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Long-Term Prognosis After Cardiac Resynchronization Therapy Is Related to the Extent of Left Ventricular Reverse Remodeling at Midterm Follow-Up

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Objectives The aim of the current study was to evaluate the relation between the extent of left ventricular (LV) reverse remodeling and clinical/echocardiographic improvement after 6 months of cardiac resynchronization therapy (CRT) as well as long-term outcome.

Background Despite the current selection criteria, individual response to CRT varies significantly. Furthermore, it has been suggested that reduction in left ventricular end-systolic volume (LVESV) after CRT is related to outcome.

Methods A total of 302 CRT candidates were included. Clinical status and echocardiographic evaluation were performed before implantation and after 6 months of CRT. Long-term follow-up included all-cause mortality and hospitalizations for heart failure.

Results Based on different extents of LV reverse remodeling, 22% of patients were classified as super-responders (decrease in LVESV ≥30%), 35% as responders (decrease in LVESV 15% to 29%), 21% as nonresponders (decrease in LVESV 0% to 14%), and 22% negative responders (increase in LVESV). More extensive LV reverse remodeling resulted in more clinical improvement, with a larger increase in LV function and more reduction in mitral regurgitation. In addition, more LV reverse remodeling resulted in less heart failure hospitalizations and lower mortality during long-term follow-up (22 ± 11 months); 1- and 2-year hospitalization-free survival rates were 90% and 70% in the negative responder group compared with 98% and 96% in the super-responder group (log-rank p value <0.001).

Conclusions The extent of LV reverse remodeling at midterm follow-up is predictive for long-term outcome in CRT patients. (J Am Coll Cardiol 2009;53:483–90) © 2009 by the American College of Cardiology Foundation

Current selection criteria for cardiac resynchronization therapy (CRT) include severe heart failure (New York Heart Association [NYHA] functional class III or IV), depressed systolic function (left ventricular ejection fraction [LVEF] <35%), and wide QRS complex (>120 ms) (1). CRT improves not only clinical status (NYHA functional class, quality of life, and exercise capacity) but also left ventricular (LV) function, with reverse LV remodeling, and decreases hospitalization and mortality rates (2–7). Despite the impressive results of CRT in the large clinical trials, response to CRT varies significantly among individuals; some patients exhibit a significant improvement in clinical status with extensive LV reverse remodeling and almost normalization of LV function, whereas other patients show deterioration of both clinical and functional parameters despite CRT. Furthermore, preliminary results demonstrated a relation between the magnitude of LV reverse remodeling and long-term survival benefit after CRT (8).

Therefore, the aims of the current study were: 1) to evaluate the relation between the extent of LV reverse remodeling and the improvement in clinical and echocardiographic parameters after 6 months of CRT; and 2) to evaluate the relation between the extent of LV reverse remod-

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Abbreviations and Acronyms

CRT = cardiac resynchronization therapy

LBBB = left bundle branch block

LV = left ventricle/ventricular

LVEDV = left ventricular end-diastolic volume

LVEF = left ventricular ejection fraction

LVESV = left ventricular end-systolic volume

NYHA = New York Heart Association

eling and long-term outcome. To permit subgroup analysis, the patients were arbitrarily divided into 4 groups, based on the extent of LV reverse remodeling after 6 months of CRT.

Methods

Patients and study protocol. The study population consisted of 302 consecutive heart failure patients who were scheduled for CRT device implantation. The selection criteria for CRT included advanced heart failure (NYHA functional class III or IV), LVEF <35%, and wide QRS complex (1). Patients with a recent myocardial infarction (<3 months) or decompensated heart failure were excluded. Etiology was considered ischemic in the presence of significant coronary artery disease (≥50% stenosis in 1 or more of the major epicardial coronary arteries) and/or a history of myocardial infarction or prior revascularization.

