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ABSTRACT

To assess long-term effects of cardiac resynchronization therapy (CRT) on left ventricular (LV) dyssynchrony and contractile function, by two-dimensional speckle-tracking echocardiography, compared with implantable cardioverter defibrillator (ICD) only in MADIT-CRT.

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Relationship between improvement in left ventricular dyssynchrony and contractile function and clinical outcome with cardiac resynchronization therapy: the MADIT-CRT trial

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Received 29 April 2011; revised 16 May 2011; accepted 18 May 2011

Aims
To assess long-term effects of cardiac resynchronization therapy (CRT) on left ventricular (LV) dyssynchrony and contractile function, by two-dimensional speckle-tracking echocardiography, compared with implantable cardioverter defibrillator (ICD) only in MADIT-CRT.

Methods and results
We studied 761 patients in New York Heart Association I/II, ejection fraction ≤30%, and QRS ≥130 ms [n = 434, CRT-defibrillator (CRT-D), n = 327, ICD] with echocardiographic studies available at baseline and 12 months. Dyssynchrony was determined as the standard deviation of time to peak transverse strain between 12 segments of apical four- and two-chamber views, and contractile function as global longitudinal strain (GLS) by averaging longitudinal strain over these 12 segments. We compared changes in LV dyssynchrony and contractile function between treatment groups and assessed relationships between these changes over the first year and subsequent outcomes (median post 1-year follow-up = 14.9 months). Mean changes in LV dyssynchrony and contractile function measured by GLS in the overall population were, respectively, −29 ± 83 ms and −1 ± 2.9%. However, both LV dyssynchrony (CRT-D: −47 ± 83 ms vs. ICD: −6 ± 76 ms, P < 0.001) and contractile function (CRT-D: −1.4 ± 3.1% vs. ICD: −0.4 ± 2.5%, P < 0.001) improved to a greater extent in the CRT-D group compared with the ICD-only group. A greater improvement in dyssynchrony and contractile function at 1 year was associated with lower rates of the subsequent primary outcome of death or heart failure, adjusting for baseline dyssynchrony and contractile function, treatment arm, ischaemic status, and change in LV end-systolic volume. Each 20 ms decrease in LV dyssynchrony was associated with a 7% reduction in the primary outcome (P = 0.047); each 1% improvement in GLS over the 12-month period was associated with a 24% reduction in the primary outcome (P < 0.001).

Conclusion
Cardiac resynchronization therapy resulted in a significant improvement in both LV dyssynchrony and contractile function measured by GLS compared with ICD only and these improvements were associated with better subsequent outcomes.

Keywords
Heart failure • Cardiac resynchronization therapy • LV dyssynchrony • LV contractile function

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Introduction

Cardiac resynchronization therapy (CRT) has been shown to reduce the risk of death or heart failure (HF), and improve functional status and left ventricular (LV) function in patients with advanced HF, LV dysfunction, and wide QRS.1–3 More recently, the Multicenter Automatic Defibrillator Implantation Trial—Cardiac Resynchronization Therapy (MADIT-CRT), Resynchronization Reverse Remodeling in Systolic Left Ventricular Dysfunction (REVERSE), and Resynchronization—Defibrillation for Ambulatory Heart Failure Trial (RAFT) trials have broadened CRT indications to mildly symptomatic patients.4–6 Previous studies have demonstrated that improvement in LV size and performance may be among the most important contributors to improved outcomes in patients receiving CRT.7–10 However, response to CRT varies significantly among selected individuals and ~30% of the patients do not appear to improve clinically or exhibit favourable echocardiographic remodelling. Recent studies have suggested that both LV mechanical dyssynchrony and contractile function are important determinants of CRT benefit.11–13 Yet, it remains unclear to what extent improvement in LV dyssynchrony and/or LV contractile function translates into better clinical responses after CRT.

