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Cardiac Resynchronization Therapy in Asymptomatic or Mildly Symptomatic Heart Failure Patients in Relation to Etiology

Results From the REVERSE (REsynchronization reVErses Remodeling in Systolic Left vEntricular Dysfunction) Study

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Objectives The purpose of this study was to determine the effects of cardiac resynchronization therapy (CRT) with respect to heart failure etiology among patients in the REVERSE (REsynchronization reVErses Remodeling in Systolic Left vEntricular Dysfunction) study.

Background CRT improves outcomes in New York Heart Association functional class III/IV heart failure with wide QRS with a more pronounced effect on left ventricular (LV) reverse remodeling in nonischemic patients.

Methods A total of 277 patients with nonischemic heart disease (IHD) and 333 with IHD etiology in New York Heart Association functional class I or II with QRS ≥120 ms and left ventricular ejection fraction ≤40% received a CRT (± implantable cardioverter-defibrillator) and were randomized to CRT-ON or CRT-OFF for 12 months. The primary end point was the percentage of patients worsened by the HF clinical composite response, and multiple prespecified secondary end points were evaluated regarding etiology using univariable and multivariable analysis.

Results At baseline, IHD patients were significantly older and had more comorbidities and less dyssynchrony than non-IHD patients. In non-IHD patients, 10% worsened in CRT-ON compared with 19% in CRT-OFF ($p = 0.01$). In IHD patients, 20% worsened in the CRT-ON compared with 24% in the CRT-OFF group ($p = 0.10$). Non-IHD patients assigned to CRT-ON improved more in left ventricular end-systolic volume index than IHD patients. Randomization to CRT, left bundle branch block, and wider QRS duration independently predicted response to both end points, whereas non-IHD etiology was an independent predictor only for left ventricular end-systolic volume index.

Conclusions This substudy of REVERSE shows that CRT reverses left ventricular remodeling with a more extensive effect on nonischemic patients. Etiology was, however, not an independent predictor of clinical response. (REsynchronization reVErses Remodeling in Systolic Left vEntricular Dysfunction [REVERSE]; NCT00271154) (J Am Coll Cardiol 2010;56:1826–31) © 2010 by the American College of Cardiology Foundation

Cardiac resynchronization therapy (CRT) improves symptoms, heart failure (HF) morbidity and mortality in New York Heart Association (NYHA) functional class III or IV patients with left ventricular (LV) dysfunction, and QRS prolongation (1–4). CRT also progressively improves LV function, suggesting that CRT might also delay disease progression in mildly symptomatic patients (5,6). This hypothesis was tested in the REVERSE (REsynchronization reVErses Remodeling in Systolic Left vEntricular Dysfunction) study (7). The overall results confirm that

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CRT induces reverse LV remodeling and delays the time to first HF-related hospitalization over 12 months with further improvement over time (8). It has been suggested that the response by CRT treatment is affected by etiology, in particular regarding reverse remodeling (9–11). The aim of this report was to study the REVERSE results in relation to nonischemic compared with ischemic HF etiology.

Methods

Patient population. Eligible patients had American College of Cardiology/American Heart Association stage C (7), NYHA functional class I or II HF with QRS duration ≥120 ms, left ventricular ejection fraction (LVEF) ≤40%, and LV end-diastolic diameter ≥55 mm. Ischemic heart disease (IHD) was defined as a history of myocardial infarction or coronary revascularization and/or evidence of 2- or 3-vessel disease by coronary angiography and non-IHD as the absence of these criteria.

Study design, procedures, and end points. Patients were assessed at baseline, underwent implantation, and randomly assigned to active CRT (CRT-ON) or to control (CRT-OFF) ± implantable cardioverter-defibrillator and evaluated at 1, 3, 6, and 12 months in a double-blind fashion (7). The primary end point was the percentage of patients worsened by the HF clinical composite response (7). Left ventricular end-systolic volume index (LVESVi) was the prospectively powered secondary end point.