The study protocol included baseline 2-dimensional echocardiography to measure LVEF and LV volumes as well as tissue Doppler imaging to assess LV dyssynchrony. Clinical evaluation included assessment of NYHA functional class, quality of life (using the Minnesota Living with Heart Failure questionnaire) (9), and evaluation of exercise capacity using the 6-min walking test (10). At 6 months follow-up, clinical status, LV volumes, and LVEF were reassessed. During long-term follow-up after implantation, survival and cardiac transplantation as well as hospitalization for decompensated heart failure were reported.

Definition of response. Patients who died, were hospitalized, and/or functionally deteriorated before the 6-month follow-up were discarded from further analysis. The remaining group consisted of clinically improved and unchanged patients at 6 months, and was divided into subgroups based on the reduction in left ventricular end-systolic volume (LVESV) after 6 months of CRT. The specific subgroups were negative responders: patients with an increase in LVESV; nonresponders: patients with a decrease in LVESV ranging from 0% to 14%; responders: patients with a decrease in LVESV ranging from 15% to 29%; and super-responders: patients with a decrease in LVESV ≥30%.

Echocardiographic evaluation. Echocardiographic images were obtained with a 3.5-MHz transducer in the left lateral decubitus position using a commercially available system (Vivid Seven, General Electric-Vingmed, Milwaukee, Wisconsin). Standard 2-dimensional and color Doppler data, triggered to the QRS complex, were saved in cine-loop format for offline analysis (EchoPAC version 6.0.1, GE Medical Systems, Horten, Norway). Left ventricular end-diastolic volume (LVEDV) and LVESV were derived, and LVEF was calculated from the conventional apical 2- and 4-chamber images, using the biplane Simpson's technique (11).

The severity of mitral regurgitation was graded semi-quantitatively from color-flow Doppler images using the apical 4-chamber views. Mitral regurgitation was graded on a 4-point scale: none, mild (jet area/left atrial area <20%), moderate (jet area/left atrial area 20% to 45%), and severe (jet area/left atrial area >45%) (12).

For tissue Doppler imaging, color-coded images of the 4- and 2-chamber apical views of 3 consecutive heart beats were stored for offline analysis. Data were analyzed using commercially available software (EchoPAC version 6.0.1, GE Medical Systems). To determine LV dyssynchrony, the sample volume was placed in the LV basal parts of the anterior, inferior, basal, and lateral wall, and per region, the time interval between the onset of QRS complex and the peak systolic velocity was derived. LV dyssynchrony was defined as the maximal delay between peak systolic velocities among the 4 LV walls. Based on previous data, a cutoff value of 65 ms was used as a marker of LV dyssynchrony (13).

Long-term follow-up. Chart review, device interrogation, and telephone contact were assessed during long-term follow-up after device implantation. Events were defined as death (due to heart failure, other cardiac cause, or noncardiac cause) or cardiac transplantation, and hospitalization for decompensated heart failure. Since the subgroups were formed after 6 months of CRT, the composite of death, cardiac transplantation, and hospitalizations for heart failure occurring after the 6-month follow-up evaluation was the primary end point of the study.

Device implantation. A coronary sinus venogram was obtained using balloon catheter, followed by the insertion of the LV pacing lead. An 8-F guiding catheter was used to position the LV lead (Easytrak 4512-80, Guidant Corporation, St. Paul, Minnesota; or Attain-SD 4189, Medtronic Inc., Minneapolis, Minnesota) in the coronary sinus. The preferred position was a lateral or posterolateral vein (14). The right atrial and ventricular leads were positioned conventionally. All leads were connected to a dual-chamber biventricular implantable cardioverter-defibrillator (Contak Renewal II or H195, Guidant Corporation; or Insync III or Insync Sentry, Medtronic Inc.).

Statistical analysis. Continuous variables are expressed as mean ± SD. Categorical data are summarized as frequencies and percentages. Differences in baseline characteristics between the 4 different subgroups were analyzed using 1-way analysis of variance (continuous variables) and chi-square (dichotomous variables) as appropriate. The paired Student t test was used to compare continuous data within the subgroups during follow-up. The McNemar test was used to compare NYHA functional class and severity of mitral regurgitation during follow-up within the different subgroups. Event and survival curves were determined according to the Kaplan-Meier method, with comparisons of cumulative event rates by the log-rank test. For all tests, a p value <0.05 was considered statistically significant.