Over the past years, measures of LV synchrony and contractile function by speckle tracking appeared to be more robust than measures utilizing Doppler-based techniques.14–16 We thus utilized speckle-tracking strain analysis, which permits the assessment of both LV dyssynchrony and contractile function in a reproducible and angle-independent manner to test the hypothesis that CRT restores LV performance by improving synchrony and contractile function and to assess the relationship between these changes over the first year of therapy and subsequent outcomes.

Methods

Patient population

MADIT-CRT randomized patients with mildly symptomatic HF [New York Heart Association (NYHA) class I or II if ischaemic, NYHA class II if non-ischaemic], ejection fraction (EF) <30%, and QRS ≥ 130 ms. A total of 1820 patients were enrolled from December 2004 through April 2008 at 110 centres in the USA, Canada, and Europe. Patients were randomly assigned in a 3:2 ratio to receive CRT-defibrillator (CRT-D) therapy or implantable cardioverter-defibrillator (ICD)-only therapy. Additional details regarding inclusion and exclusion criteria have been published previously.4,17 Stratification included clinical centre and ischaemic status.

Echocardiograms were obtained according to a study protocol at baseline, just prior to device implantation, and at 1 year. The first 201 patients had undergone follow-up echocardiography with the device turned off as requested by the Food and Drug Administration. These patients are not included in this analysis. The protocol was amended so that follow-up studies would be performed with the device on. A total of 761 patients (ICD, n = 327; CRT, n = 434) had paired echocardiograms with device turned on and image quality sufficient for dyssynchrony and strain analysis based on B-mode speckle-tracking methods. Patients with non-DICOM images and frame rate <30 Hz, missing view, or insufficient two-dimensional (2D) image quality (i.e. contrast application, endocardial dropout, out of plane images) were excluded from the analysis (Figure 1).

Echocardiographic analysis

Standard echocardiographic parameters, including LV volumes and EF, were analysed with an offline analysis workstation as described previously.7 Echocardiographic response was defined as a 15% decrease in LV end-diastolic volume. Left ventricular dyssynchrony and contractile function indices were measured using B-mode speckle-tracking software (algorithm based on velocity vector imaging, Amid, Cardiac

![Figure 1](https://example.com/figure1.png) Feasibility of speckle-tracking analysis in consecutive patients.
Performance Imaging, TomTec, 1.0) that circumvents angle dependency and identifies cardiac motion by tracking multiple reference points. The endocardial borders were traced in the end-systolic frame of the 2D images from the apical four- and two-chamber views. Speckles were tracked frame-by-frame throughout the LV myocardium over the course of two or more cardiac cycles: basal, mid, and apical regions of interest were created. Segments that failed to track were manually adjusted. If two or more segments could not be tracked, the measurements were considered as unreliable and the study was excluded from the analysis. Tracings in each view were performed by a single investigator blinded to treatment assignment, clinical/demographical data, and clinical outcomes.

Mechanical dyssynchrony of the LV was determined as the standard deviation of regional time-to-peak transverse strain (in ms), measured during systole, across all 12 anatomic wall segments of the apical four- and two-chambers views.18–20 Of note, both transverse and radial strain assess myocardial thickening in the same direction but the nomenclature is different based on which the view is utilized (transverse strain is the preferred term when acquired from the apical views). Global longitudinal strain (GLS), a detailed measure of LV contractile function, was calculated as the average of peak longitudinal strain across the 12 segments of the apical four- and two-chamber views.21 Figure 2 illustrates changes in LV dyssynchrony and contractile function measured by GLS in a CRT-D patient. Intra- and interobserver variability was assessed in 75 randomly selected patients with a broad range of LVEF. The coefficients of variation were 13.8 and 15.4% for time-to-peak transverse strain and 7.7 and 8.0% for longitudinal strain, respectively.

