB was associated with increased risk of heart failure hospitalization or death. Kronborg et al,²⁴ who studied 659 CRT patients with predominantly NYHA class III undergoing CRT (65%) or CRT-D (35%) treatment, showed increased mortality in LBBB patients compared with RBBB or right ventricular-pacing patients. The present study included patients with less advanced heart failure and used defibrillators in all patients, and the CRT-D arm showed that mortality in LBBB patients was lower than that in RBBB and IVCD patients. All of the above cohorts were dominated by patients with more advanced heart failure, in whom CRT devices had been implanted for clinically approved indications. The present findings in patients with less advanced heart failure who were participating in a large prospective trial demonstrated that LBBB patients but not RBBB and IVCD patients experienced significant reductions in heart failure progression.

The questions raised by the present study include why LBBB patients benefit clinically from CRT, whereas RBBB and IVCD patients do not show any reduction in cardiac events; why the remodeling of the LV observed in RBBB and

IVCD patients is not accompanied by a reduction in cardiac events; and whether CRT could increase the risk of cardiac events in patients without LBBB. In LBBB, the LV free wall is activated with significant delay compared with the inter-ventricular septum, and generalized dyssynchrony is present in the majority of patients with LBBB.^{25–28} RBBB is associated with early activation of the LV free wall and has less of a delay of the septum and therefore less dyssynchrony.²⁷ Similarly, IVCD patients, who usually present with a less prolonged QRS complex, show less (but more heterogeneous) dyssynchrony than LBBB patients.^{28,29} Thus, the benefit derived from CRT may reflect more LV dyssynchrony in LBBB than in non-LBBB patients. The nature of conduction delay might also be different in LBBB and non-LBBB patients. The delay in non-LBBB patients is most likely caused by generalized slow conduction in LV that is related to ischemic endocardial damage rather than to discrete bundle-branch disease.³⁰ The non-LBBB patient group in the present study was dominated by ischemic patients, who usually respond less favorably to CRT than nonischemic patients. It is possible that non-LBBB patients might require more time to derive clinical benefit from CRT than LBBB patients, but other factors might also play a role, including localization of LV pacing. The present data from MADIT-CRT indicate that LBBB patients from the CRT-D arm of the study had on average a 23% reduction in LV end-diastolic volume, whereas non-LBBB patients had a 16% reduction associated with CRT-D therapy. It is possible that the magnitude of this remodeling effect of CRT in non-LBBB patients is not sufficient to translate into a clinical effect measured by reduction of heart failure events in the limited 2.4-year follow-up period. RBBB is associated with a significant activation delay of the right ventricular free wall, and LV pacing might decrease LV delay but also might contribute to an increase in right ventricular delay.^{26,27,31} IVCD patients do not present with bundle-branch block, and their QRS