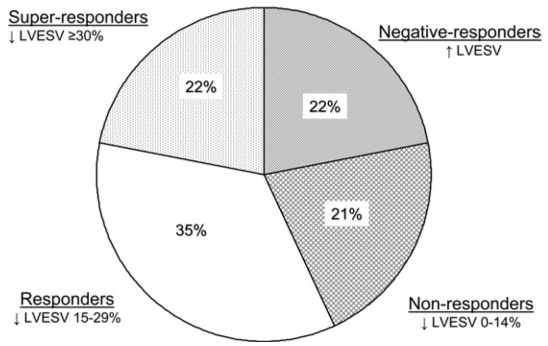

Figure 1 **Extent of LV Reverse Remodeling After 6 Months of CRT**

Distribution of patients according to extent of left ventricular (LV) reverse remodeling after 6 months of cardiac resynchronization therapy (CRT). LVESV = left ventricular end-systolic volume.

Results

Patients. The study population consisted of 302 consecutive patients (253 men, mean age 66 ± 10 years). All patients had advanced heart failure symptoms with most patients (94%) in NYHA functional class III. Underlying etiology of cardiomyopathy was ischemic in 58% of patients and idiopathic in 42%. Patients had severely depressed LV function (mean LVEF 25 ± 8%) with extensive LV dilation (mean LVEDV 227 ± 78 ml and mean LVESV 172 ± 68 ml). Mean extent of LV dyssynchrony was 78 ± 46 ms. Medication included diuretics in 90%, angiotensin-converting enzyme inhibitors in 90%, beta-blockers in 74%, and spironolactone in 53% of patients. Device and lead implantation was successful in all patients without major procedure-related complications.

Follow-up after CRT. Sixteen patients were removed from further analysis at 6 months follow-up; 10 died, 2 deteriorated in functional class, and 4 were hospitalized for decompensated heart failure before the 6-month follow-up. Of the remaining 286 patients, 164 patients (57%) showed an improvement of 1 NYHA functional class and 34 patients (12%) showed an improvement of 2 NYHA functional classes, whereas 88 patients (31%) remained unchanged ($p < 0.001$ vs. baseline) at 6 months follow-up. In addition, both quality of life and exercise capacity improved at 6 months (respectively from 36 ± 19 to 25 ± 20, and walking distance from 321 ± 107 m to 395 ± 111 m, both $p < 0.001$). Furthermore, LVEF improved modestly (from 25 ± 8% to 32 ± 10%, $p < 0.001$), with a reduction in LV volumes; LVEDV decreased from 226 ± 78 ml to 200 ± 77 ml and LVESV from 170 ± 67 ml to 139 ± 67 ml (both $p < 0.001$) at 6 months. In addition, 107 patients (37%) showed a reduction in mitral regurgitation of at least 1 grade, 152 (53%) remained unchanged, and 27 (10%) showed worsening of mitral regurgitation after 6 months of CRT ($p < 0.001$).

During follow-up (22 ± 11 months, range 6 to 53 months), 37 patients died (13%). Cause of death was decompensated heart failure in 26, other cardiac cause in 7, and noncardiac cause in 4 patients. One patient underwent heart transplantation. In addition, hospitalizations for decompensated heart failure were noted in 21 patients (7%).

Subgroup analysis according to extent of LV reverse remodeling after 6 months of CRT. The extent of LV reverse remodeling after 6 months varied among patients, ranging from an increase in LVESV of 38% and a decrease in LVESV of 78%, with a mean reduction of 18 ± 22%. Sixty-three patients (22%) showed deterioration in LVESV after 6 months of CRT and were classified as negative responders (for definitions see Methods section). Furthermore, 60 patients (21%) showed LV reverse remodeling of 0% to 14% and were classified as nonresponders. LV reverse remodeling of 15% to 29% was noted in 100, and these patients were classified as responders (35%). In 63 patients (22%), extensive LV reverse remodeling ≥30% was reported,