Statistical methods. All results were analyzed according to the intention-to-treat principle. All p values reported are nominal, and all statistical tests are 2 sided. Kaplan-Meier analysis was used to analyze time to first HF hospitalization. The log-rank test was used to assess significance. Student's *t* test was used for comparisons of means, and the Fisher exact test was used to compare proportions. Randomization, etiology, and their interaction were examined for secondary end points using analysis of variance methods. A logistic regression model was used for multivariable analysis of the clinical composite response at 12 months and a regression model for change in the LVESVi from baseline to 12 months. Backward stepwise elimination was used to reduce the model to factors with p values <0.05. Baseline factors considered were randomization group, etiology, age, sex, NYHA functional class, systolic blood pressure, LVEF, LVESVi, left bundle branch block (LBBB), baseline QRS duration, at least 50% target dose of beta-blockers, glomerular filtration rate, diabetes, history of hypertension, coronary artery bypass graft, and previous percutaneous coronary intervention.

Results

Study population. Baseline characteristics (Table 1) show that the 277 IHD patients were significantly older and had more comorbidities than the 333 non-IHD patients. LVEF was significantly higher in IHD compared with non-IHD patients. Non-IHD patients more often were female, less often received a concomitant implantable cardioverter-defibrillator, had larger LV dimensions, wider QRS width, and longer intraventricular mechanical delay duration (Table 1). LBBB was significantly more frequent in non-IHD patients. IHD patients less often received at least 50% of the target dose of beta-blockers.

Abbreviations and Acronyms

CRT = cardiac resynchronization therapy
HF = heart failure
IHD = ischemic heart disease
LBBB = left bundle branch block
LV = left ventricular
LVEF = left ventricular ejection fraction
LVESVi = left ventricular end-systolic volume index
NYHA = New York Heart Association

Effects on primary and secondary end points at 12 months. Compared with control, CRT significantly reduced the percentage of patients worsened by the HF composite response in non-IHD patients but not in IHD patients (Fig. 1). Compared with CRT-OFF, the LVESVi significantly improved in both groups at 12 months, with a greater improvement in non-IHD CRT-ON patients (-29.5 ± 30.6 ml/m^2 vs. -7.0 ± 25.5 ml/m^2, $p < 0.0001$) compared with IHD CRT-ON patients (-9.5 ± 24.1 ml/m^2 vs. 3.1 ± 20.6 ml/m^2, $p < 0.0001$) (Fig. 2). In an analysis of variance model, randomization ($p < 0.0001$), etiology ($p < 0.0001$), and their interaction ($p = 0.045$) were all predictors of LVESVi change over 12 months (Table 2). In the non-IHD group, LVEF significantly improved by 7.5 ± 9.3% in the CRT-ON group after 12 months compared with 1.4 ± 7.2% in CRT-OFF group ($p < 0.0001$). In the IHD group, it improved by 2.2 ± 8.5% in CRT-ON compared with 0.3 ± 6.0% in CRT-OFF ($p = 0.03$). The change in LVEF was associated with randomization ($p < 0.0001$), etiology ($p < 0.0001$) and the interaction between the 2 ($p < 0.008$).

In non-IHD patients, CRT significantly improved the Minnesota Living With Heart Failure Quality of Life Questionnaire score, whereas the 6-min walk distance was unaffected (Table 2). Among baseline NYHA functional class II patients, 43% of CRT-ON non-IHD patients improved to NYHA functional class I compared with 32% of CRT-OFF patients ($p = 0.09$). In NYHA functional class II IHD patients, 35% of CRT-ON patients improved to NYHA functional class I compared with 20% of CRT-OFF patients ($p = 0.02$). In a logistic regression model, the interaction term of randomization and NYHA functional class was not significant ($p = 0.52$).

