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CME

Cardiac Resynchronization Therapy Is More Effective in Women Than in Men

The MADIT-CRT (Multicenter Automatic Defibrillator Implantation Trial With Cardiac Resynchronization Therapy) Trial

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CME Objective for This Article: At the conclusion of this activity, the learner should be able to identify the factors related to sex-specific outcomes for death and heart failure events in the MADIT-CRT trial.

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Cardiac Resynchronization Therapy Is More Effective in Women Than in Men

The MADIT-CRT (Multicenter Automatic Defibrillator Implantation Trial With Cardiac Resynchronization Therapy) Trial

Objectives The purpose of this study was to investigate the factors related to sex-specific outcomes for death and heart failure events in the MADIT-CRT (Multicenter Automatic Defibrillator Implantation Trial With Cardiac Resynchronization Therapy) trial.

Background In the MADIT-CRT trial, women seemed to achieve a better result from resynchronization therapy than men.

Methods All 1,820 patients (453 female and 1,367 male) enrolled in the MADIT-CRT trial were included in this sex-specific outcome analysis that compared the effect of cardiac resynchronization therapy with defibrillator (CRT-D) relative to implanted cardioverter-defibrillator (ICD) on death or heart failure (whichever came first), heart failure only, and death at any time.

Results Female patients were more likely to have nonischemic cardiomyopathy and left bundle branch block and less likely to have renal dysfunction than male patients. Overall, female patients had a better result from CRT-D therapy than male patients, with a significant 69% reduction in death or heart failure (hazard ratio: 0.31, $p < 0.001$) and 70% reduction in heart failure alone (hazard ratio: 0.30, $p < 0.001$). Women had a significant 72% reduction in all-cause mortality in the total population (hazard ratio: 0.28, $p = 0.02$) and significant 82% and 78% reductions in mortality in those with QRS ≥150 ms and with left bundle branch block conduction disturbance, respectively, with sex-by-treatment interactions for mortality reduction significant at $p < 0.05$ in each of these 3 patient groups. These beneficial CRT-D effects among women were associated with consistently greater echocardiographic evidence of reverse cardiac remodeling in women than in men.

Conclusions Women in the MADIT-CRT trial obtained significantly greater reductions in death or heart failure (whichever came first), heart failure alone, and all-cause mortality with CRT-D therapy than men, with consistently greater echocardiographic evidence of reverse cardiac remodeling in women than in men. (Multicenter Automatic Defibrillator Implantation Trial With Cardiac Resynchronization Therapy [MADIT-CRT]; NCT00180271). (J Am Coll Cardiol 2011;57:813–20)

Cardiac resynchronization therapy with defibrillator (CRT-D) is an approved treatment for patients with advanced stages of heart failure in the setting of widened QRS, and this therapy is associated with reduction in symptoms, improvement in functional capacity, and decrease in hospitalization and mortality (1). The recently reported randomized MADIT-CRT (Multicenter Automatic Defibrillator Implantation Trial With Cardiac Resynchronization Therapy) trial demonstrated that CRT-D treated patients with New York Heart Association (NYHA) functional class I and II heart failure symptoms, left ventricular ejection fraction (LVEF) ≤0.30 and QRS ≥130 ms had a 34% reduction in the risk of heart failure or death, whichever came first, when compared with patients treated with an implantable cardioverter-defibrillator (ICD) (2). In this substudy from the MADIT-CRT trial, we report the sex-specific outcomes with CRT-D versus ICD therapy and explore the factors associated with the more favorable response to this therapy in women than in men.

