Cardiac Resynchronization Therapy

Reverse Remodeling and the Risk of Ventricular Tachyarrhythmias in the MADIT-CRT (Multicenter Automatic Defibrillator Implantation Trial–Cardiac Resynchronization Therapy)

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Objectives
We aimed to evaluate the relationship between echocardiographic response to cardiac resynchronization therapy (CRT) and the risk of subsequent ventricular tachyarrhythmias (VTAs).

Background
Current data regarding the effect of CRT on the risk of VTA are limited and conflicting.

Methods
The risk of a first appropriate implantable cardioverter-defibrillator (ICD) therapy for VTA (including ventricular tachycardia, ventricular fibrillation, and ventricular flutter) was compared between high- and low-echocardiographic responders to CRT defibrillator (CRT-D) therapy (defined as ≥25% and <25% reductions, respectively, in left ventricular end-systolic volume [LVESV] at 1 year compared with baseline) and ICD-only patients enrolled in the MADIT-CRT (Multicenter Automatic Defibrillator Implantation Trial–Cardiac Resynchronization Therapy).

Results
The cumulative probability of a first VTA at 2 years after assessment of echocardiographic response was highest among low responders to CRT-D (28%), intermediate among ICD-only patients (21%), and lowest among high responders to CRT-D (12%), with p < 0.001 for the overall difference during follow-up. Multivariate analysis showed that high responders to CRT-D experienced a significant 55% reduction in the risk of VTA compared with ICD-only patients (p < 0.001), whereas the risk of VTA was not significantly different between low responders and ICD-only patients (hazard ratio [HR]: 1.26; p = 0.21). Consistently, assessment of response to CRT-D as a continuous measure showed that incremental 10% reductions in left ventricular end-systolic volume were associated with corresponding reductions in the risk of subsequent VTA (HR: 0.80; p < 0.001), VTA/death (HR: 0.79; p < 0.001), ventricular tachycardia (HR: 0.80; p < 0.001), and ventricular fibrillation/ventricular flutter (HR: 0.75; p = 0.044).

Conclusions
In patients with left ventricular dysfunction enrolled in the MADIT-CRT trial, reverse remodeling was associated with a significant reduction in the risk of subsequent life-threatening VTAs. (Multicenter Automatic Defibrillator Implantation Trial–Cardiac Resynchronization Therapy [MADIT-CRT]; NCT00180271) (J Am Coll Cardiol 2011; 57:2416–23) © 2011 by the American College of Cardiology Foundation

Cardiac resynchronization therapy (CRT) has been shown to reduce heart failure (HF) hospitalizations and mortality among selected patients with HF (1–3). However, there is a controversy regarding the effect of CRT on the risk of life-threatening ventricular tachyarrhythmia (VTA). Several studies (4–7) showed a reduction in the risk of VTA...
associated with CRT and suggested that the significant improvements in left ventricular volumes could account for this effect. Other studies (8–10) suggested that left ventricular epicardial activation in CRT may cause dispersion of repolarization and prolongation of the QT interval, thereby predisposing to VTA.

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In the present study, we aimed to explore the association between the reverse remodeling effects of cardiac resynchronization therapy with defibrillator (CRT-D) therapy on the left ventricle at 1 year post-implantation and the risk of subsequent VTA. We hypothesized that the magnitude of reduction in left ventricular volumes after CRT-D implantation is inversely related to the risk of subsequent life-threatening VTA.

Methods

Study population. The design and results of the MADIT-CRT (Multicenter Automatic Defibrillator Implantation Trial–Cardiac Resynchronization Therapy) study were reported previously (3). Briefly, 1,820 patients enrolled at 110 centers in the United States, Canada, and Europe who had ischemic or nonischemic cardiomyopathy, an ejection fraction of <0.30, and prolonged intraventricular conduction with QRS >130 ms were randomized to receive CRT-D or implantable cardioverter-defibrillator (ICD) therapy in a 3:2 ratio. Screened patients were excluded from enrollment if they had an existing indication for CRT, New York Heart Association functional class III/IV in the past 90 days before enrollment, an implanted pacemaker, coronary artery bypass graft surgery, percutaneous coronary intervention, or myocardial infarction within the past 90 days before enrollment. Echocardiograms were obtained according to a study-specific protocol at baseline, which was before device implantation (n=1,809) and at 1 year (n=626 in the ICD group; n=752 in the CRT-D group). Paired echocardiograms at baseline and at 12 months with the device turned on were available for 1,372 patients who composed the present study population. Of the 448 patients who did not undergo 12-month device-on echocardiography, 408 did not have paired sample data due to an initial request by the U.S. Food and Drug Administration for CRT pacing to be turned off during the 1-year echocardiography (which was subsequently reversed), and 40 patients died during the first 12 months of follow-up.