Table 1 **Baseline Characteristics of the Different Subgroups (Defined According to the Extent of LV Reverse Remodeling After 6 Months of CRT)**

Variable	NEG (n = 63)	NON (n = 60)	RESP (n = 100)	SUPER (n = 63)	p Value
Age (yrs)	65 ± 10	65 ± 12	66 ± 11	67 ± 9	0.8
Sex (M/F)	54/9	51/9	85/15	48/15	0.4
NYHA functional class (III/IV)	55/8	57/3	96/4	63/0	0.04
Ischemic etiology	47 (74%)	41 (68%)	51 (51%)	25 (40%)	<0.001
QRS duration (ms)	142 ± 33	156 ± 30	163 ± 28	161 ± 33	<0.001
LBBB	32 (51%)	46 (77%)	78 (78%)	49 (78%)	0.001
SR/AF/paced	50/9/4	47/7/6	75/8/17	49/5/9	0.4
LVEF (%)	26 ± 8	24 ± 8	26 ± 8	25 ± 8	0.2
LVEDV (ml)	215 ± 75	233 ± 78	224 ± 73	231 ± 78	0.6
LVESV (ml)	160 ± 61	181 ± 78	168 ± 63	175 ± 69	0.3
MR moderate-to-severe	12 (19%)	12 (20%)	11 (11%)	9 (14%)	<0.001
LV dyssynchrony (ms)	50 ± 36	58 ± 35	93 ± 40	101 ± 45	<0.001

AF = atrial fibrillation; CRT = cardiac resynchronization therapy; LBBB = left bundle branch block; LV = left ventricular; LVEDV = left ventricular end-diastolic volume; LVEF = left ventricular ejection fraction; LVESV = left ventricular end-systolic volume; MR = mitral regurgitation; NEG = negative responders; NON = nonresponders; NYHA = New York Heart Association; RESP = responders; SR = sinus rhythm; SUPER = super-responders.