Methods

Trial design. The design and primary results of the MADIT-CRT trial were recently published (2). Briefly, the MADIT-CRT study was designed to determine whether CRT-D therapy would reduce the risk of death or heart failure events in patients with mild cardiac symptoms, a reduced ejection fraction, and wide QRS complex when compared to ICD therapy. The patients were randomly assigned in a 3:2 ratio to receive either CRT-D or ICD. From December 22, 2004, through April 23, 2008, a total of 1,820 patients were enrolled at 110 hospital centers. Primary analyses included Cox proportional-hazards regression for heart failure alone and for death at any time and evaluation of 10 prespecified categorical subgroups and treatment interactions. The effects of CRT-D in 7 of these subgroups were

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presented in the primary analysis of the MADIT-CRT trial (age, sex, NYHA functional class and substrate, QRS duration, LVEF, left ventricular end-diastolic volume, and left ventricular end-systolic volume) and 2 interaction effects between subgroup and treatment were identified. The CRT-D therapy was associated with a greater benefit in women than in men, and in patients with QRS duration ≥150 than <150 ms.

The protocol was approved by the institutional review board at each of the participating centers. Patients of either sex who were at least 21 years of age were enrolled

in the study if they had ischemic cardiomyopathy (NYHA functional class I or II) or nonischemic cardiomyopathy (NYHA functional class II only), sinus rhythm, an ejection fraction of ≤0.30, and prolonged intraventricular conduction with a QRS duration of ≥130 ms. All eligible subjects met the guideline indication for ICD therapy. Patients were excluded from enrollment for a variety of reasons as previously reported (2).

Table 1 Patient Characteristics by Sex

	Women (n = 453)	Men (n = 1,367)
Age, yrs	64 ± 11	65 ± 11
Race		
White*	86	92
Black*	12	6
Other	2	2
Cardiac history		
Ischemic heart disease NYHA functional class I*	5	18
Ischemic heart disease NYHA functional class II*	23	46
Nonischemic heart disease NYHA functional class II*	72	36
NYHA functional class III or IV >3 months before enrollment	10	10
Treatment for hypertension	64	63
Atrial fibrillation >1 month before enrollment*	7	13
Diabetes mellitus	31	30
Cigarette smoking*	9	13
Body mass index ≥30 kg/m^2	34	37
Coronary artery bypass surgery*	12	35
Cardiac findings at enrollment		
Systolic blood pressure, mm Hg	122 ± 18	123 ± 17
Diastolic blood pressure, mm Hg*	71 ± 11	72 ± 11
Blood urea nitrogen >25 mg/dl*	19	26
Creatinine ≥1.4 mg/dl*	9	26
Left bundle branch block*	87	65
Right bundle branch block*	4	15
QRS duration, ms	158 ± 17	158 ± 20
QRS duration >150 ms	67	64
Left ventricular ejection fraction*	0.23 ± 0.05	0.24 ± 0.05
6-min walk distance, m*	328 ± 107	371 ± 105
Echocardiogram/Doppler, baseline		
LVEDV index, ml/m^2	122 ± 27	124 ± 29
LVESV index, ml/m^2	87 ± 21	89 ± 24
LAV index, ml/BSA	46 ± 10	47 ± 10
Medications at baseline		
Aldosterone antagonist	36	30
Amiodarone*	3	9
Angiotensin-converting enzyme inhibitors*	72	79
Angiotensin-receptor blockers*	26	19
Beta-blockers*	97	92
Digitalis*	36	22
Diuretics*	75	68
Lipid-lowering statin drugs*	53	72

Values are mean ± SD or %. *Indicates $p < 0.01$.

BSA = body surface area; LAV = left atrial volume; LVEDV = left ventricular end-diastolic volume; LVEF = left ventricular ejection fraction; LVESV = left ventricular end-systolic volume; NYHA = New York Heart Association.

Abbreviations and Acronyms

CRT-D = cardiac resynchronization therapy with defibrillator

ICD = implanted cardioverter-defibrillator

LBBB = left bundle branch block

LVEF = left ventricular ejection fraction

NYHA = New York Heart Association

Echocardiographic studies. Two-dimensional echocardiography (3) was performed at baseline and at the 1-year follow-up in 1,417 patients to assess changes in the left ventricular volumes, left atrial volume, and ejection fraction in the 2 treatment groups. Volumes were estimated by averaging those derived from the 2- and 4-chamber views according to Simpson's method, and the ejection fraction was calculated using a standardized protocol. Volumes were indexed for body surface area.