Echocardiographic methods. Echocardiographic parameters were measured in the core echocardiography laboratory according to established American Society of Echocardiography protocols (11). Left ventricular volumes were measured by Simpson’s method of disks in the apical 4- and 2-chamber views and averaged. Left ventricular ejection fraction and left ventricular mass were calculated according to standard methods (11).

Device programming and interrogation. Commercially available transvenous devices (Boston Scientific, Natick, Massachusetts) were used in the trial. Standard techniques were used to implant the CRT-D and ICD-only devices. Device testing and programming were performed as reported previously (12). Devices were programmed to monitor + therapy, with a protocol recommendation to a setting of the ventricular tachycardia (VT) zone at 180 beats/min, and the ventricular fibrillation (VF) zone at 250 beats/min. Sensitivity was programmed according to physician discretion. Detection was 2.5 s for the VT zone and 1.0 s for the VF zone. The protocol recommended programming the VT zone first therapy to burst-type antitachycardia pacing with 8 pulses at 88% of the measured cycle length with a 10-ms decrement between bursts, then shock therapy; second therapy should be shock at the defibrillation threshold plus at least 10 J (if possible). The remaining therapies should be maximal energy shocks. All shocks should be biphasic. The ICDs were interrogated quarterly, after which ICD shocks and disks were sent to the core laboratory for categorization and final evaluation of detected arrhythmias. An arrhythmia episode was defined as any type of therapy that is rendered including antitachycardia pacing and shock. VT was defined as the ventricular rate up to 250 beats/min; VF was defined as ventricular rate faster than 250 beats/min with disorganized ventricular electrograms; ventricular flutter (VFL) was defined as a ventricular rate faster than 250 beats/min and monomorphic. Only appropriate therapy delivered for VTA (i.e., VT, VF, or VFL) was considered in the present study.

Definitions and outcome measures. An echocardiographic response was defined as the percentage of reduction in left ventricular end-systolic volumes (LVESVs) between enrollment and 1 year (calculated as the difference between 1-year cardiac volumes and baseline cardiac volumes, divided by baseline cardiac volumes). CRT-D patients were categorized into 2 groups based on their echocardiographic response: high responders (defined as ≥25% reduction in LVESV at 1 year post-implantation) and low responders (defined as <25% reduction in LVESV at 1 year post-implantation). Possibly due to different enrollment criteria, echocardiographic response to CRT was more pronounced in the MADIT-CRT study compared with previous studies among patients with more advanced HF. Thus, the definition of nonresponse used in previous studies (<15% reduction in LVESV at 6 months post-implantation, comprising
approximately one-third of CRT–treated patients) (13–15), included only a minority (<10%) of those who received a CRT-D device in the MADIT-CRT study. Accordingly, we used the definition of nonresponse in this study as <25% reduction in LVESV at 1 year post implantation comprising one-fourth of CRT–treated patients.

The primary endpoint of the current study was defined as the first occurrence of appropriate ICD therapy for VTA (including VT, VF, or VFL) after the assessment of echocardiographic response. Secondary endpoints included appropriate ICD therapy for VTA or death, VF/VFL, the separate occurrence of VT, VF, VFL, and a first appropriate ICD shock.