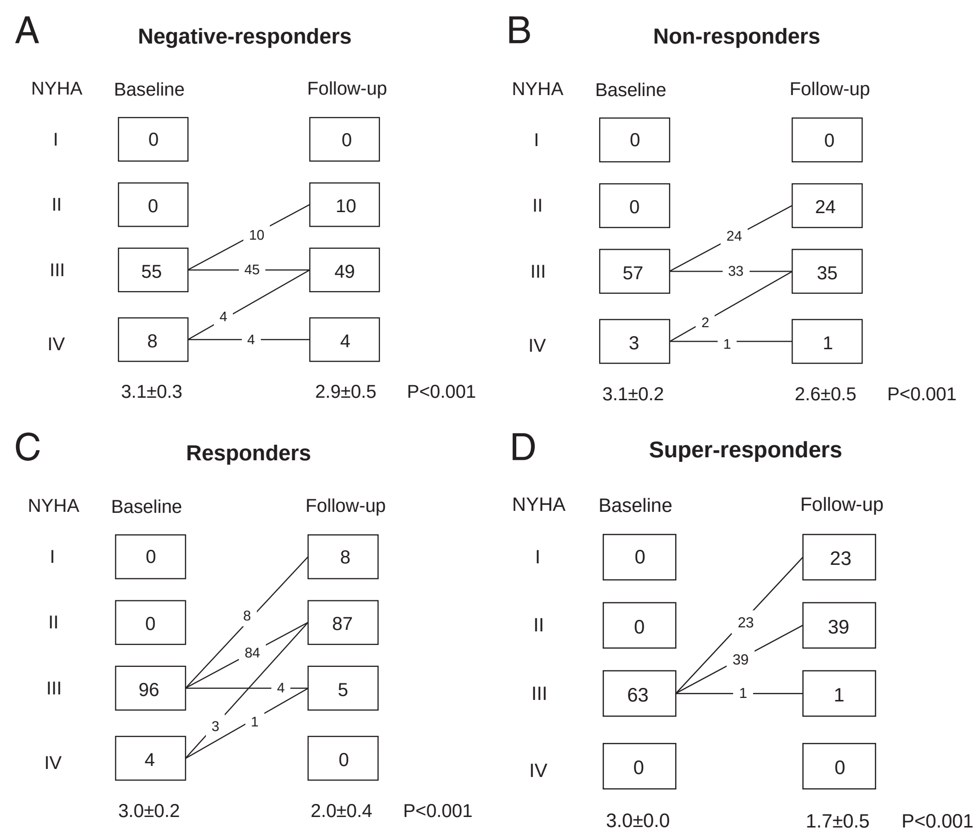

Figure 2 **Improvement in NYHA Functional Class After 6 Months of CRT**

Changes in New York Heart Association (NYHA) functional class after 6 months of cardiac resynchronization therapy (CRT) according to the different response groups.

and these were classified as super-responders (Fig. 1). Baseline characteristics between the 4 subgroups were comparable, except for less severe heart failure symptoms (lower NYHA functional class), more often nonischemic cardiomyopathy, longer QRS duration, more often left bundle branch block (LBBB) configuration, and more extensive LV dyssynchrony in super-responders (Table 1).

Response to CRT versus extent of LV reverse remodeling. Mean NYHA functional class improved significantly in all groups at 6 months after CRT; in negative responders from 3.1 ± 0.3 to 2.9 ± 0.5, in nonresponders from 3.1 ± 0.2 to 2.6 ± 0.5, in responders from 3.0 ± 0.2 to 2.0 ± 0.4, and in super-responders from 3.0 ± 0.0 to 1.7 ± 0.5 (for all, $p < 0.001$). Individual changes within each subgroup are presented in Figure 2.

As demonstrated in Figure 3 (panel A), super-responders showed greater improvement in quality-of-life score (Δ17 ± 13) as compared with the other subgroups (Δ8 ± 15, Δ13 ± 18, and Δ14 ± 16, respectively, for negative responders, nonresponders, and responders, $p = 0.024$). In addition, a trend was noted for larger improvement in walking distance (Fig. 3B) in patients with more extensive LV reverse remodeling.

Regarding echocardiographic parameters, negative responders showed no improvement in LVEF after 6 months of CRT (from 26 ± 8% to 26 ± 8%, p = NS), whereas the other 3 response groups showed significant improvement in LVEF; nonresponders showed a mean improvement of 5 ± 5% in LVEF, responders of 8 ± 7%, and the greatest improvement was observed in super-responders (15 ± 9%, $p < 0.001$) (Fig. 3C). Also, super-responders showed greatest reduction in LVEDV after CRT (Fig. 3D). Reduction in mitral regurgitation was more pronounced in patients with more LV reverse remodeling; 13%, 22%, 48%, and 62% of negative responders, nonresponders, responders, and super-responders, respectively, improved at least 1 grade in mitral regurgitation ($p < 0.001$).

Long-term follow-up after 6 months of CRT according to extent of LV reverse remodeling. Mortality rates decreased in parallel to the extent of LV reverse remodeling, with only 1 death in the super-responder group ($p < 0.001$) (Table 2). One-year survival rates were 92% in the negative-responder group, 95% in the nonresponder group, 97% in the responder group, and 100% in the super-responder group, respectively (log-rank $p < 0.001$) (Fig. 4A). The same trend was noted for the number of patients hospitalized for decompensated heart failure (Fig. 4B).