Statistical analysis. For categorical variables, the chi-square statistic was used to assess group differences. For continuous variables, comparisons were performed using the *t* test for independent samples. Cumulative survival curves were determined by Kaplan-Meier analysis (4), with statistical comparison by the log-rank method. The Cox proportional-hazards regression model (5) was used to calculate the risk for specified end points, and selective treatment interactions were evaluated. Outcome analyses were performed according to the intention-to-treat principle. The Wilcoxon rank-sum test was used to evaluate the absolute change in the median difference in echocardiographic parameters between female and male patients who had paired baseline and 12-month recordings. All p values are 2-tailed and have not been adjusted for the stopping rule. Analyses used version 3.0 of the database, which was released on September 30, 2009.

Results

Clinical characteristics. The clinical characteristics of 453 women and the 1,367 men are presented in Table 1. The female patients were more likely to have nonischemic cardiomyopathy and left bundle branch block conduction pattern than male patients, whereas men were more likely to have ischemic heart disease, prior coronary revascularization, and renal dysfunction than women. The patients were well treated with appropriate cardiac medications, but there were some significant differences in medication utilization between women and men (Table 1).

End point analyses. The primary end point of heart failure or death (whichever came first) occurred in 376 patients: 29 of 275 (11%) in women with CRT-D, 51 of 178 (29%) in women with ICD, 159 of 814 (20%) in men with CRT-D, and 137 of 553 (25%) in men with ICD. These end points included 54 deaths and 322 heart failure events. Kaplan-Meier estimates of the probability of the primary end point in women and men with CRT-D and ICD therapy

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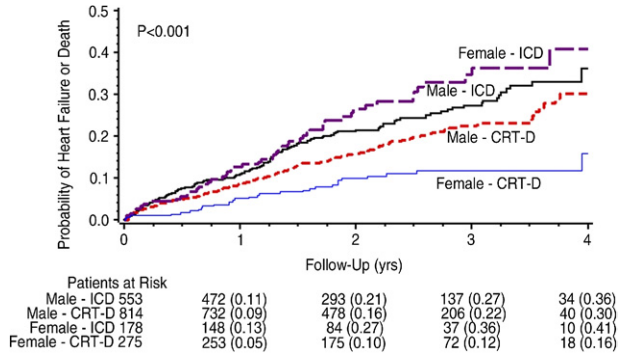

Figure 1 **Kaplan-Meier Estimates of Cumulative Probability of Heart Failure or Death Stratified by Sex and ICD or CRT-D Therapy**

The 4 curves reflect the probability of heart failure or death, whichever comes first, over time in women and men having the device therapy—implanted cardioverter-defibrillator (ICD) or cardiac resynchronization therapy with defibrillator (CRT-D)—to which they were randomized. Women randomly assigned to CRT-D therapy **(blue line)** had the best result. The **purple line** indicates female ICD therapy; the **black line** indicates male ICD therapy; and the **red line** indicates male CRT-D therapy.

are shown in Figure 1. Overall, women receiving CRT-D therapy had a significantly better outcome than women receiving ICD therapy and men receiving ICD or CRT-D therapy during an average follow-up duration of 2.4 years.

The hazard ratios for CRT-D to ICD therapy in women and men for heart failure or death (whichever came first), heart failure only, or death at any time in the overall study population as well as by disease etiology, QRS duration, and left bundle branch block (LBBB) conduction disturbance are presented in Table 2. For all 3 outcomes, women achieved better results from CRT-D therapy than men, with significant differences between the sexes (interaction $p < 0.05$) for all 3 outcomes in the total population and for 2 of the 3 outcomes in those with nonischemic cardiomyopathy, QRS <150 ms, and LBBB (Table 2). The CRT-D therapy was associated with significantly reduced mortality in women ($p = 0.02$) but not in men in the total population (Table 2 and Fig. 2), in women with QRS ≥150 ms, and in women with LBBB conduction disturbance (Table 2). In these 3 mortality analyses, the sex-by-treatment interactions were significant at $p < 0.05$ (Table 2).

