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# Dyssynchrony and the Risk of Ventricular Arrhythmias

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OBJECTIVES The aim of our study was to evaluate the relationship between left ventricular (LV) dyssynchrony and the risk of ventricular tachycardia (VT) or ventricular fibrillation (VF) in patients enrolled in the MADIT-CRT (Multicenter Automatic Defibrillator Implantation Trial—Cardiac Resynchronization Therapy) trial.

BACKGROUND Intraventricular mechanical dyssynchrony might be an important factor in ventricular arrhythmogenesis by enhancing electrical heterogeneity in heart failure patients. The effects of dyssynchrony have not yet been evaluated in a large cohort of implantable cardioverter-defibrillator (ICD) and cardiac resynchronization therapy with defibrillator (CRT-D) patients.

METHODS LV dyssynchrony was measured at baseline and at 12-months by speckle-tracking echocardiography, defined as the standard deviation of time to peak systolic strain in 12 LV myocardial segments. The endpoint was the first VT/VF/death or VT/VF. LV dyssynchrony was evaluated in 764 left bundle branch block (LBBB) patients and in 312 non-LBBB patients.

RESULTS Baseline LV dyssynchrony was not predictive of VT/VF/death or VT/VF in LBBB or non-LBBB patients in either treatment arm. In CRT-D patients with LBBB, improvement in LV dyssynchrony over a year was associated with significantly lower incidence of VT/VF/death ($p < 0.001$) and VT/VF ($p < 0.001$) compared to ICD patients and to CRT-D patients with unchanged or worsening dyssynchrony. Among LBBB patients, 15% decrease in LV dyssynchrony was associated with lower risk of VT/VF/death (hazard ratio: 0.49, 95% confidence interval: 0.24 to 0.99, $p = 0.049$) and VT/VF (hazard ratio: 0.30, 95% confidence interval: 0.12 to 0.77, $p = 0.009$) as compared to ICD patients. Patients without LBBB receiving CRT-D did not show reduction in VT/VF/death or in VT/VF in relation to improving dyssynchrony when evaluating cumulative event rates or risk of events.

CONCLUSIONS Baseline LV dyssynchrony did not predict VT/VF/death or VT/VF in mild heart failure patients with or without LBBB. CRT-induced improvement of LV dyssynchrony was associated with significant reduction of ventricular arrhythmias in patients with LBBB. (Multicenter Automatic Defibrillator Implantation Trial With Cardiac Resynchronization Therapy [MADIT-CRT]; NCT00180271) (J Am Coll Cardiol Img 2013;6: 432–44) © 2013 by the American College of Cardiology Foundation

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Cardiac resynchronization therapy (CRT) has been shown to improve heart failure symptoms, quality of life, and to reduce heart failure hospitalizations in moderate or severe heart failure patients (1–5). CRT corrects the dyssynchronous left ventricular (LV) activation pattern, thereby increasing the LV systolic function, inducing reverse remodeling and improving the long-term survival (6–8).

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The MADIT-CRT (Multicenter Automatic Defibrillator Implantation Trial–Cardiac Resynchronization Therapy) study has recently demonstrated that CRT combined with an implantable cardioverter-defibrillator (CRT-D) reduces heart failure or death in mildly symptomatic or asymptomatic heart failure patients with severe left ventricular dysfunction and a prolonged QRS (9). The MADIT-CRT and the RAFT (Resynchronization-Defibrillation for Ambulatory Heart Failure Trial) studies showed that patients with left-bundle branch block (LBBB) benefit the most from CRT compared to non-LBBB patients, including patients with right-bundle branch block (RBBB) and with intraventricular conduction delay (IVCD) (10,11).

Heart failure patients are at high risk of ventricular tachyarrhythmias associated with worse outcome (12). Furthermore, some studies indicated proarrhythmic effects of CRT (13–15), whereas others demonstrated antiarrhythmic effects, explained by improved hemodynamic status and left ventricular reverse remodeling (16–19).

Intraventricular mechanical dyssynchrony might play an important role in the development of VT/VF by abnormal mechanical and subsequent electrical activation inducing electrical heterogeneity. This association has not yet been investigated in a randomized clinical trial on implantable cardioverter defibrillator (ICD) and CRT-D patients.

The aim of the present study was to investigate the association between LV dyssynchrony, CRT-induced change in LV dyssynchrony, and the risk of VT/VF/death or VT/VF events in patients with LBBB and with non-LBBB, enrolled in the MADIT-CRT study.

## METHODS

**Patient population.** The MADIT-CRT trial was a prospective randomized multicenter trial designed to determine whether CRT-D therapy would reduce the primary endpoint of heart failure events or death in mildly symptomatic or asymptomatic heart failure patients (ischemic cardiomyopathy with New York Heart Association functional class I or II, nonischemic cardiomyopathy with New York Heart Association functional class II) with severely depressed left ventricular ejection fraction (LVEF) ≤30% and a wide QRS (≥130 ms). The design, protocol (20), and results (9) of the study had been published earlier. A total of 1,820 patients were enrolled in 110 study centers in the United States, Canada, and Europe. Patients were in sinus rhythm and met the guideline criteria for ICD therapy. Patients were randomly assigned to CRT-D or ICD alone in a 3:2 ratio. Screened patients were excluded from enrollment, as specified earlier (20).

**Echocardiographic methods.** Echocardiography investigators and sonographers from each enrolling sites were qualified to perform echocardiography according to the approved echocardiography protocol. Recordings were analyzed off-line at the Brigham and Women's Hospital, Boston, Massachusetts, as an independent echocardiography core laboratory.

LV mechanical dyssynchrony was measured using B-mode speckle tracking software (Amid Cardiac Performance Imaging, TomTec 1.0, Unterschleissheim, Germany), and analyzed off-line, as reported previously (21). On the still 2-dimensional images, the endocardium was traced in end systole in the apical 4- and 2-chamber views. Segments were manually adjusted if the tracking was suboptimal. In case of at least 2 segments that could not be tracked, the study was excluded from the analy-

**ABBREVIATIONS AND ACRONYMS**

**ATP** = antitachycardia pacing
**CI** = confidence interval
**CRT** = cardiac resynchronization therapy
**CRT-D** = cardiac resynchronization therapy with defibrillator
**ECG** = electrocardiogram
**HR** = hazard ratio
**ICD** = implantable cardioverter defibrillator
**IVCD** = intraventricular conduction delay
**LAV** = left atrial volume
**LBBB** = left bundle branch block
**LVEDV** = left ventricular end-diastolic volume
**LVEF** = left ventricular ejection fraction
**LVESV** = left ventricular end-systolic volume
**RBBB** = right bundle branch block
**VF** = ventricular fibrillation
**VT** = ventricular tachycardia

Dentistry. Dr. Kutyifa has received honoraria from Biotronik, Servier, and Boston Scientific. Dr. Al-Ahmad receives honoraria from Medtronic, Boston Scientific, and St. Jude Medical. Dr. Gibinski has consultancy agreements with and speaker fees from Biotronik and Boston Scientific; his wife is a Boston Scientific employee. Dr. Wang receives honoraria from Medtronic and Boston Scientific; and fellowship support from Medtronic, Boston Scientific, and St. Jude Medical. Dr. Merkely has a relationship with Boehringer Ingelheim; and a financial relationships with Biotronik, Medtronic, and St. Jude Medical. Dr. Solomon receives research support from Boston Scientific. Dr. Moss has received a research grant from Boston Scientific. Dr. Zareba has a research grant from Boston Scientific. All other authors have reported they have no relationships relevant to the contents of this paper to disclose.