**Statistical analysis.** Baseline characteristics among CRT-D high and low responders and ICD-only patients were compared with Kruskal-Wallis and Mann-Whitney U tests for continuous variables and with chi-square test for categorical variables. The relationship between echocardiographic changes from baseline to follow-up and the occurrence of the primary and secondary endpoints subsequent to the 1-year echocardiogram (landmark-type analysis) was assessed using Cox proportional hazards methods. Covariates included in the model were identified using a best subset procedure among variables that were predictive of the endpoint and were unbalanced among the 3 groups, including sex, ischemic etiology, QRS ≥150 ms, left bundle branch block, and LVESV indexed to body surface area at baseline. In addition, age assessed as a continuous measure and blood urea nitrogen ≥25 mg/dl were also forced as additional covariates in the multivariate models. The effect of echocardiographic response to CRT-D therapy was assessed both by evaluating response as a categorical variable (i.e., among high and low responders) and a continuous measure (per 10% reduction in LVESV) in the multivariate models. We also carried out a secondary analysis adjusting for LVESV indexed to body surface area measured at 1 year instead of baseline. The cumulative probability of a first VTA event and the cumulative probability of a first appro-

<table>
<thead>
<tr>
<th>Patient Characteristics by Device Implanted and Echocardiographic Response</th>
<th>CRT-D</th>
<th>Low Responders (LVESV Decrease &lt;25%, n = 220)</th>
<th>High Responders (LVESV Decrease ≥25%, n = 529)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Characteristic</td>
<td>ICD (n = 623)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age at enrollment, yrs</td>
<td>65 (57 to 72)</td>
<td>65 (58 to 72)</td>
<td>66 (57 to 73)</td>
</tr>
<tr>
<td>Female</td>
<td>25</td>
<td>16</td>
<td>28†</td>
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<tr>
<td>Diabetes mellitus</td>
<td>29</td>
<td>29</td>
<td>29</td>
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<tr>
<td>Hypertension</td>
<td>64</td>
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<td>Smoking</td>
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<tr>
<td>Currently</td>
<td>12</td>
<td>14</td>
<td>11</td>
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<tr>
<td>Previously</td>
<td>52</td>
<td>58</td>
<td>54</td>
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<tr>
<td>NYHA functional class II</td>
<td>84</td>
<td>83</td>
<td>87</td>
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<td>Ischemic etiology</td>
<td>54</td>
<td>69</td>
<td>49†</td>
</tr>
<tr>
<td>BUN, mg/dl</td>
<td>20 (16 to 25)</td>
<td>19 (15 to 26)</td>
<td>20 (16 to 26)</td>
</tr>
<tr>
<td>&gt;25 mg/dl</td>
<td>25</td>
<td>26</td>
<td>26</td>
</tr>
<tr>
<td>Creatinine, mg/dl</td>
<td>1.1 (0.9 to 1.3)</td>
<td>1.1 (1.0 to 1.4)</td>
<td>1.1 (0.9 to 1.3)</td>
</tr>
<tr>
<td>QRS, ms</td>
<td>160 (142 to 170)</td>
<td>152 (140 to 164)</td>
<td>160 (146 to 172)†</td>
</tr>
<tr>
<td>≥150 ms</td>
<td>66</td>
<td>57</td>
<td>69†</td>
</tr>
<tr>
<td>LBBB</td>
<td>71</td>
<td>57</td>
<td>77†</td>
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<tr>
<td>Echocardiography</td>
<td></td>
<td></td>
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<tr>
<td>Baseline LVEF</td>
<td>29.0 (37.2 to 31.1)</td>
<td>29.6 (27.7 to 31.4)</td>
<td>29.4 (27.6 to 31.6)</td>
</tr>
<tr>
<td>Baseline LVESV/BSA, ml/m²</td>
<td>85.1 (73.3 to 99.7)</td>
<td>83.6 (72.9 to 96.8)</td>
<td>85.4 (75.0 to 96.8)</td>
</tr>
<tr>
<td>Baseline LVEDV/BSA, ml/m²</td>
<td>119.7 (105.1 to 137.7)</td>
<td>118.7 (106.0 to 135.7)</td>
<td>120.3 (107.9 to 136.3)</td>
</tr>
<tr>
<td>Baseline LV mass/BSA, g/m²</td>
<td>105.4 (93.7 to 117.6)</td>
<td>103.3 (92.6 to 115.6)</td>
<td>105.7 (95.3 to 118.3)</td>
</tr>
<tr>
<td>LVESV/baseline volume</td>
<td>−10.1 (−15.3 to −5.4)</td>
<td>−18.0 (−21.7 to −12.1)</td>
<td>−38.1 (−46.2 to −31.2)</td>
</tr>
<tr>
<td>LVEDV/baseline volume</td>
<td>−5.7 (−8.6 to −2.8)</td>
<td>−10.0 (−12.6 to −6.6)</td>
<td>−24.3 (−31.6 to −19.1)</td>
</tr>
<tr>
<td>LV mass/baseline LV mass</td>
<td>−4.5 (−7.6 to −2.0)</td>
<td>−13.9 (−18.1 to −7.5)</td>
<td>−25.9 (−31.0 to −21.2)</td>
</tr>
<tr>
<td>LVVEF</td>
<td>3.2 (1.6 to 5.1)</td>
<td>5.8 (3.8 to 7.5)</td>
<td>12.9 (10.6 to 15.6)</td>
</tr>
</tbody>
</table>