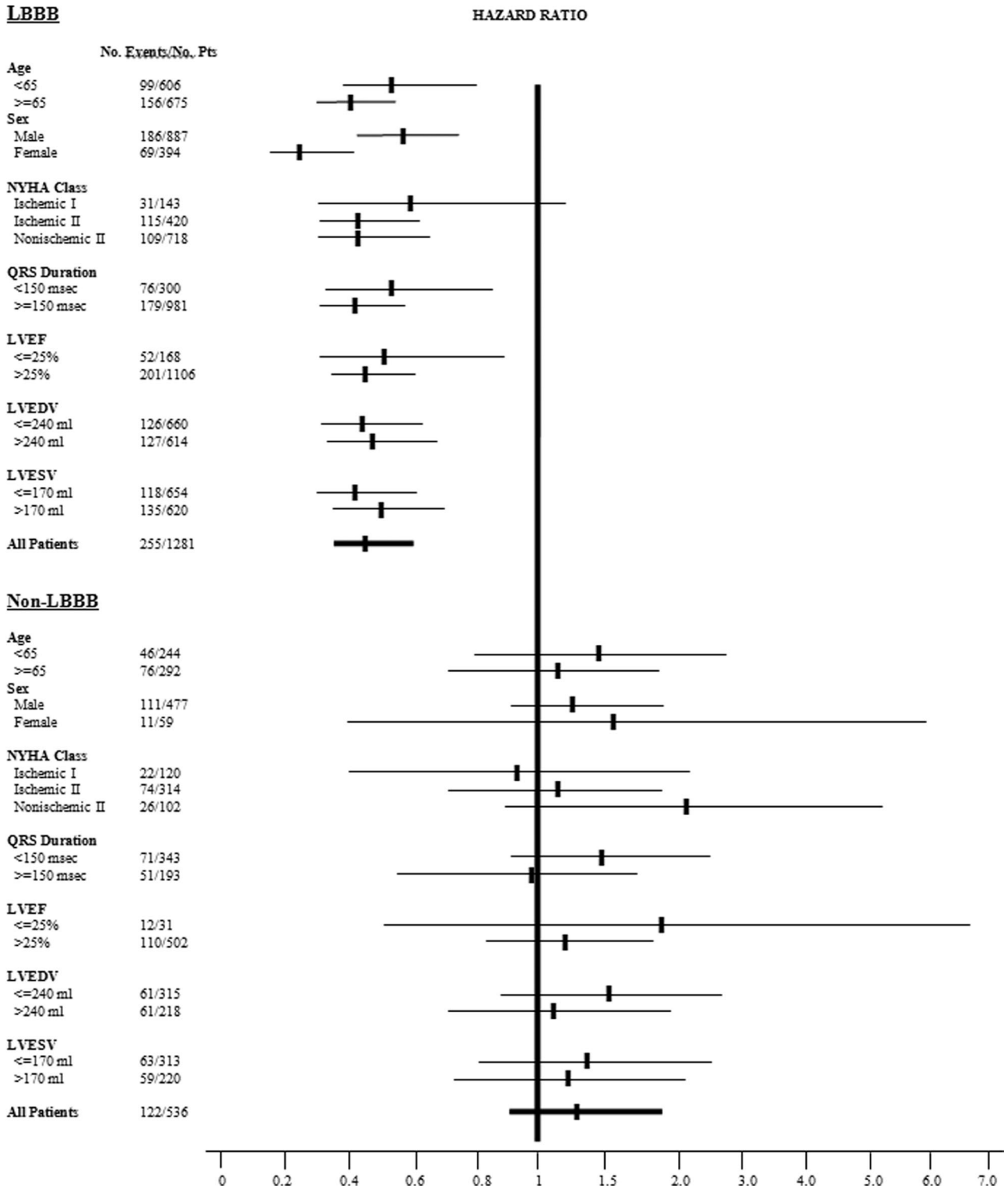


Figure 5. Relative risk of primary end point (heart failure event or death) by treatment (cardiac resynchronization therapy with defibrillator [CRT-D] versus implantable cardioverter defibrillator [ICD] only) according to selected clinical characteristics in patients with left bundle-branch block (LBBB; top) and non-LBBB patients (bottom). NYHA indicates New York Heart Association; LVEF, left ventricular ejection fraction; LVEDV, left ventricular end-diastolic volume; and LVESV, left ventricular end-systolic volume.

widening might be attributed to a more diffused delay of activation or a delay related to ischemia and fibrosis. It could be that this type of conduction delay is less amenable to CRT, but CRT might even increase the activation delay in such patients.

Study Limitations

The question could be raised as to whether the present analysis should be considered a post hoc or prespecified analysis. QRS morphology was not included in the pre-specified set of variables in the primary MADIT-CRT

Table 4. Changes in Echocardiographic Parameters at 1 Year in LBBB and Non-LBBB Patients Treated With CRT-D*

Echocardiographic Parameters	LBBB ICD (n=443)	LBBB CRT-D (n=532)	Non-LBBB ICD (n=179)	Non-LBBB CRT-D (n=216)	P, LBBB CRT-D vs Non-LBBB CRT-D†
LVEDV					
Absolute change	-14.8±14.5	-56.7±34.1	-14.4±14.2	-41.0±28.13	<0.001
Percent change	-5.9±5.7	-22.5±11.4	-5.9±5.7	-16.4±10.5	<0.001
No. of patients with >15% decrease	23 (5%)	390 (73%)	10 (6%)	119 (55%)	<0.001 (0.002)
LVESV					
Absolute change	-18.3±16.5	-62.1±31.5	-17.5±16.1	-45.7±27.3	<0.001
Percent change	-10.1±8.8	-34.8±14.8	-10.2±9.3	-26.3±15.0	<0.001
No. of patients with >15% decrease	119 (27%)	493 (93%)	50 (28%)	188 (87%)	0.010 (0.078)
LVEF					
Absolute change	3.4±3.0	11.9±5.1	3.4±3.1	8.8±4.9	<0.001
No. of patients with >5% decrease	111 (25%)	492 (92%)	56 (31%)	176 (81%)	<0.001 (0.002)
LAV					
Absolute change	-9.3±7.4	-26.3±11.5	-9.8±8.6	-22.7±12.5	<0.001
Percent change	-9.9±7.5	-29.4±12.0	-10.2±8.3	-25.2±12.2	<0.001
No. of patients with >15% decrease	99 (22%)	471 (89%)	34 (19%)	181 (83%)	0.048 (0.094)

LBBB indicates left bundle-branch block; CRT-D, cardiac resynchronization therapy with implanted defibrillator; LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume; LVEF, left ventricular ejection fraction; and LAV, left atrial volume.