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sis. Transverse strain is a measure of myocardial thickening (like radial strain from parasternal view) but the nomenclature is different as in this case the apical view is utilized for data analysis (Fig. 1). In this study, the strain curves were not smoothed, although the software does a certain amount of smoothing (by definition). The Tomtec software computes the strain from the integration of the strain-rate field; the strain-rate computation involves the spatial derivative both of velocity and of geometry slope (curvature) along the border. These derivatives are computed with a filter (window width) whose size is one-twelfth of the border length (one-half of a segment). This is made to avoid fluctuations more rapid than half the size of a segment that are most likely due to errors than to actual physiological behavior.

The measurements were evaluated by an investigator blinded to randomization data, baseline clinical characteristics, and outcomes. LV mechanical dyssynchrony was defined as the standard deviation of regional time-to-peak transverse strain, measured in the 12 segments of the left ventricle in the apical 4- and 2-chamber views (septum, lateral, anterior, and inferior walls; all of them subdivided into basal, mid, and apical segments). The intraobserver and interobserver variability for LV dyssynchrony was 13.8% and 15.4% for time-to-peak transverse strain, as reported elsewhere (21,22).

In all, 1,077 patients had digital echocardiograms of sufficient image quality to allow for 2-dimensional speckle tracking analysis (21), after excluding 607 patients with non-DICOM (Digital Imaging and Communications in Medicine) images and 136 patients with poor image quality. Therefore, we analyzed 764 patients (42%) with LBBB and 312 (17%) patients with non-LBBB at baseline. One patient whose electrocardiogram (ECG) pattern was unknown was excluded from the analysis.

Paired echocardiograms from baseline and at 12 months eligible for dyssynchrony analysis were available in 809 of 1,077 patients. The rest of the patients had either poor image quality or their CRT device was off at the time of the echocardiographic analysis. Of the 809 patients with paired echocardiograms, 336 patients received ICD device, 473 patients received CRT-D. Patients with paired echocardiograms had either LBBB ECG pattern (n = 572) or non-LBBB ECG pattern (n = 237).

**Device programming.** Commercially available transvenous single or dual chamber ICD and CRT-D devices (Boston Scientific) were implanted in this study, using standard techniques (20). Devices were programmed with a recommendation of setting the ventricular tachycardia (VT) zone at 180 beats/min and ventricular fibrillation (VF) zone at 210 beats/min. Sensitivity was programmed based on physician discretion. Detection was 2.5 s for the VT zone and 1.0 s for the VF zone. The pre-specified study protocol recommended programming the VT zone therapy to burst-type antitachycardia pacing (ATP) with 8 pulses at 88% of the measured cycle length with 10-ms decrement between bursts, and subsequent shock therapy, with the second suggestion of setting the shock at defibrillation threshold plus at least 10 J. The additional shock therapies were suggested as being maximal energy shocks.

**Patient follow-up, device interrogation.** Patients had a clinic follow-up 1 month after the device implantation and then every 3 months until the end of the trial or in case of heart failure or arrhythmic events. Clinical evaluation and ICD interrogation was performed at each follow-up visit. The ICD interrogation disks at follow-up and after ICD shocks were sent to the interrogation core laboratory (P.J.W., Stanford University) for categorization and final evaluation of detected arrhythmias with ICD therapy (ATP or shock).

**Definitions and study endpoints.** The relationship between baseline LV dyssynchrony and study endpoints was analyzed in the total patient population with LV dyssynchrony data regardless of treatment assignment, split up by LBBB and non-LBBB ECG pattern, because significant differences were demonstrated in clinical outcome and ventricular arrhythmia rate in these patient subgroups as reported elsewhere (10). Patients were grouped into quartiles of baseline LV dyssynchrony, as suggested earlier (22).

The change in LV dyssynchrony was analyzed in CRT-D and ICD patients. In this substudy, ICD patients served as a control group, as it had already been reported that ICD patients show less improvement in LV dyssynchrony than CRT-D patients (21). In this analysis, CRT-D patients with LBBB and with non-LBBB were analyzed separately. The change of LV dyssynchrony was calculated as the difference in LV dyssynchrony from baseline to the 12-month recording. CRT-D patients were categorized into 3 groups based on the change: improving, unchanged, or worsening LV dyssynchrony. Improving LV dyssynchrony was defined as a >15% decrease in LV dyssynchrony, and unchanged dyssynchrony included dyssynchrony

**Figure 1. Assessment of LV Dyssynchrony Before and After CRT-D Implantation**

Two-dimensional speckle-tracking imaging from the apical 4-chamber view **(A)** before and **(B)** after cardiac resynchronization therapy with defibrillator (CRT-D) implantation. The **curves** represent transverse strain and left ventricular (LV) dyssynchrony measured by the standard deviation of time-to-peak transverse strain in 12 LV segments. **(A)** Represents heterogeneous LV activation and significant LV dyssynchrony before CRT-D implantation, whereas **(B)** shows synchronized LV activation after CRT implantation in the same patient.

change <−15% up to +15%. Worsening dyssynchrony was defined as >15% positive change in LV dyssynchrony.

Arrhythmia episodes were defined as any type of therapy delivered including ATP and shocks. Definition of VT was set to a rate from 180 beats/min (recommended programming) up to 250 beats/min, ventricular (V) rate ≥ atrial (A) rate if 1:1 A:V, V-V changes drive AA changes. VF was defined as ventricular rate >250 beats/min with disorganized ventricular electrograms. Only appropriate therapy delivered for VT or VF was considered in the present analysis. Arrhythmia episodes were adjudicated by an independent adjudication committee blinded to treatment assignment and clinical parameters.