We explored for treatment interactions in prespecified sex-related subgroups. In patients with nonischemic cardiomyopathy and QRS ≥150 ms, the hazard ratio for heart failure or death was 0.28 ($p = 0.001$) for women and 0.72 ($p = 0.28$) for men, with a significant $p = 0.047$ interaction. In patients with nonischemic cardiomyopathy and LBBB, the hazard ratio for heart failure or death was 0.22 ($p < 0.001$) for women and 0.73 ($p = 0.24$) for men, with a significant $p < 0.005$ interaction. The interaction analyses for the end point of death in these at-risk subgroups were not significant.

Echocardiographic findings. The changes in echocardiographic volumes and ejection fraction parameters between baseline and 1-year follow-up for women and men in the total population and by disease etiology, QRS duration, and LBBB are presented in Table 3. All echocardiography parameters improved to a significantly greater degree with CRT-D therapy than with ICD therapy within both the female group and the male group ($p < 0.001$). Women had consistently greater improvements in reverse cardiac remodeling with CRT-D therapy than did men, with the most significant differences evident in the total population and in patients with QRS ≥150 ms or LBBB (Table 3).

Adverse events. Adverse events were more frequent among the CRT-D–treated patients (11%) than in the ICD-treated patients (4.5%). Women had an overall higher likelihood of all device-related adverse events than men, 10.5% versus 7.9%, respectively ($p = 0.001$). Women were more likely to have pneumothorax (3% in women vs. 0.73% in men), but men were more likely to have lead dislodgement (1.7% in women vs. 3.2% in men).

Discussion

In this substudy from the MADIT-CRT trial, 25% of the study population was female. Although men received significant benefit from CRT-D therapy, women had significantly better results with CRT-D therapy than men for death or heart failure (whichever came first), for heart failure only, and for death at any time. Women had a significant 72% reduction in all-cause mortality in the total population, with even greater reductions in mortality for those with QRS ≥150 ms or with LBBB, with significant sex-by-treatment interactions in the 3 patient groups for the mortality end point.

There were significant differences in baseline characteristics between women and men that could have contributed in part to the observed findings. A greater proportion of the female cohort had a substrate of nonischemic cardiomyopathy and an underlying LBBB pattern, but the percentage of patients with QRS ≥150 ms and the mean QRS durations were not significantly different between women and men. Women had a higher utilization of beta-blockers than men. Men had a greater proportion of ischemic cardiomyopathy and a history of atrial fibrillation and renal dysfunction compared with women. The latter 2 clinical characteristics have been associated with poor prognosis and higher risk of death in the MADIT-2 study population (6). A higher proportion of men had a right bundle branch block pattern, and an association between the presence of right bundle branch block and poor outcome with CRT has been noted (7).

In heart failure studies, women, especially those with nonischemic heart disease, have been shown to have an overall survival advantage (8), and other groups have shown that women achieve greater reduction in left