HF hospitalizations. The time to first HF hospitalization is shown in Figure 3. The overall morbidity in both randomization arms was larger in ischemic patients than in nonischemic patients, reflecting the older age and the greater baseline morbidity in the IHD patients. Non-IHD patients had a 5.3% HF hospitalization rate over 12 months in the CRT-OFF group compared with 2.9% in the CRT-ON group. The corresponding rates for IHD patients were 10.3% and 5.0%, respectively. The difference in time to

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Table 1 Patient Characteristics in Nonischemic and Ischemic Patients

	Nonischemic (n = 277)	Ischemic (n = 333)	p Value
Age, yrs	57.6 ± 11.1	66.6 ± 9.0	<0.0001
Men	67	88	<0.0001
New York Heart Association functional class II	86	80	0.07
Previous myocardial infarction	0	84	<0.0001
Previous coronary artery bypass grafting	0	52	<0.0001
Previous percutaneous coronary intervention	1	46	<0.0001
Diabetes	13	30	<0.0001
History of hypertension	44	58	0.001
Chronic obstructive pulmonary disease	7	13	0.01
Peripheral vascular disease	3	13	<0.0001
Angiotensin-converting enzyme inhibitor	83	75	0.02
Angiotensin-converting enzyme inhibitor or angiotensin-receptor blocker	98	96	0.18
Beta-adrenergic blocker	96	95	0.58
≥50% of target beta-adrenergic blocker dose	69	53	0.0001
100% of target beta-adrenergic blocker dose	44	28	<0.0001
Diuretic	81	79	0.48
Left bundle branch block	88	68	<0.0001
Right bundle branch block	5	15	<0.0001
Intrinsic QRS duration, ms	157 ± 21	150 ± 22	0.0004
Interventricular mechanical delay, ms	46.8 ± 35.7	22.7 ± 38.3	<0.0001
Left ventricular			
Ejection fraction, %	26.1 ± 6.7	27.6 ± 6.5	0.006
End-diastolic diameter, cm	7.0 ± 1.0	6.9 ± 0.8	0.28
End-systolic diameter, cm	5.9 ± 1.2	5.7 ± 0.9	0.08
End-systolic volume, cm^3	210 ± 94	190 ± 65	0.006
End-diastolic volume, cm^3	279 ± 108	261 ± 78	0.02
Mass, g	267 ± 87	274 ± 66	0.40
Glomerular filtration rate, ml/min	95.5 ± 35.7	77.9 ± 28.4	<0.0001
Heart rate, beats/min	68.4 ± 10.4	66.4 ± 10.5	0.02
Supine blood pressure, mm Hg			
Systolic	123 ± 17	126 ± 20	0.07
Diastolic	73 ± 11	72 ± 11	0.27
Body weight, kg	85.0 ± 19.5	86.6 ± 16.9	0.28
Minnesota Living With Heart Failure Quality of Life Questionnaire score	29.0 ± 20.4	26.4 ± 20.8	0.14
Kansas City Cardiomyopathy Quality of Life Questionnaire summary score	70.4 ± 19.9	74.6 ± 20.0	0.02
6-min hall walk, m	420 ± 122	374 ± 128	<0.0001
CRT-D implanted, %	79	86	0.02

Values are mean ± SD or percentage of patients in corresponding group.
CRT-D = cardiac resynchronization therapy-defibrillator.

first HF-related hospitalization between CRT-OFF and -ON in the IHD group was statistically significant (p = 0.03), although in a proportional hazards model with HF hospitalization as independent variable, randomization was significant (p = 0.03), but etiology (p = 0.12) was not. There were 4 deaths in non-IHD patients (CRT-OFF, 2.1%; CRT-ON, 1.1%; p = 0.61) and 8 deaths in IHD patients (CRT-OFF, 3.0%; CRT-ON, 1.0%; p = 0.45).

The results of models for independent predictors of both clinical composite response and change in LVESVi are shown in Table 3. History of LBBB was a significant predictor of response to both end points as was randomization (to CRT) and baseline QRS duration (long rather than short). Age was an independent predictor only for clinical response, and etiology was an independent predictor only for LVESVi. Even when age was removed from the model, etiology still was not a predictor of clinical composite response (p = 0.52). Interaction of randomization and etiology with the other significant predictors was examined by individually adding these terms into the models. No interaction terms were significant when added into the clinical composite response model; however, in the LVESVi model, all 4 predictors interacting with randomization were significant, as well as etiology with LVEF and QRS duration.