Outcomes
The primary endpoint was death from any cause or a non-fatal HF event, whichever came first. The diagnosis of HF required signs and symptoms consistent with congestive HF that was responsive to invenous decongestive therapy on an outpatient basis or an augmented decongestive regimen with oral or intravenous medications during an in-hospital stay. Adjudication of the endpoints was carried out by an independent endpoint committee that was unaware of study group assignments, as described previously.17

Statistical analysis
Changes in LV dyssynchrony and contractile function by GLS had an approximate normal distribution and were used as continuous variables in all our models. Continuous variables were expressed as mean ± SD. We categorized the patients in quartiles according to the change in dyssynchrony and contractile function measurements and applied trend tests across ordered groups to illustrate the relationship between changes in LV dyssynchrony, contractile function, demographic data, and other measures. Patients were also divided into four groups according to their median values of change in dyssynchrony (more improvement in dyssynchrony: more negative than −30 ms; less improvement in dyssynchrony: less negative than −30 ms) and change in GLS after 12 months (≥−0.8%, <−0.8%). As a more negative GLS indicates better contractile function, more negative differences in strain numbers between baseline and 1-year assessments were indicative of a greater improvement in contractile function. Pearson’s correlation coefficient was used to test the relationship between continuous variables. Between-treatment-group differences in the change in LV dyssynchrony and contractile function measured by GLS from baseline to 12 months were assessed in analysis of covariance adjusting for treatment group, ischaemic aetiology, and baseline measure of strain or dyssynchrony. The effect of treatment on LV dyssynchrony and contractile function measured by GLS was compared in the subgroups of male or female, ischaemic status, QRS width greater or less than 150 ms, and the presence of left bundle branch block (LBBB), and the interaction between subgroup and treatment effect with respect to change in dyssynchrony or strain was assessed.

The relationship between changes in LV dyssynchrony and contractile function measured by GLS from baseline to follow-up and the primary outcome subsequent to the 1-year echocardiogram (landmark analysis) was assessed using Cox’s proportional hazards methods, either adjusting for baseline LV dyssynchrony or LV contractile function measured by GLS, treatment group, ischaemic status, and change in LV end-systolic volume (LVESV), or in a more fully adjusted model, including baseline strain or dyssynchrony, treatment group, age, gender, QRS duration, LBBB, ischaemic status change in LVESV, and change in LVEF. The adjustment model included the most powerful predictors for primary outcome, which were identified from the

Figure 2 Two-dimensional speckle-tracking imaging in the apical four-chamber view in a patient before (left panel) and after cardiac resynchronization therapy-defibrillator implantation (right panel). Upper curves represent transverse strain curves, which were used to measure left ventricular dyssynchrony and lower curves represent longitudinal strain that were used to measure contractile function. Improvement in left ventricular dyssynchrony and left ventricular contractile function was shown at follow-up.
results: In the present analysis, we observed a significant improvement in both LV dyssynchrony and LV contractile function measured by GLS in the CRT-D group compared with the ICD-only group both in the total study population and within all subgroups studied. However, a significantly greater improvement in LV dyssynchrony and contractile function was observed in CRT-D patients with LBBB, non-ischaemic cardiomyopathy, and those...
Table I  Baseline characteristics by quartiles of change in transverse dyssynchrony and change in global longitudinal strain in 761 patients