The endpoint of the baseline analysis was the first episode of VT/VF or death and first VT/VF events. When analyzing the effects of LV dyssynchrony change at the 12-month follow-up, the first VT/VF events after 1 year assessment or death and first VT/VF after 1 year were considered as endpoints, excluding 25 patients with LBBB and 47 patients with non-LBBB who had VT/VF or death in the first year.

**Statistical analysis.** Continuous variables are expressed as mean ± SD. Categorical data are summarized as frequencies and percentages. Baseline clinical characteristics were compared between the pre-specified non-LBBB and LBBB subgroups, stratified by baseline LV dyssynchrony quartiles or by changes over 1 year in LV dyssynchrony, using nonparametric Wilcoxon or Kruskal-Wallis tests for continuous variables and chi-square test or Fisher exact test for dichotomous variables, as appropriate. When analyzing the effects of LV dyssynchrony change, only the first VT/VF events after the 12-month visit were considered as endpoints.

The correlation of baseline LV dyssynchrony and baseline QRS duration was analyzed using Pearson correlation method. Paired comparisons of baseline LV dyssynchrony and change in LV dyssynchrony at 12 months in LBBB and non-LBBB patients were analyzed using nonparametric Wilcoxon rank-sum test.

Cumulative probability of first VT/VF/death and VT/VF episodes was determined according to the Kaplan-Meier method, with comparisons of cumulative event rates by the log-rank test in non-LBBB and LBBB patients separate. Multivariate Cox propor-

**Table 1. Baseline Characteristics of Patients With LBBB and Baseline LV Dyssynchrony and Patients With Non-LBBB and Baseline LV Dyssynchrony**

| | Quartiles of Baseline LV Dyssynchrony (ms) in LBBB Patients | | | | | |
|---|---|---|---|---|---|---|
| | Less Dyssynchrony | | | More Dyssynchrony | | |
| | 117 ± 23 (n = 193) | 167 ± 10 (n = 189) | 208 ± 12 (n = 195) | 274 ± 41 (n = 187) | p Value | Non-LBBB Patients (n = 312) |
| Age, yrs | 65.4 ± 11.1 | 63.1 ± 11.6 | 62.8 ± 10.8 | 64.6 ± 11.2 | 0.064 | 65.0 ± 10.6 |
| Female | 45 (23) | 62 (33) | 60 (31) | 65 (35) | 0.079 | 36 (12) |
| VT/VF/death | 35 (4.6) | 45 (6.0) | 49 (6.5) | 47 (6.2) | 0.970 | 88 (29) |
| VT/VF | 24 (3.1) | 34 (4.5) | 40 (5.2) | 39 (5.1) | 0.659 | 74 (24) |
| Death | 16 (2.1) | 12 (1.6) | 12 (1.6) | 13 (1.7) | 0.356 | 22 (7) |
| Nonischemic NYHA functional class II | 96 (50) | 103 (54) | 118 (61) | 106 (57) | 0.191 | 52 (17) |
| Ischemic | 97 (50) | 86 (46) | 77 (39) | 81 (43) | 0.191 | 260 (83) |
| Prior CABG | 54 (28) | 40 (21) | 36 (18) | 34 (18) | 0.071 | 140 (45) |
| Prior non-CABG revascularization | 45 (23) | 51 (27) | 30 (15) | 37 (20) | 0.040 | 141 (45) |
| Prior MI | 71 (38) | 59 (32) | 57 (30) | 62 (34) | 0.387 | 221 (72) |
| Past atrial arrhythmias | 24 (13) | 14 (7) | 17 (9) | 13 (7) | 0.220 | 40 (13) |
| Past ventricular arrhythmias | 12 (6) | 10 (5) | 12 (6) | 11 (6) | 0.976 | 25 (8) |
| Creatinine, mg/dl | 1.19 ± 0.33 | 1.10 ± 0.30 | 1.13 ± 0.31 | 1.18 ± 0.35 | 0.031 | 1.24 ± 0.47 |
| QRS, ms | 158.6 ± 17.1 | 160.0 ± 18.1 | 163.7 ± 18.7 | 166.0 ± 19.7 | <0.001 | 144.9 ± 14.0 |
| Heart rate, beats/min | 68.6 ± 12.0 | 70.9 ± 12.3 | 68.5 ± 10.7 | 65.3 ± 9.2 | <0.001 | 66.0 ± 10.8 |
| LVEF, % | 29.5 ± 3.5 | 29.1 ± 3.5 | 28.6 ± 3.3 | 22.1 ± 5.7 | 0.037 | 30.1 ± 3.3 |
| LVEDV indexed by BSA, ml/m$^2$ | 119.1 ± 24.2 | 124.5 ± 29.6 | 129.0 ± 27.7 | 135.0 ± 34.0 | <0.001 | 117.4 ± 20.9 |
| LVESV indexed by BSA, ml/m$^2$ | 84.4 ± 19.5 | 88.7 ± 24.5 | 92.5 ± 22.2 | 97.2 ± 28.3 | <0.001 | 82.3 ± 16.4 |
| LAV indexed by BSA, ml/m$^2$ | 46.2 ± 9.7 | 45.1 ± 10.5 | 47.3 ± 9.6 | 48.2 ± 11.7 | 0.017 | 45.2 ± 10.4 |
| BNP level, pg/ml | 100.1 ± 116.7 | 107.3 ± 142.2 | 118.6 ± 158.2 | 138.8 ± 181.4 | 0.141 | 161.2 ± 198.7 |

Values are mean ± SD or n (%). Follow-up starts at enrollment.
BNP = B-type natriuretic peptide; BSA = body surface area; CABG = coronary artery bypass graft; LAV = left atrial volume; LBBB = left bundle branch block; LV = left ventricular; LVEDV = left ventricular end-diastolic volume; LVEF = left ventricular ejection fraction; LVESV = left ventricular end-systolic volume; MI = myocardial infarction; NYHA = New York Heart Association; VF = ventricular fibrillation; VT = ventricular tachycardia.

tional hazards regression analysis was used to identify and evaluate the impact of LV dyssynchrony on the endpoint of first VT/VF or death and on VT/VF events. The Cox model was adjusted for the variables showing potential imbalances in clinical characteristics in the pre-specified subgroups and for those predictive of the endpoint. Interaction p values for LBBB and non-LBBB are reported. Adjusted hazard ratios (HRs) with their 95% confidence intervals (CIs) are reported. All statistical tests were 2-sided; a p value of $<0.05$ was considered statistically significant.