Discussion

The major finding of this substudy of REVERSE was that the extent of reverse remodeling was greater in non-IHD patients. Our findings concur with results from earlier CRT studies of NYHA functional class III/IV HF patients (5,6).

We previously reported a significant correlation between electrical and mechanical dyssynchrony and reverse remodeling in REVERSE (12). It is possible that the lesser degree

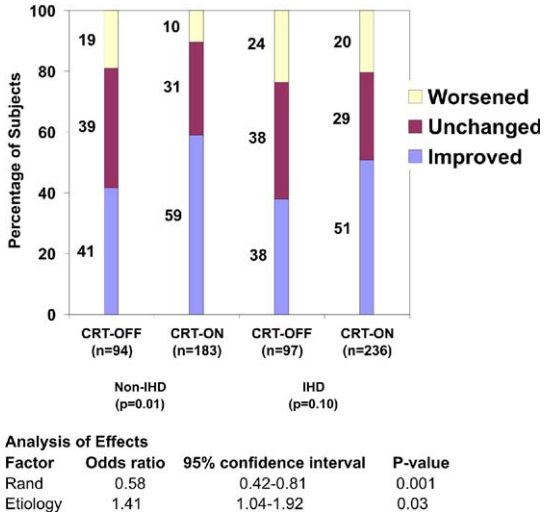

Figure 1 Distribution of the Primary End Point Regarding Worsened, Unchanged, or Improved

The p values compare cardiac resynchronization therapy (CRT)-OFF and -ON within non-ischemic heart disease (IHD) and IHD using the Fisher exact test. The analysis of effects is from a cumulative logistic regression with clinical composite response as the dependent variable in the model. Odds ratios are cumulative over improved, unchanged, and worsened. The interaction term of randomization*etiology was not significant (p = 0.44), so it is not included in the analysis of effects. Rand = randomization group (CRT-OFF or -ON).

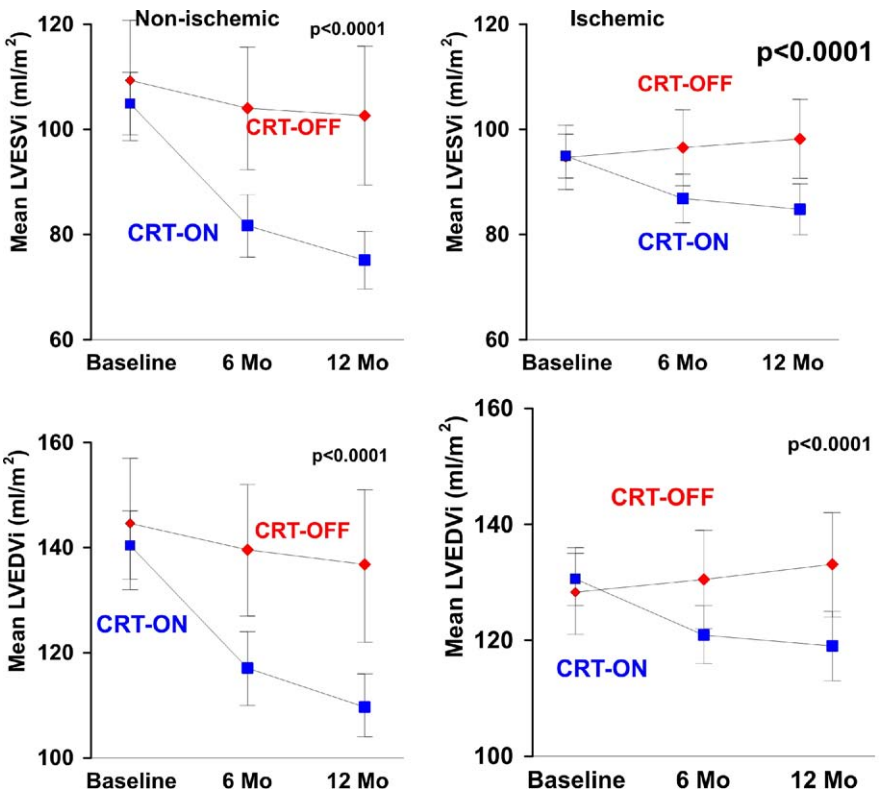

Figure 2 **Reverse Remodeling Left Ventricular End-Systolic and End-Diastolic Volume Index in Nonischemic and Ischemic Patients During CRT-ON and -OFF**