<table>
<thead>
<tr>
<th>Quartiles of change in dysynchrony</th>
<th>Quarters of change in GLS</th>
</tr>
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<tbody>
<tr>
<td>Better</td>
<td>Worse</td>
</tr>
<tr>
<td>−135 ± 45 ms (n = 191)</td>
<td>−4.8 ± 1.8% (n = 191)</td>
</tr>
<tr>
<td>−53 ± 16 ms (n = 193)</td>
<td>−1.6 ± 0.6% (n = 190)</td>
</tr>
<tr>
<td>−1 ± 16 ms (n = 187)</td>
<td>0.1 ± 0.5% (n = 190)</td>
</tr>
<tr>
<td>73 ± 43 ms (n = 190)</td>
<td>2.5 ± 1.3% (n = 190)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Age (year)</th>
<th>Female, n (%)</th>
<th>NYHA II, n (%)</th>
<th>Ischaemic, n (%)</th>
<th>Hypertension, n (%)</th>
<th>Diabetes, n (%)</th>
<th>QRS (ms)</th>
<th>RBBB, n (%)</th>
<th>LBBB, n (%)</th>
<th>LVEF (%)</th>
<th>LVEDV (mL)</th>
<th>LVESV (mL)</th>
<th>Echo-responder</th>
<th>Baseline dyssynchrony (ms)</th>
<th>Baseline GLS (%)</th>
<th>ICD-only arm</th>
<th>CRT-D arm</th>
<th>Event rate in ICD only (per 100 patients-year, 95% CI)</th>
<th>Event rate in CRT-D arm (per 100 patients-year, 95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>64 ± 11</td>
<td>56 (29%)</td>
<td>164 (86%)</td>
<td>89 (47%)</td>
<td>120 (63%)</td>
<td>48 (25%)</td>
<td>160 ± 19</td>
<td>19 (10%)</td>
<td>145 (76%)</td>
<td>29.7 ± 3.3</td>
<td>247 ± 55</td>
<td>175 ± 44</td>
<td>115 (61%)</td>
<td>−9.2 ± 2.7</td>
<td>48 (15%)</td>
<td>143 (33%)</td>
<td>14.9 (7.4–29.9)</td>
<td>4.0 (1.9–8.4)</td>
<td></td>
</tr>
<tr>
<td>63 ± 12</td>
<td>59 (31%)</td>
<td>162 (84%)</td>
<td>99 (51%)</td>
<td>119 (62%)</td>
<td>51 (26%)</td>
<td>158 ± 19</td>
<td>21 (11%)</td>
<td>137 (71%)</td>
<td>29.6 ± 3.5</td>
<td>243 ± 58</td>
<td>172 ± 48</td>
<td>92 (48%)</td>
<td>−8.9 ± 2.8</td>
<td>73 (22%)</td>
<td>120 (27%)</td>
<td>10.9 (5.9–20.2)</td>
<td>6.4 (3.3–12.3)</td>
<td></td>
</tr>
<tr>
<td>64 ± 11</td>
<td>45 (24%)</td>
<td>150 (80%)</td>
<td>107 (57%)</td>
<td>115 (62%)</td>
<td>48 (26%)</td>
<td>157 ± 21</td>
<td>15 (8%)</td>
<td>139 (74%)</td>
<td>29.8 ± 3.2</td>
<td>250 ± 55</td>
<td>176 ± 43</td>
<td>71 (38%)</td>
<td>−8.9 ± 3.1</td>
<td>93 (28%)</td>
<td>94 (22%)</td>
<td>10.3 (5.7–18.6)</td>
<td>7.4 (3.5–15.6)</td>
<td></td>
</tr>
<tr>
<td>66 ± 10</td>
<td>32 (17%)</td>
<td>160 (84%)</td>
<td>121 (64%)</td>
<td>116 (61%)</td>
<td>61 (32%)</td>
<td>156 ± 19</td>
<td>29 (15%)</td>
<td>120 (63%)</td>
<td>28.9 ± 3.3</td>
<td>254 ± 63</td>
<td>182 ± 52</td>
<td>50 (26%)</td>
<td>−8.4 ± 2.8</td>
<td>113 (35%)</td>
<td>77 (18%)</td>
<td>15.9 (10.6–24.0)</td>
<td>8.8 (4.2–18.3)</td>
<td></td>
</tr>
<tr>
<td>63 ± 12</td>
<td>74 (39%)</td>
<td>166 (87%)</td>
<td>66 (35%)</td>
<td>121 (64%)</td>
<td>45 (24%)</td>
<td>160 ± 18</td>
<td>11 (6%)</td>
<td>155 (81%)</td>
<td>30.1 ± 3.1</td>
<td>242 ± 48</td>
<td>170 ± 38</td>
<td>136 (72%)</td>
<td>−8.6 ± 2.8</td>
<td>54 (16%)</td>
<td>137 (32%)</td>
<td>4.2 (1.4–13.1)</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>63 ± 11</td>
<td>33 (17%)</td>
<td>161 (85%)</td>
<td>109 (57%)</td>
<td>120 (63%)</td>
<td>57 (30%)</td>
<td>159 ± 19</td>
<td>18 (9%)</td>
<td>140 (74%)</td>
<td>29.1 ± 3.2</td>
<td>257 ± 58</td>
<td>183 ± 48</td>
<td>77 (41%)</td>
<td>−8.1 ± 2.7</td>
<td>85 (26%)</td>
<td>105 (24%)</td>
<td>13.0 (7.6–22.4)</td>
<td>3.3 (1.4–8.0)</td>
<td></td>
</tr>
<tr>
<td>66 ± 11</td>
<td>44 (23%)</td>
<td>152 (80%)</td>
<td>119 (63%)</td>
<td>125 (66%)</td>
<td>50 (26%)</td>
<td>156 ± 21</td>
<td>27 (14%)</td>
<td>123 (65%)</td>
<td>29.6 ± 3.6</td>
<td>248 ± 66</td>
<td>176 ± 53</td>
<td>68 (36%)</td>
<td>−8.9 ± 2.7</td>
<td>88 (27%)</td>
<td>102 (23%)</td>
<td>13.1 (7.8–22.1)</td>
<td>7.6 (4.0–14.6)</td>
<td></td>
</tr>
<tr>
<td>65 ± 11</td>
<td>41 (22%)</td>
<td>157 (83%)</td>
<td>122 (64%)</td>
<td>115 (61%)</td>
<td>56 (30%)</td>
<td>157 ± 20</td>
<td>28 (15%)</td>
<td>123 (65%)</td>
<td>29.2 ± 3.6</td>
<td>248 ± 57</td>
<td>177 ± 46</td>
<td>47 (25%)</td>
<td>56 (30%)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>18.5 (12.2–28.1)</td>
<td>56 (30%)</td>
<td></td>
</tr>
</tbody>
</table>