**Medications**

- Beta-blockers: 93
- ACEIs/ARB: 96
- Aldosterone receptor antagonist: 31
- Class III antiarrhythmic agent use: 7.2

Values are presented as % or median (interquartile range). †p < 0.05 for comparison between low and high responders.
propriate ICD shock, subsequent to the 1-year echocardiogram, by echocardiographic response to CRT-D and in ICD-only patients were graphically displayed according to the Kaplan-Meier method with comparison of cumulative events by the log-rank test. All p values were 2 sided, and a p value <0.05 was considered significant. Analyses were conducted with SAS software version 9.2 (SAS Institute, Cary, North Carolina).

**Results**

Among the 1,372 study patients, 623 were in the ICD-only group and 749 were in the CRT-D group (by intention-to-treat analysis). In the latter group, 529 were high responders (defined as ≥25% reduction in LVESV), and 220 patients were low responders (<25% reduction in LVESV). The distribution of demographic and clinical characteristics, including age at enrollment, diabetes mellitus, New York Heart Association functional class, renal function measures, cardiac chambers volumes, and medications was similar among the ICD-only group and the 2 CRT-response subgroups (Table 1). However, there was a gradual increase in the proportion of patients with nonischemic cardiomyopathy, left bundle branch block, QRS >150 ms on baseline electrocardiography, and female patients among the low-response, ICD-only, and high-response groups, respectively (Table 1). Comparison of parameters of echocardiographic response at 1 year showed that high responders exhibited also greater reductions in left ventricular end-diastolic volume (LVEDV) and left ventricular mass than low-response patients and that low-response patients exhibited significantly greater reductions in left ventricular volumes and left ventricular mass than patients in the ICD-only group (Table 1). In addition, only 4.8% of ICD-only patients had ≥25% reduction in LVESV.

**Relationship between echocardiographic response to CRT-D and the risk of subsequent VTAs.** The median follow-up time to a first VTA event after the 1-year post-enrollment echocardiogram was 1.24 years (interquartile range 0.67 to 1.82 years). Among the 1,372 study patients, 55 patients (4%) died during follow-up, and 184 patients (13%) experienced appropriate ICD therapy for VTA (170 patients experienced appropriate ICD therapy for VT, 38 patients for VF/VFL, 29 for VF, and 16 for VFL).

Kaplan-Meier survival analysis showed that the cumulative probability of a first occurrence of VTA 2 years after assessment of echocardiographic response was highest among low responders to CRT-D (28%), intermediate among ICD-only patients (21%), and lowest among high responders to CRT-D (12%), with p < 0.001 for the overall difference during follow-up (Fig. 1). Similarly, the 2-year cumulative probability of the endpoints VTA or death and the separate occurrence of VT or VF/VFL was highest among low responders, intermediate among ICD-only patients, and lowest among high responders to CRT-D (p < 0.001 for all) (Fig. 2).