## RESULTS

Of the 1,077 patients with sufficient echocardiographic images, in patients with non-LBBB (n = 312), 32 patients with ICD (27.1%), and 56 patients (28.9%) with CRT-D reached the endpoint of VT/VF/death (p = 0.74); in the LBBB subgroup (n = 764), 87 patients with ICD (29.3%) and 89 patients (19.1%) with CRT-D had VT/VF or death (p = 0.001) from enrollment. During the mean follow-up of 2.3 ± 0.9 years, 188 patients (17.7%) had VT, 55 (5.2%) had VF, and 75 patients died (7%), 22 of them (2%) after a VT or VF event. After the 12-month follow-up, 77 of 572 patients (13.4%) with LBBB had VT/VF/death, and 56 of them (9.8%) had VT or VF. In patients with non-LBBB, 40 of 237 (16.8%) patients had VT/VF or death, and 34 of them (14.3%) had VT or VF.

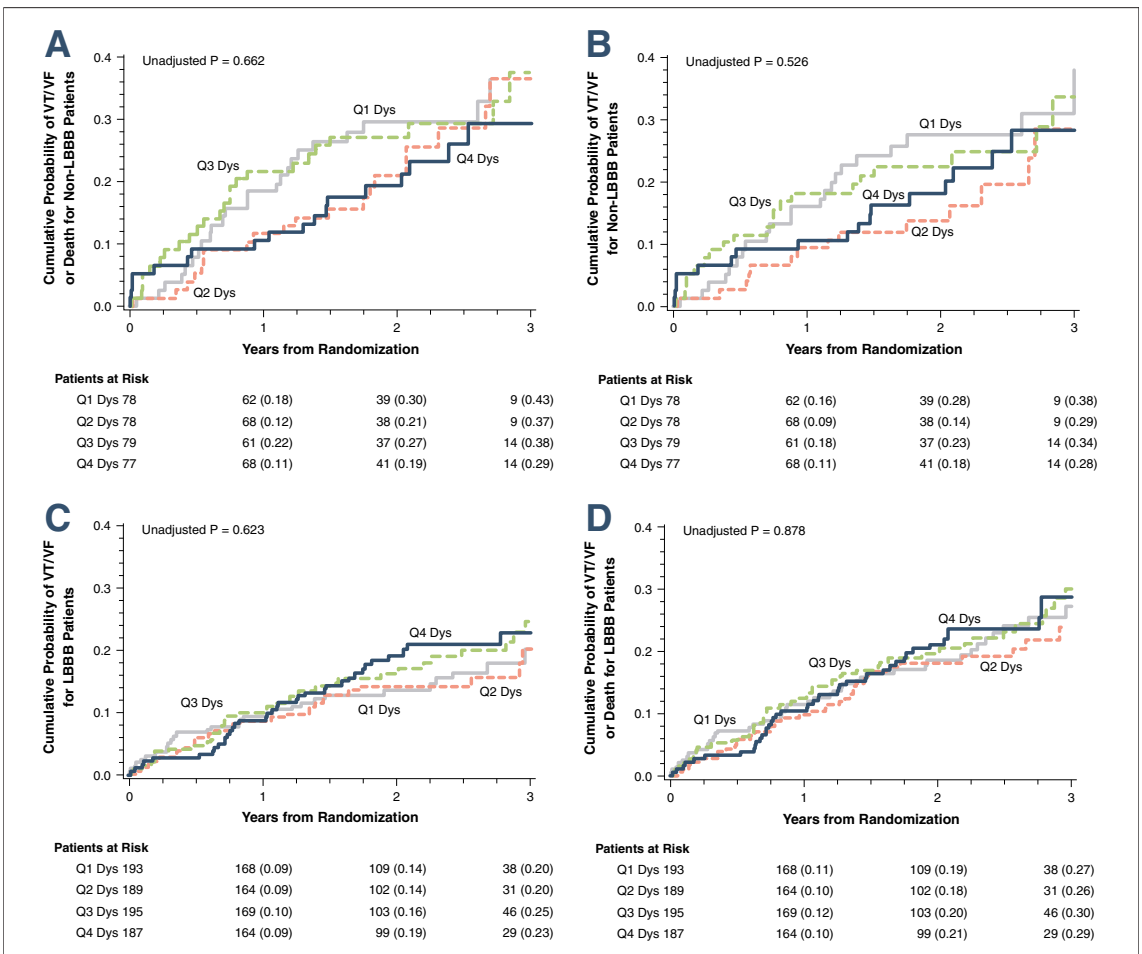


**Figure 2. Cumulative Probability of VT/VF/Death and VT/VF Within Quartiles of Baseline Dyssynchrony**

Kaplan-Meier estimates of the cumulative probability of **(A)** ventricular tachycardia (VT)/ventricular fibrillation (VF)/death in non–left bundle branch block (LBBB) patients, **(B)** VT/VF in non-LBBB patients, **(C)** VT/VF/Death in LBBB patients, and **(D)** VT/VF in LBBB patients within quartiles of baseline dyssynchrony (Dys). The Kaplan-Meier graphs present no association between baseline left ventricular (LV) dyssynchrony quartiles and incidence of ventricular tachyarrhythmic events in implantable cardioverter-defibrillator (ICD) patients. These results were consistent in patients with LBBB and non-LBBB electrocardiogram patterns. The majority of patients with non-LBBB had ischemic cardiomyopathy (83%) compared to LBBB patients.

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**Table 2. Baseline LV Dyssynchrony and the Risk of Ventricular Arrhythmic Events in the Total Patient Population, Stratified by LBBB Electrocardiogram Pattern**

| | Baseline LV Dyssynchrony*† | | | | | |
|---|---|---|---|---|---|---|
| | Non-LBBB (312 Patients/87 Events) | | | LBBB (764 Patients/172 Events) | | |
| Endpoint VT/VF/Death | Hazard Ratio | 95% CI | p Value | Hazard Ratio | 95% CI | p Value |
| Baseline dyssynchrony Q2 | 1.25 | 0.74–2.13 | 0.41 | 1.06 | 0.67–1.67 | 0.81 |
| Baseline dyssynchrony Q3 | 0.82 | 0.43–1.56 | 0.54 | 0.93 | 0.59–1.45 | 0.75 |
| Baseline dyssynchrony Q4 | 0.73 | 0.40–1.35 | 0.32 | 1.00 | 0.63–1.60 | 0.98 |
| | Non-LBBB (312 Patients/73 Events) | | | LBBB (764 Patients/136 Events) | | |
| Endpoint VT/VF | Hazard Ratio | 95% CI | p Value | Hazard Ratio | 95% CI | p Value |
| Baseline dyssynchrony Q2 | 1.04 | 0.57–1.90 | 0.90 | 1.21 | 0.70–2.06 | 0.50 |
| Baseline dyssynchrony Q3 | 0.81 | 0.41–1.60 | 0.54 | 1.12 | 0.67–1.89 | 0.67 |
| Baseline dyssynchrony Q4 | 0.76 | 0.40–1.45 | 0.41 | 1.24 | 0.72–2.13 | 0.43 |

*Q1 was used as reference group. †The model is adjusted for treatment, age at enrollment, ventricular arrhythmia episodes in the past, female sex, QRS duration, left ventricular ejection fraction, previous revascularization, myocardial infarction in the past, and left ventricular end-systolic volume index.
CI = confidence interval; other abbreviations as in Table 1.