The p values compare change from baseline to 12 months between cardiac resynchronization therapy (CRT)-ON and -OFF (2-sample *t* test). **Error bars** represent 95% confidence intervals.

of dyssynchrony in IHD patients partly explained the less extent of reverse remodeling by CRT. Indeed, LBBB and QRS duration were multivariate predictors of reverse remodeling by CRT, but IHD etiology was not. It can also be speculated that CRT is less effective when contractility is impaired by extensive myocardial scar tissue, even in the presence of conduction delay. This could reflect the less "plasticity" of myocardial scar tissue to both dilate and shrink and confirms previous CRT study results in NYHA functional class III/IV patients (9–11). A further reason could be that IHD patients in REVERSE were older and had more comorbidities. When these factors were assessed in a logistic regression model, LBBB, longer baseline QRS, and randomization to CRT were the only independent predictors of response in the primary end point, but HF etiology was not, indicating that clinical benefits of CRT

Table 2 **12-Month Results by Randomization in the Non-IHD and IHD Groups and Their Interaction by Regression Model**

	Non-IHD			IHD			ANOVA p Values		
Parameter	CRT-OFF (n = 94)	CRT-ON (n = 183)	p Value*	CRT-OFF (n = 97)	CRT-ON (n = 236)	p Value*	Rand	Etiology	Interaction
LVESVi	−7.0 ± 25.5	−29.5 ± 30.6	<0.0001	3.1 ± 20.6	−9.5 ± 24.1	<0.0001	<0.0001	<0.0001	0.045
LVEDVi	−8.2 ± 29.4	−30.3 ± 32.3	<0.0001	4.1 ± 25.5	−10.6 ± 29.5	<0.0001	<0.0001	<0.0001	0.19
LVEF	1.4 ± 7.2	7.5 ± 9.3	<0.0001	0.3 ± 6.0	2.4 ± 8.5	0.03	<0.0001	<0.0001	0.008
IVMD	2.2 ± 32.2	−16.0 ± 42.1	0.0009	−2.1 ± 35.2	−10.4 ± 43.5	0.13	0.001	0.87	0.23
6-min hall walk	20 ± 108	20 ± 99	0.99	17 ± 103	6 ± 105	0.40	0.56	0.36	0.55
MN LWHF	−6.6 ± 14.3	−10.9 ± 17.5	0.04	−6.7 ± 17.4	−6.5 ± 16.6	0.92	0.18	0.16	0.14
KC QoL	9.1 ± 14.9	11.0 ± 18.2	0.43	8.0 ± 17.2	7.0 ± 17.3	0.67	0.79	0.12	0.40

*p value comparing CRT-ON and -OFF within the etiology subgroup. The final 3 columns are p values for randomization, etiology, and the interaction randomization*etiology terms in a regression model with the parameter as the dependent variable.

ANOVA = analysis of variance; CRT = cardiac resynchronization therapy; IHD = ischemic heart disease; IVMD = intraventricular mechanical delay; KC QoL = Kansas City Cardiomyopathy Quality of Life Questionnaire (higher score is better); LVESVi = left ventricular end-systolic volume index; MN LWHF = Minnesota Living With Heart Failure Quality of Life Questionnaire (lower score is better); Rand = randomization.