Table 2 Risk of Death or Heart Failure by Sex

Study Group End Points	CRT-D:ICD Hazard Ratio* (p Value), 95% Confidence Interval		Interaction p Value
	Women	Men	
Total population (453, 1,365)			
Death or heart failure (80, 296)	0.31 (<0.001)	0.72 (<0.01)	<0.01
	0.19–0.50	0.57–0.92	
Heart failure only (73, 249)	0.30 (<0.001)	0.65 (0.001)	<0.01
	0.18–0.50	0.50–0.84	
Death at any time (20, 107)	0.28 (0.02)	1.05 (0.83)	<0.03
	0.10–0.79	0.70–1.57	
Disease etiology			
Ischemic heart disease (125, 874)			
Death or heart failure (25, 216)	0.32 (0.01)	0.65 (<0.01)	NS
	0.13–0.78	0.49–0.86	
Heart failure only (23, 180)	0.31 (0.01)	0.58 (0.001)	NS
	0.12–0.76	0.43–0.79	
Death at any time (5, 83)	0.17 (0.13)	0.99 (0.95)	NS
	0.02–1.66	0.62–1.57	
Nonischemic heart disease (328, 493)			
Death or heart failure (55, 80)	0.30 (<0.001)	0.96 (0.86)	<0.01
	0.17–0.54	0.60–1.53	
Heart failure only (50, 69)	0.31 (<0.001)	0.88 (0.62)	<0.01
	0.17–0.56	0.54–1.45	
Death at any time (15, 24)	0.33 (0.07)	1.34 (0.52)	NS
	0.10–1.10	0.55–3.31	
QRS duration			
QRS <150 ms (148, 497)			
Death or heart failure (25, 122)	0.30 (<0.01)	1.09 (0.66)	<0.01
	0.12–0.73	0.74–1.60	
Heart failure only (23, 107)	0.26 (<0.01)	1.08 (0.72)	<0.01
	0.10–0.65)	0.71–1.60	
Death at any time (8, 42)	0.40 (0.23)	1.20 (0.59)	NS
	0.09–1.80	0.62–2.34	
QRS ≥150 ms (305, 870)			
Death or heart failure (55, 174)	0.30 (<0.001)	0.55 (<0.001)	NS
	0.17–0.54	0.40–0.75	
Heart failure only (50, 142)	0.31 (<0.001)	0.45 (<0.001)	NS
	0.17–0.58	0.32–0.64	
Death at any time (12, 65)	0.18 (<0.05)	1.03 (0.90)	<0.05
	0.04–0.89	0.61–1.75	
Conduction disturbance			
Non-LBBB (59, 478)			
Death or heart failure (11, 111)	1.97 (0.40)	1.15 (0.51)	NS
	0.40–9.64	0.76–1.76	
Heart failure only (10, 96)	1.95 (0.41)	1.04 (0.88)	NS
	0.40–9.53	0.67–1.61	
Death at any time	—	—	—
LBBB (394, 887)			
Death or heart failure (69, 185)	0.23 (<0.01)	0.53 (<0.01)	0.01
	0.13–0.40	0.39–0.72	
Heart failure only (63, 153)	0.22 (0.01)	0.47 (<0.01)	0.03
	0.12–0.40	0.34–0.66	
Death at any time (17, 68)	0.22 (0.01)	0.84 (0.50)	0.04
	0.07–0.70	0.67–1.61	

Numbers in parentheses represent patient counts (female, male) in the header rows and event counts in rows with event types. In the non–left bundle branch block (LBBB) group, the Cox regression model for death at any time was unstable owing to a paucity of death events, so hazard ratios are not provided. *Adjusted for history of atrial arrhythmias, ischemic status and New York Heart Association functional class, race, creatinine, left ventricular ejection fraction, distance walked in 6-min test, and left atrial volume. Medications did not make a significant contribution to the analyses.

CRT-D = cardiac resynchronization therapy with defibrillator; ICD = implantable cardioverter-defibrillator; NS = not significant ($p > 0.05$).

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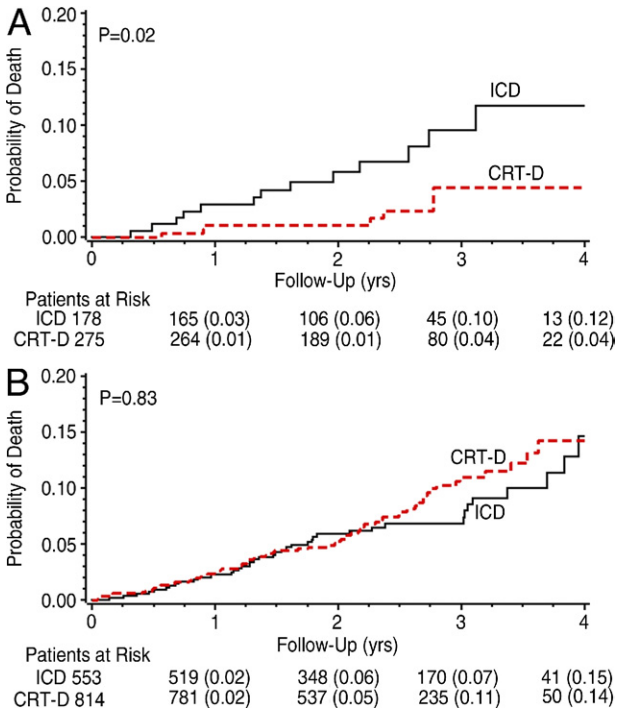