**Baseline left ventricular dyssynchrony.** Patients with non-LBBB (n = 312) and LBBB (n = 764) ECG pattern showed marked heterogeneity of LV dyssynchrony before device implantation irrespective of the QRS duration ($r^2 = 0.025$, $p < 0.001$). LBBB patients exhibited more significant LV dyssynchrony than non-LBBB patients (186.5 ± 62.1 ms vs. 167.5 ± 74.5 ms, p = 0.001).

The most relevant baseline clinical characteristics in LBBB and non-LBBB patients are listed in Table 1. LBBB patients with more pronounced LV dyssynchrony had wider QRS complexes and worse echocardiographic parameters, lower left ventricular ejection fraction, and higher end-diastolic and end-systolic volumes. Non-LBBB patients had wider QRS-complexes and significantly lower heart rate with increasing LV dyssynchrony. Many patients had normal B-type natriuretic peptide values, reflecting the mildly symptomatic, asymptomatic heart failure patient population. The extent of LV dyssynchrony at baseline represented by quartiles was not predictive of higher incidence of VT/VF/death or VT/VF in non-LBBB or LBBB patients (Fig. 2).

When assessing the risk of events, patients with non-LBBB or LBBB ECG pattern did not show increased risk of VT/VF or death and VT/VF (Table 2) with increasing quartiles of baseline dyssynchrony. Consistent with this, baseline dyssynchrony was not predictive of subsequent VT/VF/death or VT/VF in ICD or CRT-D patients (Table 3).

CRT-D treatment did not modify the relationship between LV dyssynchrony and VT/VF/death

**Table 3. Baseline LV Dyssynchrony and the Risk of Ventricular Arrhythmic Events in the Total Patient Population, Stratified by Treatment Arm**

| | Baseline LV Dyssynchrony*† | | | | | |
|---|---|---|---|---|---|---|
| | ICD (416 Patients/117 Events) | | | CRT-D (661 Patients/139 Events) | | |
| Endpoint VT/VF/Death | Hazard Ratio | 95% CI | p Value | Hazard Ratio | 95% CI | p Value |
| Baseline dyssynchrony Q2 | 1.18 | 0.68–2.05 | 0.56 | 1.07 | 0.68–1.69 | 0.77 |
| Baseline dyssynchrony Q3 | 1.25 | 0.73–2.16 | 0.42 | 0.65 | 0.39–1.07 | 0.09 |
| Baseline dyssynchrony Q4 | 0.95 | 0.55–1.75 | 0.98 | 0.83 | 0.51–1.35 | 0.46 |
| | ICD (416 Patients/98 Events) | | | CRT-D (661 Patients/107 Events) | | |
| Endpoint VT/VF | Hazard Ratio | 95% CI | p Value | Hazard Ratio | 95% CI | p Value |
| Baseline dyssynchrony Q2 | 0.92 | 0.50–1.72 | 0.80 | 1.29 | 0.76–2.19 | 0.35 |
| Baseline dyssynchrony Q3 | 1.27 | 0.71–2.28 | 0.42 | 0.74 | 0.42–1.32 | 0.30 |
| Baseline dyssynchrony Q4 | 0.97 | 0.52–1.80 | 0.93 | 1.06 | 0.61–1.85 | 0.84 |

*Q1 was used as reference group. †The model is adjusted for treatment, age at enrollment, ventricular arrhythmia episodes in the past, female sex, QRS duration, left ventricular ejection fraction, previous revascularization, myocardial infarction in the past, and left ventricular end-systolic volume index.
CRT-D = cardiac resynchronization therapy with defibrillator; ICD = implantable cardioverter-defibrillator; other abbreviations as in Tables 1 and 2.

**Table 4. Baseline Clinical Characteristics of ICD and CRT-D Patients Stratified by Change in LV Dyssynchrony at 1 Year**

| | ICD (n = 336) | CRT-D Patients Dyssynchrony Worsening (n = 96) | CRT-D Patients Dyssynchrony No Change (n = 96) | CRT-D Patients Dyssynchrony >15% Improving (n = 281) | p Value |
|---|---|---|---|---|---|
| Age at enrollment, yrs | 64.0 ± 11.1 | 66.9 ± 10.3 | 64.5 ± 11.5 | 63.8 ± 11.1 | 0.077 |
| Female | 83 (25) | 11 (11) | 21 (22) | 85 (30) | 0.003 |
| Change in LV dyssynchrony at 1 yr | −7 ± 77 | 70 ± 49 | −4 ± 17 | −98 ± 57 | <0.001 |
| VT/VF/death after 1 yr | 69 (267) | 21 (75) | 10 (86) | 30 (251) | 0.001 |
| VT/VF after 1 yr | 59 (277) | 15 (81) | 6 (90) | 22 (259) | <0.001 |
| Death after 1 yr | 16 (320) | 8 (88) | 4 (92) | 9 (272) | 0.223 |
| Nonischemic NYHA functional class II | 149 (44) | 31 (32) | 37 (39) | 148 (53) | 0.002 |
| Ischemic | 187 (56) | 65 (68) | 59 (61) | 133 (47) | 0.002 |
| LBBB at baseline | 234 (70) | 54 (56) | 72 (75) | 212 (75) | 0.003 |
| RBBB at baseline | 45 (13) | 13 (14) | 9 (9) | 25 (9) | 0.273 |
| IVCD at baseline | 57 (17) | 29 (30) | 15 (16) | 43 (15) | 0.008 |
| Prior CABG | 97 (29) | 34 (35) | 33 (34) | 56 (20) | 0.004 |
| Non-CABG revascularization before enrollment | 91 (27) | 38 (40) | 27 (28) | 68 (24) | 0.038 |
| MI before enrollment | 139 (42) | 55 (58) | 48 (50) | 102 (37) | 0.002 |
| Atrial arrhythmias before enrollment | 37 (11) | 15 (16) | 9 (10) | 26 (9) | 0.365 |
| Ventricular arrhythmias before enrollment | 23 (7) | 5 (5) | 7 (8) | 17 (6) | 0.897 |
| Creatinine at baseline, mg/dl | 1.17 ± 0.32 | 1.20 ± 0.31 | 1.25 ± 0.41 | 1.14 ± 0.32 | 0.099 |
| QRS at baseline, ms | 158.7 ± 20.8 | 152.0 ± 18.9 | 156.6 ± 16.7 | 159.2 ± 18.3 | 0.004 |
| Heart rate at baseline, beats/min | 68.0 ± 11.3 | 66.2 ± 10.5 | 69.4 ± 10.4 | 66.7 ± 10.7 | 0.102 |
| LVEF at baseline, % | 29.2 ± 3.3 | 30.3 ± 3.4 | 29.5 ± 3.3 | 29.7 ± 3.5 | 0.033 |
| LVEDV indexed by BSA, ml/m$^2$ | 126.2 ± 29.7 | 121.7 ± 25.9 | 129.9 ± 26.1 | 122.4 ± 24.4 | 0.024 |
| LVESV indexed by BSA, ml/m$^2$ | 89.8 ± 24.1 | 85.4 ± 21.1 | 92.0 ± 21.0 | 86.5 ± 20.3 | 0.017 |
| LAV indexed by BSA, ml/m$^2$ | 46.7 ± 10.1 | 45.0 ± 11.1 | 45.6 ± 10.4 | 45.2 ± 10.2 | 0.072 |
| BNP level at baseline, pg/ml | 116.8 ± 133.1 | 179.9 ± 202.0 | 135.3 ± 148.7 | 147.0 ± 213.2 | 0.049 |