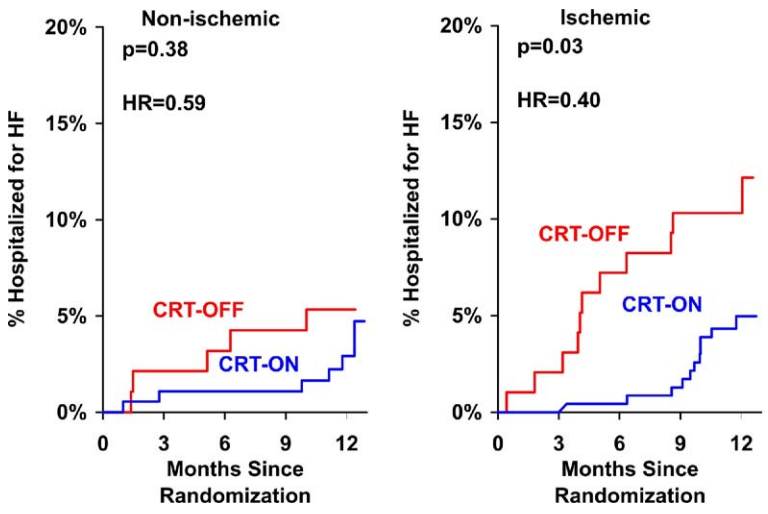

Figure 3 Time to First Heart Failure–Related Hospitalization in Nonischemic and Ischemic Patients During CRT-ON and -OFF, Respectively

CRT = cardiac resynchronization therapy; HF = heart failure; HR = hazard ratio.

occurred irrespective of age and etiology. These results agree with those of the CARE-HF (CArdiac REsynchronization in Heart Failure) study in which the clinical benefit was similar in non-IHD and IHD patients despite less reverse LV remodeling, more advanced age, and more comorbidities in IHD patients. As in REVERSE, etiology was not an independent predictor of response to CRT by multivariable analysis (10). Our study suggests that LBBB and baseline QRS duration are important determinants of response to CRT in mild HF beyond reverse remodeling.

The treatment goal in mild HF strives to keep patients as long as possible from worsening. REVERSE was the first randomized, controlled CRT study with this perspective but was not designed to study morbidity and mortality. MADIT-CRT (The Multicenter Automatic Defibrillator Implantation Trial–Cardiac Resynchronization Therapy) (13) found a significant reduction in HF events predominantly by reduction of HF hospitalization independent of etiology or age but restricted to patients with baseline QRS duration of at least 150 ms. The results from MADIT-CRT

Table 3 Assessment of Independent Predictors of Response

	Clinical Composite Response			LVESVi		
	Odds Ratio	95% CI	p Value	Regression Coefficient	95% CI	p Value
Randomization (CRT-ON)	0.56	0.40 to 0.79	0.0008	18.4	13.8 to 23.0	<0.0001
Age, yrs	0.98	0.97 to 1.00	0.03			
QRS duration, ms	1.01	1.00 to 1.02	0.05	−0.14	−0.24 to −0.03	0.01
History of LBBB	0.66	0.45 to 0.97	0.03	−6.7	−12.1 to −0.3	0.01
Etiology (nonischemic)				12.7	8.2 to 17.3	<0.0001
Sex			—			—
NYHA functional class II	0.31	0.21 to 0.48	<0.0001			
Systolic blood pressure, mm Hg			—			—
LVEF				0.99	0.66 to 1.33	<0.0001
LVESVi, ml/m^2	0.995	0.990 to 0.999	0.03			
Beta-blocker ≥50% target dose			—			—
Glomerular filtration rate, ml/min			—			—
Diabetes			—			—
History of hypertension			—			—
Coronary artery bypass graft			—			—
Previous PCI			—			—

The p values are for factor effect in a multivariable logistic regression model for clinical composite score at 12 months and a multivariable regression model for change in LVESVi from baseline to 12 months. For dichotomous variables, the state more likely to see improvement is indicated.

CI = confidence interval; LBBB = left bundle branch block; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association; other abbreviations as in Table 2.

are very concurrent with the REVERSE results and most likely over time will translate into a wider use of CRT in mildly symptomatic patients to prevent disease progression.

Study limitations. The multivariable models included 16 terms that were believed to be potentially predictive of results. Inclusion of this many terms may result in overfitting of the models.