Figure 2 **Kaplan-Meier Estimates of the Cumulative Probability of Death in Women and Men by Device Therapy**

(A) Women had a significantly lower probability of death over time with CRT-D **(red line)** than with ICD **(black line)**. **(B)** Men had similar probability of death over time with CRT-D therapy **(red line)** or with ICD therapy **(black line)**. Abbreviations as in Figure 1.

ventricular volumes and improvement in LVEF than men after CRT therapy (9). No prior study has demonstrated a significantly greater benefit from device therapy for women than men regarding mortality or cardiac-related outcomes in an overall study population or by disease etiology. In the current MADIT-CRT analysis, CRT-D:ICD hazard ratios were significantly better for women than for men for all 3 end points in the total population and for 2 of the 3 end points in those with nonischemic cardiomyopathy (see sex-by-treatment interaction p values in Table 2). Women with nonischemic cardiomyopathy were uniquely responsive to CRT relative to men, and the reason for this sex-related beneficial effect is unclear. It is possible that among patients with heart disease, the risk of heart failure is greater for women than for men, resulting in a greater benefit from preventive CRT-D therapy in women.

It is generally appreciated that in subjects without heart disease, women have, on average, approximately 10 ms shorter QRS durations than men (10). In subjects with heart failure, prolongation of QRS ≥120 ms occurs in 14% to 47% of patients overall (11). In the MADIT-CRT trial, we used the same entry criteria of QRS ≥130 ms for both women and men. Thus, for any given QRS duration ≥130 ms, women might have, on a relative basis, more conduction disturbance and greater cardiac dyssynchrony than men, and this might explain why women were more responsive to cardiac resynchronization therapy than men in this trial. It is interesting that LBBB was present in 70% of the MADIT-CRT patients and in 87% of female patients. Although both sexes with LBBB benefited from CRT-D therapy, women with LBBB achieved a significantly better result with this therapy than did men with LBBB (Table 2).

Several major CRT trials involved patients with NYHA functional class III and IV heart failure (9,12–14). In the MIRACLE (Multicenter InSync Randomized Clinical Evaluation) study (14), 32% of the study group were women; and among women receiving CRT, there was a reduction in heart failure hospitalization or death compared with the control group (hazard ratio: 0.157, p = 0.002). No differences were seen among men for either end point with CRT, even when accounting for baseline demographics and heart failure etiology (14). In the COMPANION (Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure) trial, women made up 33% of the study population, and these patients had a 56% reduction in the risk of sudden cardiac death with CRT-D compared with optimal pharmacologic therapy, with female sex associated with reduced risk in conjunction with CRT-D therapy (hazard ratio: 0.56, p = 0.003) (9). When CRT or CRT-D therapy was compared to optimal pharmacologic therapy in COMPANION, these therapies were similarly beneficial in reducing mortality in women and men, and there were no significant sex-by-treatment interactions (15). In the CARE-HF (Cardiac Resynchronization in Heart Failure) study, about 25% of the study group were women, but the CRT to medical therapy hazard ratios for women and men for the primary end point (death or hospitalization) were similar, in the 0.62 to 0.64 range (12). In the recently reported European cohort of the REVERSE (Resynchronization Reverses Remodeling in Systolic Left Ventricular Dysfunction) trial involving 162 patients with NYHA functional class I and II heart failure, LVEF ≤0.35, and QRS ≥120 ms, approximately 20% of the subjects were female, and the clinical composite end point of worsened heart failure was reduced to a similar degree with CRT therapy in women and men (16). This REVERSE trial had higher LVEF and less prolonged QRS duration criteria for enrollment than the MADIT-CRT study did, and there was limited power to find sex differences in outcome in view of the small number of patients in the trial.