Values are mean ± SD or n (%).
IVCD = intraventricular conduction delay; RBBB = right bundle branch block; SBP = systolic blood pressure; other abbreviations as in Tables 1, 2, and 3.

(p = 0.27) or VT/VF (p = 0.47) in the total patient population.

**Change in left ventricular dyssynchrony.** At 12-month follow-up, CRT-D patients with LBBB (n = 338) showed significant decrease in LV dyssynchrony as compared to baseline (138.0 ± 63.3 ms vs. 189.4 ± 63.4 ms, respectively, p < 0.001). CRT-D patients with LBBB exhibited a greater decrease of LV dyssynchrony as compared to CRT-D patients with non-LBBB (n = 135) (−19.2 ± 49.5 ms vs. −2.1 ± 56.4 ms, p = 0.001).

ICD patients showed minimal changes in LV dyssynchrony as compared to patients with an implanted CRT-D (ICD 6.3 ± 50.7 ms vs. CRT-D −14.3 ± 52.1 ms; p < 0.001). However, 37.5% (126 of 336 patients) of the ICD patients exhibited a 15% improvement in LV dyssynchrony as compared to 59% in the CRT-D group (281 of 473 patients, p < 0.001). Furthermore, 111 of 336 patients (33%) in the ICD group worsened LV dyssynchrony compared to 96 of 473 patients (20%) in the CRT-D group (p < 0.001).

The most relevant clinical characteristics of ICD and CRT-D patients, stratified by the change of LV dyssynchrony are listed in Table 4. Patients with improving LV dyssynchrony were more likely to be female, younger, and have higher frequency of nonischemic etiology of heart failure as compared to unchanged, or worsening dyssynchrony patients, or to those with an implanted ICD. The B-type natriuretic peptide level was significantly lower in patients with improving LV dyssynchrony. The left ventricular end-diastolic and end-systolic volume percent change and left atrial volume percent change were greater in patients with improving LV dyssynchrony than in patients with no change or worsening dyssynchrony or ICD patients, showing evidence of more pronounced left ventricular reverse remodeling. There was no difference in drug treatment among the patient subgroups. Patients with improving dyssynchrony had more often LBBB, and less often RBBB ECG pattern, than patients with worsening dyssynchrony or with an implanted ICD.

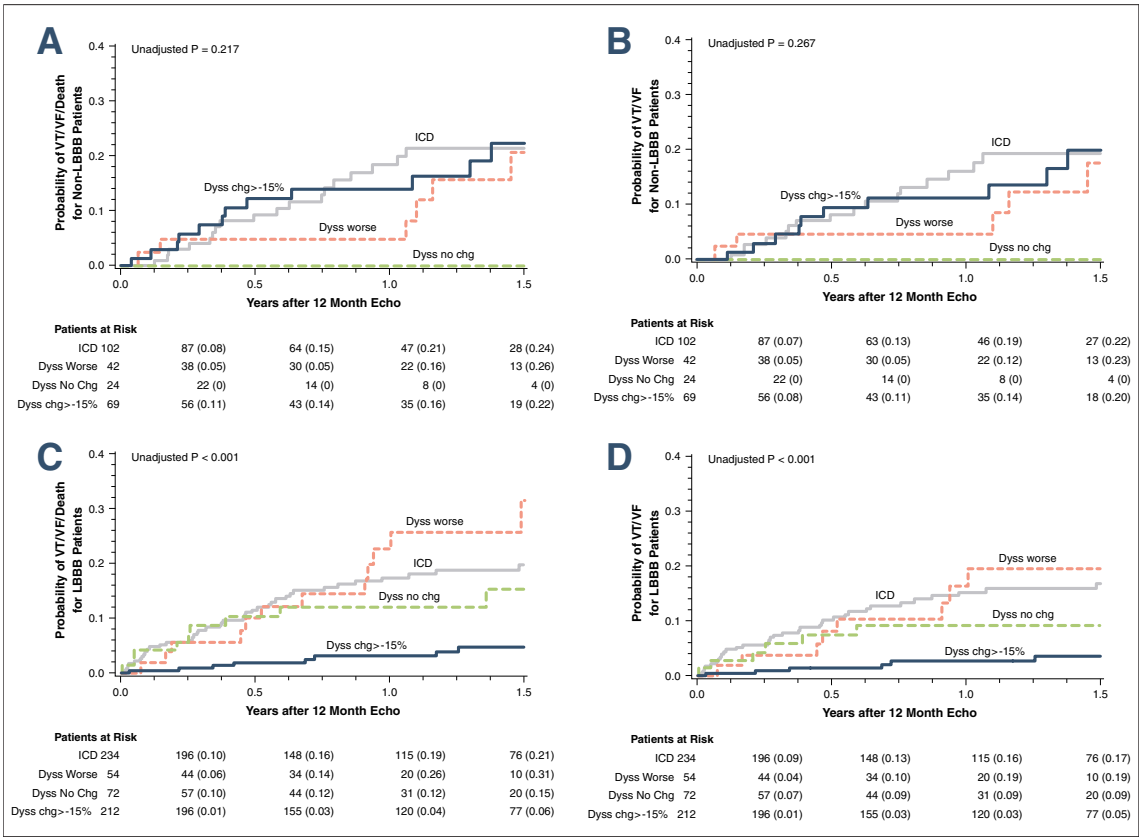


**Figure 3. Cumulative Probability of VT/VF/Death and VT/VF by Change in LV Dyssynchrony**

Kaplan-Meier estimates of the cumulative probability of **(A)** VT/VF/death in non-LBBB patients, **(B)** VT/VF in non-LBBB patients, **(C)** VT/VF/Death in LBBB patients, **(D)** VT/VF in LBBB patients. In CRT-D patients with LBBB, a >15% decrease in LV dyssynchrony (Dyss) at 1-year was associated with less VT/VF/death and VT/VF as compared to ICD patients or to CRT-D patients with unchanged, or worsening LV dyssynchrony. In CRT-D patients with non-LBBB, we did not find an association between improved LV dyssynchrony and lower incidence of ventricular tachyarrhythmias. Patients with non-LBBB had mainly ischemic cardiomyopathy compared to LBBB patients. Abbreviations as in Figures 1 and 2.