NTHA, New York Heart Association; RBBB, right bundle branch block; LBBB, left bundle branch block; LVEF, left ventricular ejection fraction; LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume.
with wider QRS. These changes were related to subsequent outcomes, suggesting that improvements in both synchrony and contractile function may account for a considerable portion of the benefit of CRT.

Several echocardiographic studies have shown that CRT acutely improves haemodynamic status then induces reduction in LV volumes, associated with an increase in LVEF and a structural reverse remodelling of the LV, as well as improvements in mitral regurgitation severity after long-term CRT. These benefits are now well established. However, whether these benefits are specifically due to improvements in synchrony or contractile function remains unknown. Although limited by the absence of outcomes data, prior smaller studies have shown significant improvement in LV dyssynchrony and contractile function after CRT. Our study confirms these earlier findings in a large multicentre study. Moreover, our results demonstrate a weak relationship between the changes in LV dyssynchrony and contractile function measured by GLS, suggesting that overall benefits may result from a more coordinated contraction of the LV with improved contractile efficiency. Although we can speculate that improvement in contractile function may be the result of improvement in synchrony, this remains only an association and our data cannot determine which is causal.

In our population, we observed substantial variation in the extent of LV resynchronization with CRT, although the vast majority of patients revealed some degree of reduction in LV

Figure 3 Changes in left ventricular dyssynchrony and contractile function in implantable cardioverter defibrillator-only and cardiac resynchronization therapy-defibrillator groups. Data are presented as mean ± SD. Between-treatment-group differences in the change in left ventricular dyssynchrony and left ventricular contractile function measures from baseline to 12 months were assessed in analysis of covariance adjusting for treatment group, ischaemic aetiology, and baseline measure of dyssynchrony or strain.
Figure 4 Change in left ventricular contractile function measured by global longitudinal strain according to quartiles of change in dyssynchrony within-treatment group. Data are expressed as mean ± SEM. Note: the greater the absolute per cent reduction in left ventricular strain, the greater the improvement in left ventricular contractile function.