Conclusions

Women in the MADIT-CRT trial obtained significantly greater reductions in death or heart failure (whichever came first), heart failure alone, and all-cause mortality with

Table 3 Changes in Median Echocardiographic Parameters Between Baseline and 1-Year Follow-Up for ICD– and CRT-D–Treated Patients by Sex, Disease Etiology, and QRS Duration

Echocardiography Parameters	Women		Men		CRT-D F vs. M p Value*
	ICD	CRT-D	ICD	CRT-D	
Total, n	154	184	469	565	
ΔLVEDV ml/BSA	−9	−29	−7	−22	<0.001
ΔLVESV ml/BSA	−10	−31	−8	−27	<0.001
ΔLAV ml/BSA	−5	−13	−4	−11	0.001
ΔLVEF points	+0.03	+0.13	+0.03	+0.10	0.001
Ischemic heart disease, n	40	52	294	359	
ΔLVEDV ml/BSA	−9	−22	−6	−21	0.05
ΔLVESV ml/BSA	−11	−28	−8	−25	<0.05
ΔLAV ml/BSA	−5	−13	−4	−11	<0.01
ΔLVEF points	+0.04	+0.13	+0.03	+0.10	<0.01
Nonischemic heart disease, n	114	132	175	206	
ΔLVEDV ml/BSA	−8	−30	−7	−28	0.06
ΔLVESV ml/BSA	−9	−33	−10	−31	0.11
ΔLAV ml/BSA	−5	−14	−4	−12	0.10
ΔLVEF	+0.03	+0.13	+0.03	+0.12	<0.01
QRS <150 ms, n	45	58	166	200	
ΔLVEDV ml/BSA	−7	−23	−7	−19	<0.05
ΔLVESV ml/BSA	−9	−27	−8	−23	<0.05
ΔLAV ml/BSA	−5	−12	−4	−10	0.14
ΔLVEF points	+0.04	+0.12	+0.03	+0.10	<0.01
QRS ≥150 ms, n	109	126	303	365	
ΔLVEDV ml/BSA	−9	−32	−7	−25	<0.001
ΔLVESV ml/BSA	−10	−36	−8	−29	<0.001
ΔLAV ml/BSA	−5	−14	−4	−12	<0.001
ΔLVEF	+0.03	+0.13	+0.03	+0.11	<0.001
Non-LBBB, n	20	25	159	192	
ΔLVEDV ml/BSA	−9	−20	−7	−19	0.173
ΔLVESV ml/BSA	−10	−25	−9	−22	0.118
ΔLAV ml/BSA	−4	−11	−4	−10	0.232
ΔLVEF	+0.03	+0.10	+0.03	+0.09	0.230
LBBB, n	134	159	309	373	
ΔLVEDV ml/BSA	−8	−30	−6	−25	0.001
ΔLVESV ml/BSA	−10	−33	−8	−29	0.002
ΔLAV ml/BSA	−5	−14	−4	−12	0.002
ΔLVEF points	+0.03	+0.13	+0.03	+0.11	<0.01

Note: The number of patients (n) in each category reflect the number of patients in the ΔLVEF analyses, with slightly fewer patients in the other echocardiographic parameters because of a total of 14 patients with missing BSA values. The symbol Δ indicates change in echocardiographic parameter between baseline and 1-year follow-up. Echocardiographic volumes are corrected for BSA. Negative signs (−) indicate reduction in volumes, and positive signs (+) indicate increase in ejection fractions. *The p value (Wilcoxson rank-sum test) for difference in median echocardiography parameter when comparing effect of CRT-D in women (F) versus men (M).

Abbreviations as in Tables 1 and 2.

CRT-D therapy than men. These more favorable results for women were associated with consistently greater echocardiographic evidence of reverse cardiac remodeling in women than in men.

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