In CRT-D patients with LBBB, a >15% decrease in LV dyssynchrony was associated with significantly lower incidence of VT/VF/death ($p < 0.001$) and VT/VF ($p < 0.001$) as compared to ICD patients or to patients with CRT-D and unchanged, or CRT-D and worsening LV dyssynchrony (Figs. 3C and 3D). However, in CRT-D patients without LBBB, we observed no relationship between the changes in LV dyssynchrony and VT/VF/death or VT/VF events compared to the control group of ICD implanted patients (Figs. 3A and 3B).

Bundle branch block pattern significantly modified the relationship between improving dyssynchrony and the outcome of VT/VF or death ($p = 0.01$), and consistent with these findings, significant interaction was found between bundle branch pattern and dyssynchrony with regard to VT/VF ($p = 0.009$) (Table 5).

At 1 year, CRT-D patients with LBBB and a >15% improvement in LV dyssynchrony showed significant, 51% risk reduction of VT/VF or death compared to ICD patients (HR: 0.49, 95% CI: 0.24 to 0.99, $p = 0.049$) after adjustment for relevant clinical covariates (Table 5).

Consistent with these findings, CRT-D patients with LBBB and improving LV dyssynchrony had a significant, 70% risk reduction in VT/VF events as compared to patients with an implanted ICD device (HR: 0.30, 95% CI: 0.12 to 0.77, $p = 0.01$). CRT-D patients with non-LBBB ECG pattern and a >15% improvement in LV dyssynchrony did not show decrease in the risk of VT/VF/death (HR: 1.12, 95% CI: 0.48 to 2.58, $p = 0.80$) or VT/VF events (HR: 1.05, 95% CI: 0.42 to 2.61, $p = 0.92$) as compared to patients with an implanted ICD (Table 5).

Importantly, worsening dyssynchrony was not associated with an increased risk of VT/VF/death or VT/VF in either bundle branch block pattern as compared to ICD patients (Table 5).

**Table 5. Change in LV Dyssynchrony and Risk of Ventricular Arrhythmic Events in CRT-D LBBB and Non-LBBB Patients**

| | Change in LV Dyssynchrony* | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | Non-LBBB Patients (237 Patients/40 Events) | | | | LBBB Patients (572 Patients/77 Events) | | | |
| Endpoint VT/VF/Death Parameter | No. of Patients | Hazard Ratio | 95% CI | p Value | No. of Patients | Hazard Ratio | 95% CI | p Value | Interaction p Value |
| Dyssynchrony improving 15%:ICD | 69:102 | 1.12 | 0.48–2.58 | 0.80 | 212:234 | 0.49 | 0.24–0.99 | 0.049 | 0.01 |
| Dyssynchrony no change:ICD | 24:102 | NA | | | 72:234 | 1.13 | 0.49–2.60 | 0.78 | NA |
| Dyssynchrony worsening:ICD | 42:102 | 1.07 | 0.46–2.52 | 0.88 | 54:234 | 1.80 | 0.83–3.90 | 0.14 | 0.53 |
| | | Non-LBBB Patients (237 Patients/34 Events) | | | | LBBB Patients (572 Patients/56 Events) | | | |
| Endpoint VT/VF Parameter | No. of Patients | Hazard Ratio | 95% CI | p Value | No. of Patients | Hazard Ratio | 95% CI | p Value | Interaction p Value |
| Dyssynchrony improving 15%:ICD | 69:102 | 1.05 | 0.42–2.61 | 0.92 | 212:234 | 0.30 | 0.12–0.77 | 0.01 | 0.009 |
| Dyssynchrony no change:ICD | 24:102 | NA | | | 72:234 | 0.58 | 0.18–1.89 | 0.37 | NA |
| Dyssynchrony worsening:ICD | 42:102 | 0.90 | 0.35–2.32 | 0.83 | 54:234 | 0.95 | 0.35–2.60 | 0.93 | 0.94 |

*The model is adjusted for age at enrollment, previous ventricular arrhythmias, left ventricular ejection fraction, female sex, myocardial infarction in the past, revascularization in the past, QRS duration, and left ventricular end-diastolic volume percent change.
NA = not applicable; other abbreviations as in Tables 1, 2, and 3.

CRT-D patients with LBBB and no VT/VF events exhibited a significant decrease in LV dyssynchrony as compared to patients with LBBB and VT/VF events, who did not decrease or even increased the degree of LV dyssynchrony from baseline ($p = 0.014$). In CRT-D patients with non-LBBB, the change in LV dyssynchrony was not associated with a decrease of VT/VF events ($p = 0.994$) (Fig. 4).

## DISCUSSION

This study demonstrated that CRT-D patients with LBBB and improving LV dyssynchrony at 1 year had significant risk reduction of the first VT/VF/death and VT/VF as compared to ICD patients. Worsening dyssynchrony in CRT-D patients was not associated with increased risk of the first VT/VF/death or VT/VF as compared to ICD patients. CRT-D patients with non-LBBB did not show decrease in the first VT/VF/death or VT/VF with improving LV dyssynchrony compared to ICD patients. Baseline LV dyssynchrony was not predictive of increased risk of first VT/VF/death or VT/VF in asymptomatic or mildly symptomatic heart failure patients in either treatment arm with either bundle branch pattern.

Previous studies suggested that LV dyssynchrony might be related to cardiac events in heart failure patients (23). Cho et al. (24,25) demonstrated that mechanical dyssynchrony was a powerful predictor of mortality or cardiac events in heart failure patients with normal and wide QRS. Penicka et al. (26), Fauchier et al. (27), and Bader et al. (28) reported that LV dyssynchrony was prognostic of cardiac endpoints. These studies analyzed heart failure patients without implantable devices (ICD or CRT) and used either radionuclide technique or pulsed-wave tissue Doppler imaging to evaluate LV dyssynchrony.