Changes in RBBB and IVCD patients were similar to those observed in combined cohort of non-LBBB patients.

* $P < 0.01$ for all comparisons of ICD vs CRT-D within LBBB or non-LBBB groups.

† P values in this column are unadjusted with the exception that values shown in parentheses represent significance of comparison between LBBB and non-LBBB patients in multivariate logistic regression model with dichotomized echocardiography as dependent variable after adjustment for sex, ischemic or nonischemic cardiomyopathy, and prior history of heart failure hospitalization.

report; however, prespecified analyses for the ECG Core Laboratory plan (developed 5 years ago and approved by the Food and Drug Administration) included QRS morphology as a key variable to be evaluated. From the planning perspective, QRS morphology was prespecified; however, it was not included in the set of variables presented in the primary MADIT-CRT manuscript because QRS duration >150 ms was considered more important. We realize that subgroup analyses in studied LBBB and non-LBBB patient cohorts have limited statistical power and should be considered as post hoc analyses, with cautious interpretation of the reported probability values.

An additional limitation of the present study is the relatively short duration of follow-up (29 months on average), which precludes determination of whether CRT-D therapy is likely to influence mortality in studied patients. The estimated 25% reduction in the risk of mortality in LBBB patients was an expected trend. At the same time, the hazard ratio of 1.79 ($P=0.097$) for CRT-D versus ICD-only therapy for predicting mortality in non-LBBB patients raises concerns regarding a possible adverse effect of CRT in non-LBBB patients. Extended follow-up of studied patients is needed to determine whether these trends will be confirmed.

Classic LBBB patterns and LBBB-like QRS morphology that is categorized as IVCD might be challenging to differentiate. However, the present analysis of LBBB-like patients combined with classic LBBB patients yielded very similar results, which indicates that slight differences in interpretation of ECGs do not affect results meaningfully. Additional ECG-based methods of quantifying ventricular activation, as

recently proposed by Sweeney et al,³² might be considered as an alternative to QRS pattern recognition.

Conclusions

In conclusion, heart failure patients with NYHA class I (ischemic only) or NYHA class II (both ischemic and nonischemic) and ejection fraction $\leq 30\%$ who present with LBBB derive substantial clinical benefit from CRT-D: a reduction in heart failure progression and a reduction in the risk of ventricular tachyarrhythmias. No evidence of clinical benefit was observed in patients with a non-LBBB QRS pattern (RBBB or IVCD).

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CLINICAL PERSPECTIVE

There is an increasing interest and need to identify heart failure patients who benefit from cardiac resynchronization therapy (CRT), as well as those who do not. In patients with a wide QRS complex who qualify for CRT, QRS morphology indicates different conduction delays, represented on the ECG as left bundle-branch block (LBBB), right bundle-branch block (RBBB), or nonspecific intraventricular conduction disturbances. The Multicenter Automatic Defibrillator Implantation Trial–Cardiac Resynchronization Therapy (MADIT-CRT) demonstrated that in patients with mild to moderate heart failure, CRT with defibrillator implantation (CRT-D) significantly reduced the risk of heart failure events or death compared with treatment with only an implantable cardioverter-defibrillator. This analysis of the MADIT-CRT trial data demonstrated that compared with non-LBBB patients (those with RBBB or nonspecific intraventricular conduction disturbances), patients with LBBB QRS morphology showed significant clinical benefit from CRT-D therapy, as measured by reduced risk of heart failure event or death and risk of ventricular tachycardia/fibrillation or death. Non-LBBB patients did not benefit clinically despite a significant reduction in left ventricular volumes. These findings formed the basis for recent Food and Drug Administration approval of new broadened indications for CRT in mild or asymptomatic heart failure patients with LBBB. There is still a question as to whether CRT therapy should be used in non-LBBB patients even when advanced heart failure is present and which non-LBBB patients might still benefit clinically from CRT. Further research investigating the rationale, mechanisms, and clinical benefit is needed to determine whether CRT therapy should be pursued in non-LBBB patients.



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