Conclusions

This substudy of REVERSE shows that CRT reverses LV remodeling with a more extensive effect in non-IHD patients. Etiology was, however, not an independent predictor of clinical response. Longer observation periods and larger patient groups are needed to firmly determine the influence of etiology on CRT response.

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REFERENCES

1. Cazeau S, Leclercq C, Lavergne T, et al. Effects of multisite biventricular pacing in patients with heart failure and intraventricular conduction delay. N Engl J Med 2001;344:873–80.
2. Abraham WT, Fisher WG, Smith AL, et al., MIRACLE Study Group. Multicenter InSync Randomized Clinical Evaluation. Cardiac resynchronization in chronic heart failure. N Engl J Med 2002;346:1845–53.
3. Bristow MR, Saxon LA, Boehmer J, et al., Comparison of Medical Therapy, Pacing and Defibrillation in Heart Failure (COMPANION) Investigators. Cardiac-resynchronization therapy with or without an implantable defibrillator in advanced chronic heart failure. N Engl J Med 2004;350:2140–50.
4. Cleland JG, Daubert JC, Erdmann E, et al. The effect of cardiac resynchronization on morbidity and mortality in heart failure. N Engl J Med 2005;352:1539–49.
5. St John Sutton MG, Plappert T, Abraham WT, et al., Multicenter InSync Randomized Clinical Evaluation (MIRACLE) Study Group. Effect of cardiac resynchronization therapy on left ventricular size and function in chronic heart failure. Circulation 2003;107:1985–990.
6. Ghio S, Freemantle N, Scelsi L, et al. Long-term left ventricular reverse remodelling with cardiac resynchronization therapy: results from the CARE-HF trial. Eur J Heart Fail 2009;11:480–8.
7. Linde C, Abraham WT, Gold MR, St John Sutton M, Ghio S, Daubert C, REVERSE (REsynchronization reVErses Remodeling in Systolic left vEntricular dysfunction) Study Group. Randomized trial of cardiac resynchronization in mildly symptomatic heart failure patients and in asymptomatic patients with left ventricular dysfunction and previous heart failure symptoms. J Am Coll Cardiol 2008;52:1834–43.
8. Daubert JC, Gold MR, Abraham WTR, et al., the REVERSE Study Group. Prevention of disease progression by cardiac resynchronization therapy in patients with asymptomatic or mildly symptomatic left ventricular dysfunction. J Am Coll Cardiol 2009;54:1837–46.
9. Sutton MG, Plappert T, Hilpisch KE, Abraham WT, Hayes DL, Chinchoy E. Sustained reverse left ventricular structural remodelling with cardiac resynchronisation therapy at one year is a function of etiology. Quantitative Doppler-echocardiographic evidence from the Multicenter InSync Randomized Clinical Evaluation (MIRACLE). Circulation 2006;113:266–72.
10. Wikstrom G, Blomström-Lundqvist C, Andren B, et al., CARE-HF study investigators. The effects of aetiology on outcome in patients treated with cardiac resynchronisation therapy in the CARE-HF trial. Eur Heart J 2009;30:782–8.
11. DiBiase L, Auricchio A, Sorgente A, et al. The magnitude of reverse remodelling irrespective of aetiology predicts outcome of heart failure patients treated with cardiac resynchronisation therapy. Eur Heart J 2008;29:2497–505.
12. St John Sutton M, Ghio S, Plappert T, et al. Cardiac resynchronization therapy induces major structural and functional reverse remodeling in patients with New York Heart Association Class I/II heart failure. Circulation 2009;120;1858–65.
13. Moss AJ, Jackson Hall W, Cannom DS, et al., the MADIT-CRT Trial Investigators. Cardiac-resynchronization therapy for the prevention of heart-failure events. N Engl J Med 2009;361:1329–38.

Key Words: cardiac resynchronization therapy ■ heart failure ■ randomized, controlled trial ■ biventricular pacing ■ reverse remodeling.

APPENDIX

For a list of the 73 centers that contributed to this study, please see the online version of this article.