However, several other studies demonstrated that a greater degree of baseline LV dyssynchrony predicts better outcome after CRT implantation (29–37). The MIRACLE (Multicenter InSync Randomized Clinical Evaluation) and the CARE-HF (Cardiac Resynchronization–Heart Failure) trials showed that interventricular mechanical delay was a powerful prognostic factor of better outcome in both the control and the treatment group (32).

Haguaa et al. (38) showed that mechanical dispersion assessed by strain echocardiography was an independent predictor of arrhythmia events in a smaller patient cohort after myocardial infarction. LBBB patients were excluded from this analysis. Another paper from this group showed similar effects of dyssynchrony in nonischemic cardiomyopathy patients (39).

Our study is the first report to analyze VT/VF events and LV dyssynchrony in mild heart failure patients with LBBB and an implanted CRT-D device and comparing them to patients with non-LBBB. Although previous work has shown improvement in ventricular remodeling associated with improvement in synchrony (21,22,40–42), we also demonstrated that improved synchrony might translate into reduction of ventricular arrhythmic events in LBBB patients. The reduction of VT/VF

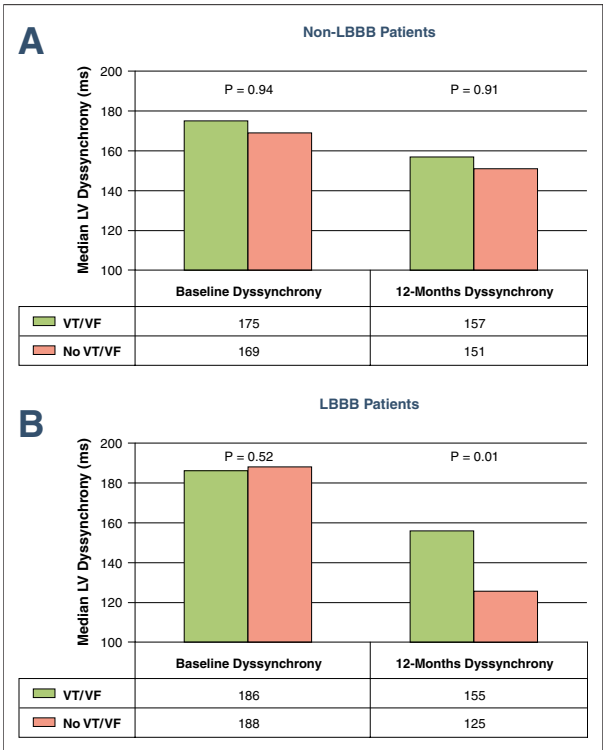


**Figure 4. Change in LV Dyssynchrony in CRT-D Non-LBBB and LBBB Patients With Ventricular Arrhythmic Events or No Events**

**(A)** In CRT-D patients with non-LBBB, there was no difference in baseline or 12-month LV dyssynchrony whether patients had a ventricular tachyarrhythmic event **(green bars)** or did not **(pink bars)**. **(B)** In CRT-D patients with LBBB and no ventricular arrhythmias, there was a significant decrease in LV dyssynchrony, whereas in patients with ventricular tachyarrhythmias, no decrease in LV dyssynchrony was observed. Abbreviations as in Figures 1 and 2.

episodes in LBBB patients with improving LV dyssynchrony might be explained by the more homogenous left ventricular mechanical activation followed by the electrical resynchronization itself ("mechanical to electrical feedback"). Electrical resynchronization is characterized by more uniform alterations in refractoriness, which might result in reduction of macro re-entry arrhythmias (27). The reduction in LV dyssynchrony might be correlated to the reduction in LV volumes and favorable outcome as reported in this patient cohort previously (21).

In the present study, LV dyssynchrony improvement at 1 year, but not baseline LV dyssynchrony was proven to be a strong predictor of ventricular tachyarrhythmic events even after adjustment for left ventricular end-diastolic volume change in the multivariate Cox-model. We hypothesize that improvement in LV dyssynchrony and reverse remodeling are both surrogate markers of a favorable arrhythmic response to CRT.

Patients with non-LBBB receiving CRT-D did not appear to benefit from improvement in LV dyssynchrony. One possible explanation for this lack of benefit might be the significant overlap of non-LBBB ECG pattern and patients with ischemic etiology, in whom there may be a more heterogeneous left ventricular activation and a greater degree of ischemic scar which likely contributes to arrhythmogenesis. Although CRT is able to reduce LV dyssynchrony and the heterogeneity of left ventricular activation, the arrhythmogenic potential represented by the scar tissue might remain the same.

The strength of this analysis is ICD patients serving as a control group and the change in LV dyssynchrony at 1 year was categorized into 3 groups: improving, unchanged, or worsening LV dyssynchrony. Importantly, patients with dyssynchrony improvement showed significant risk reduction in ventricular arrhythmic events, whereas patients with worsening dyssynchrony did not show an increased risk of ventricular arrhythmias.

A small proportion of ICD patients exhibited a 15% improvement in LV dyssynchrony, which might be contributed to the improved medical treatment in this patient group. These data are in alignment with our previous study on LV dyssynchrony (21).

**Study limitations.** A possible limitation of our study is the higher variation of LV dyssynchrony measurements when compared to other established echocardiographic data (LVEF or LV volumes). The number of patients in the unchanged and worsening LV dyssynchrony subgroups was small, especially in the non-LBBB patient group, which might be a limitation of this analysis. There are limited numbers of speckles to track in the transverse direction and the reproducibility of this method has therefore been questioned. However, speckle tracking imaging has better reproducibility than magnetic resonance imaging tagging or other echo modalities to assess LV dyssynchrony (43). In addition, we reported excellent reproducibility with this technique in our echocardiography laboratory (22). Another limitation of this analysis might be that we only evaluated strain during systole; however, maximum shortening might occur during diastole (post-systolic shortening) in patients with LBBB.

## CONCLUSIONS

Our study demonstrates that CRT-induced improvement in LV dyssynchrony in patients with LBBB was associated with significant risk reduction of first VT/VF/death and VT/VF as compared to ICD patients. In asymptomatic or mildly symptom-

atic heart failure patients with LBBB ECG pattern undergoing CRT implantation, lack of improvement in LV dyssynchrony with CRT might be helpful to identify patients at higher risk of subsequent ventricular tachyarrhythmias.

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**Key Words:** cardiac resynchronization therapy ■ heart failure ■ implantable cardioverter-defibrillator ■ ventricular arrhythmia ■ ventricular dyssynchrony.