Figure 5 (A) Effect of treatment on left ventricular dyssynchrony in subgroups. (B) Effect of treatment on left ventricular contractile function in subgroups.
Table 2  Relationship between changes in left ventricular dyssynchrony and contractile function measured by global longitudinal strain and primary outcome

<table>
<thead>
<tr>
<th></th>
<th>Improvement in dyssynchrony (per 20 ms decrease)</th>
<th>Improvement in LV contractility (per 1% point improvement)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unadjusted HR</td>
<td>0.93 (0.89–0.98), P = 0.007</td>
<td>0.84 (0.78–0.91), P &lt; 0.001</td>
</tr>
<tr>
<td>Adjusted HR for baseline, treatment, ischaemic status, ΔLVESV</td>
<td>0.93 (0.87–0.99), P = 0.047</td>
<td>0.76 (0.66–0.85), P &lt; 0.001</td>
</tr>
<tr>
<td>Multivariate*</td>
<td>0.95 (0.89–1.02), P = 0.17</td>
<td>0.77 (0.68–0.86), P &lt; 0.001</td>
</tr>
</tbody>
</table>

Landmark analysis (n = 715). Eighty-two primary endpoints (52 in the ICD-only group and 30 in the CRT group); events rate per 100 patients-year were, respectively, 13.1 and 6.1 in the ICD-only vs. CRT-D group.

#Adjusted for baseline LV dyssynchrony or GLS, treatment, ischaemic status, ΔLVESV, ΔLVEF, age, gender, QRS, and LBBB.

Table 3  Hazard ratio for primary outcome after 1 year according change in left ventricular dyssynchrony and contractile function

<table>
<thead>
<tr>
<th></th>
<th>Better contractile function, less dyssynchrony (n = 212)</th>
<th>Better contractile function, more dyssynchrony (n = 156)</th>
<th>Worse contractile function, less dyssynchrony (n = 158)</th>
<th>Worse contractile function, more dyssynchrony (n = 189)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unadjusted HR</td>
<td>1.79 (0.81–3.94), P = 0.15</td>
<td>2.75 (1.34–5.63), P = 0.006</td>
<td>3.36 (1.70–6.64), P &lt; 0.0001</td>
<td>2.78 (1.34–5.77), P = 0.006</td>
</tr>
<tr>
<td>Adjusted HR*</td>
<td>1.11 (0.48–2.56), P = 0.80</td>
<td>2.99 (1.43–6.28), P = 0.004</td>
<td>3.36 (1.70–6.64), P &lt; 0.0001</td>
<td>2.78 (1.34–5.77), P = 0.006</td>
</tr>
</tbody>
</table>

#Adjusted for baseline strain or dyssynchrony, treatment, ischaemic status, ΔLVESV, age, gender, QRS, and LBBB.

dyssynchrony (72% of the patients in the CRT-D group). The presence of large areas of scar tissue throughout the LV,13,30 the presence of scar in the area of the LV pacing lead,31 or a suboptimal lead position32,33 may explain the lack of LV resynchronization in some patients. Other factors such as gender34 and QRS morphology35 also identify patients who appear to derive more benefit of CRT.

Few studies have examined changes in multidirectional strain, a measure of contractile function, after CRT, and the relationship with LV reverse remodelling.27–29 In 141 patients with HF, Delgado et al. demonstrated that improvement in global LV strain after CRT was a long-term effect and was related to the extent of LV reverse remodelling. However, significant improvement in multidirectional strain and significant reverse remodelling was noted only in responders.27 In our population, ~78% of the patients in the CRT-D group had improved contractile function to some extent, as measured by LV GLS. Improvements in the ICD-only group were likely due to optimized medical therapy, with 96% of the patients receiving angiotensin-converting enzyme-inhibitors or angiotensin receptor blocker, 93% receiving β-blockers, and 31% aldosterone antagonists.