Consistent with these findings, multivariate analysis (Table 2) demonstrated that high responders had a significant 55% lower risk of VTA (p < 0.001) compared with ICD-only patients, whereas the risk of VTA among low responders was not significantly different from ICD-only patients (hazard ratio: 1.26; p = 0.20). Notably, in the CRT-D group, high responders exhibited a significant 64% lower risk of VTA compared with low responders (p <
Similarly, the risk of the endpoints VTA or death and the separate occurrence of VT or VF/VFL was significantly lower among high responders as compared with both ICD-only patients and low responders. Similar results were found in a subanalysis adjusting for LVESV indexed to body surface area measured at 1 year instead of baseline. In addition, low responders exhibited a 34% (p = 0.08) increased risk of VTA or death and a 40% (p = 0.07) increased risk of VT compared with ICD-only patients, suggesting a possible trend toward increased arrhythmic risk in this subset of CRT-D patients.

Reverse remodeling and the risk of appropriate ICD shocks. High responders to CRT-D exhibited a significantly lower cumulative probability for a first appropriate ICD shock at 2 years (5%) compared with both low responders and ICD-only patients (14% and 12%, respectively), with p < 0.001 for comparison of the overall difference during follow-up (Fig. 3). Consistently, multivariate analysis demonstrated that high responders had a 66% lower risk of a first appropriate ICD shock compared with both ICD-only patients and low responders to CRT-D (Table 2).

Relationship between the magnitude of echocardiographic response to CRT-D and the risk of subsequent VTAs. In the CRT-D group, we observed a direct relationship between improvement in LVESV at 1 year and the reduction in the risk of subsequent life-threatening VTAs (Table 3). In this analysis, every 10% reduction in LVESV was associated with a significant 20% adjusted lower risk of VTA, a 21% lower risk of VTA or death, a 20% lower risk of VT, and a 21% lower risk of VT or VF/VFL.
of VT, and a prominent 25% reduction in the adjusted risk of VF/VFL. In addition, unadjusted analysis of the effects of LVESV reduction on VF and VFL separately showed that every 10% reduction in LVESV was associated with a 21% (p = 0.129) and 33% (p = 0.018) reduction in the risk of VF and VFL, respectively.

Figure 4 shows an inverse relationship between deciles of LVESV change and cumulative probability of VTA at 1.5-year post-assessment of echocardiographic response. Consistently, improvements in other measures of remodeling also showed reductions in the risk of subsequent life-threatening VTA: every 10% reduction in LVEDV, a 10% reduction in left ventricular mass, and a 1% increase in left ventricular ejection fraction was associated with a 26% (p = 0.001), a 26% (p = 0.004), and an 8% (p < 0.001) adjusted lower risk of VTA, respectively.

**Discussion**

The present study demonstrates a direct relationship between the magnitude of echocardiographic response to CRT and a reduction in subsequent VTA risk in mildly symptomatic patients with left ventricular dysfunction. We showed that patients with a high echocardiographic response to CRT-D exhibit a significant reduction in the risk of life-threatening VTA events, whereas VTA risk among patients with a low echocardiographic response to CRT-D was not significantly different from that of ICD-only patients. These findings suggest that the process of reverse remodeling induced by CRT results in both mechanical and electrical stability of the left ventricle, leading to a lower risk of both HF and arhythmic events among patients who show a favorable echocardiographic response after device implantation.

**Comparison with previous studies.** Several small studies have shown a reduction in the cumulative probability of VTA with CRT-D compared with a control group of ICD-only patients (4–6). Recently, Di Biase et al. (7) analyzed data from the InSync ICD Italian registry; the study did not analyze the effects of reverse remodeling as a continuous measure, but did show a significant reduction in VTA episodes and shock therapies between responders (defined as >10% improvement in LVEDV) and nonresponders. Previous data regarding the association between CRT-D therapy and reduction in VTA risk, however, are not consistent. Recently, Markowitz et al. (16) reported that reverse remodeling did not predict VTA episodes and suggested that due to the short follow-up time of these studies, no significant reduction in VTA risk was observed. In the present study, derived from a large multicenter clinical trial, we evaluated the association between reverse remodeling with CRT-D (assessed both as a categorical and a continuous measure) and the subsequent risk of VTA.
events. We showed that a favorable (≥25% reduction in LVESV) echocardiographic response to CRT-D is associated with a significant 55% reduction in the risk of VTA compared with ICD-only therapy and with a 64% risk reduction compared with a lower echocardiographic response. Furthermore, the relatively long follow-up time of the present study (with follow-up beginning at the 1-year echocardiographic assessment of reverse remodeling and ending up to 3 years post-implantation) facilitated a comprehensive analysis of the relationship between the extent of reverse ventricular remodeling (as a continuous measure) and the burden of ventricular arrhythmia, demonstrating that incremental 10% reductions in LVESV with CRT-D therapy are independently associated with a corresponding 20% reduction in the risk of VTA.