Changes in LV dyssynchrony and contractile function measured by GLS were related to the extent of the LV reverse remodelling in both treatment groups, but to a greater extent in the CRT-D group. These results confirm, in a large population, the beneficial effects of CRT on LV mechanics and the relationship between these changes and outcome. Although these benefits of CRT are seen across subgroups, the greatest improvement in LV dyssynchrony and LV contractile function was observed in CRT-D patients with LBBB, non-ischaemic cardiomyopathy, and those with wider QRS, similar to the greater benefit observed in these subgroups in the overall MADIT-CRT population.4,35

The goal of the present analysis was to explore the pathological mechanisms that lead to improved outcome in patients receiving CRT, but not to define a cut-off for LV dyssynchrony or to compare the various methods to assess dyssynchrony. We demonstrated that improvement in LV dyssynchrony and GLS at 1 year was predictive of a subsequent primary outcome of death or HF, adjusting for baseline, treatment group, and ischaemic status. Improvement in contractile function seems more closely related to clinical outcome than improvement in synchrony. In a fully adjusted model, only improvement in LV GLS remained a significant predictor of the primary outcome of death or HF, even after adjustment for change in LVEF. These assessments may have value in the evaluation of a CRT patient post-device implantation as a way to determine response early after implantation.

Our analysis is strengthened by the availability of detailed clinical characteristics and advanced echocardiographic measures in a large sample size, the availability of long-term clinical outcomes data, and the presence of a control group (ICD alone). We utilized a primary definition based on clinical response (survival free of event) rather than an arbitrary echocardiographic definition, as agreement between different methods to define response to cardiac...
resynchronization therapy has proven poor. Nevertheless, several limitations of this post hoc analysis should be noted. Although the investigators were blinded to the treatment assignment, the coronary sinus leads were occasionally visible in the apical view, an unavoidable problem in echocardiographic evaluation of CRT trials. As echocardiograms were obtained only at baseline and 12 months, we cannot determine how rapidly these changes in LV dyssynchrony and contractile function occurred. In addition, 201 patients underwent 12-month echocardiograms with devices turned off, in response to an early FDA request, and were not included in this analysis. We cannot assess the relationship between changes in LV synchrony and contractile function and outcomes in those patients who died or did not undergo the 12-month on-therapy echocardiogram. Only 761 patients (42% of the original cohort) had paired echocardiographic data available with devices turned off, in response to an early FDA request, and the coronary sinus leads were occasionally visible in the apical view, an unavoidable problem in echocardiographic evaluation, the coronary sinus leads were occasionally visible in the apical view, an unavoidable problem in echocardiographic evaluation of CRT trials. As echocardiograms were obtained only at baseline and 12 months, we cannot determine how rapidly these changes in LV dyssynchrony and contractile function occurred. In addition, 201 patients underwent 12-month echocardiograms with devices turned off, in response to an early FDA request, and were not included in this analysis. We cannot assess the relationship between changes in LV synchrony and contractile function and outcomes in those patients who died or did not undergo the 12-month on-therapy echocardiogram. Only 761 patients (42% of the original cohort) had paired echocardiographic data available with devices turned on and adequate image quality for 2D speckle tracking. Still, this analysis represents the largest series of patients in a randomized controlled trial with these measures and outcome data available.

In summary, cardiac resynchronization therapy resulted in significantly greater improvement in both LV dyssynchrony and LV contractile function compared with ICD only, and changes in these measures were related to subsequent outcomes, suggesting that improvements in both synchrony and contractile function may account for a considerable portion of the benefit of CRT.

**Funding**

The MADIT-CRT trial was funded by Boston Scientific through a research grant to the University of Rochester, which in turn provided funding for core laboratories, including the echocardiography core laboratory.

**Conflict of interest:** S.D.S, E.F., W.J.H., W.Z., and A.J.M. have received research support for the conduct of the MADIT-CRT trial from Boston Scientific through a grant to the University of Rochester. S.D.S. and M.A.P. have served as consultants to Boston Scientific.

**References**