Experimental studies and a few case reports (8,9) suggested that CRT may promote ventricular arrhythmogenesis, possibly due to reversal of the normal sequence of activation induced by left ventricular epicardial pacing that may lead to prolongation of the QT interval and an increase in the transmural dispersion of repolarization (10). In the current study, we dichotomized responders and nonresponders at the approximate lower quartile of LVESV change (at the 25% level) and observed a trend toward increased risk of VTA or death among low responders to CRT-D compared with ICD-only patients (hazard ratio: 1.34; p = 0.08). These findings are consistent with those reported earlier and suggest that CRT might have potential proarrhythmic effects in an important subset of mildly symptomatic HF patients. Thus, it is possible that CRT has 2 opposing effects: the dominant effect is inducing reverse remodeling and therefore reducing arrhythmia risk, but in a subset of patients who do not demonstrate significant reverse remodeling, CRT may be proarrhythmic, possibly due to reversal of the normal sequence of activation in the left ventricle, altering repolarization and therefore predisposing to reentry or early afterdepolarization.

The magnitude of reverse remodeling correlates with a reduction in ventricular arrhythmia risk. It was previously shown that left ventricular size and adverse remodeling predict ventricular arrhythmias (17). The present study demonstrated that the extent of reverse ventricular remodeling during the first year after device implantation is inversely related to the risk of future VTA events. Every 10% reduction in LVESV was associated with a significant reduction in all the following endpoints: VTA, VTA/death, and VT, whereas the most striking reduction was in VF/VFL events. Consistent results were also observed for other measures of reverse remodeling including reductions in LVEDV, left ventricular mass, and increase in left ventricular ejection fraction.

Study limitations. Echocardiograms were obtained at baseline and 12 months; we could not evaluate the relationship between changes in ventricular size and arrhythmia events in those patients who did not undergo 12-month device-on echocardiography. The lack of randomization according to echocardiographic response is also a limitation. However, the present results were obtained after adjustment for multiple clinical covariates, further suggesting the consistency of our findings regarding the association between
the extent of reverse remodeling and subsequent VTA risk. The MADIT-CRT study excluded patients with New York Heart Association functional class III/IV in the past 90 days before enrollment; thus, our results may not apply to this population.

Conclusions

CRT was recently shown to reduce HF or death and improve measures of left ventricular size in mildly symptomatic HF patients with a left ventricular ejection fraction ≤30% and wide QRS (3). The reverse remodeling effects were concordant with the reduction in the endpoint of death or HF event (18). Our findings extend this observation and show that responders to CRT-D therapy derive a significant reduction in the risk of life-threatening VTA, suggesting that reverse remodeling had a dual effect of both HF and VTA risk reduction in the MADIT-CRT study population. The importance of the dual effect of CRT-D therapy among responders is underscored by the fact that ventricular arrhythmias and ICD shocks are associated with a reduction in quality of life and with a poor prognosis among patients with an indication for an ICD (19,20) and stress the importance of reverse remodeling as a marker of both HF and VTA risk after CRT-D implantation.

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REFERENCES

11. Lang RM, Bierig M, Devereux RB, et al. Recommendations for chamber quantification: a report from the American Society of Echocardiography’s Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. J Am Soc Echocardiogr 2005;18:1440–63.

Key Words: cardiac resynchronization therapy, heart failure, implantable cardioverter-defibrillator, reverse remodeling, ventricular arrhythmia.