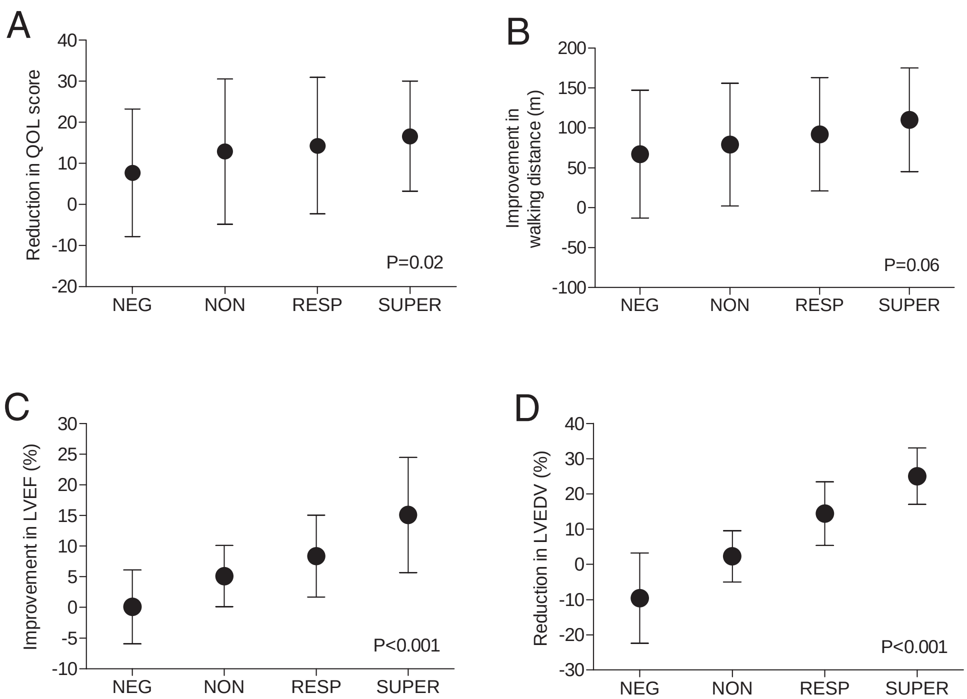

Figure 3 **Clinical and Echocardiographic Improvement After 6 Months of CRT**

Improvement in clinical **(A and B)** and echocardiographic **(C and D)** parameters at 6 months follow-up in the different response groups; negative responders (NEG) were defined by an increase in left ventricular end-systolic volume, nonresponders (NON) an intermediate decrease (0% to 14%), responders (RESP) a moderate decrease (15% to 29%), and super-responders (SUPER) a high decrease (≥30%) in left ventricular end-systolic volume after 6 months of follow-up. CRT = cardiac resynchronization therapy.

In addition, 1- and 2-year hospitalization-free survival rates were, respectively, 90% and 70% in the negative-responder group, 93% and 84% in the nonresponder group, 97% and 90% in the responder group, and 98% and 96% in the super-responder group (log-rank $p < 0.001$) (Fig. 4C). Separate comparisons revealed significant differences in hospitalization-free survival between super-responders, negative responders ($p < 0.001$ vs. super-responders), and nonresponders ($p < 0.001$ vs. super-responders), and a trend for better outcome when compared with responders to CRT ($p = 0.06$ vs. responders).

Discussion

The findings in the current study can be summarized as follows: 1) the extent of reverse LV remodeling varies significantly among patients undergoing CRT, and 22% can be considered super-responders; 2) more extensive LV reverse remodeling was related to greater clinical and functional improvement after 6 months of CRT; and 3) more LV reverse remodeling resulted in better survival and less hospitalization for decompensated heart failure after 6 months of CRT.

Differences in magnitude of response to CRT—previous studies. At present, only 1 study reported on "super-response" after CRT (15,16). Blanc et al. (15) investigated 29 patients with nonischemic dilated cardiomyopathy, LBBB, and mean LVEF of 21%. After 12 months of CRT, 5 patients (17%) exhibited normalization in LVEF (>50%) associated with clinical improvement to NYHA functional class I to II; these patients were defined as "super-responders." A subsequent study in 84 CRT candidates (with ischemic and nonischemic cardiomyopathy) reported

Table 2 **Events During Long-Term Follow-Up According to the Extent of LV Reverse Remodeling After CRT**

Variable	NEG (n = 63)	NON (n = 60)	RESP (n = 100)	SUPER (n = 63)	p Value
Follow-up (months)	21 ± 10	21 ± 10	22 ± 12	25 ± 10	0.1
Death	18 (29%)	10 (17%)	8 (8%)	1 (2%)	<0.001
Hospitalizations for HF	11 (17%)	3 (5%)	6 (6%)	1 (2%)	0.05
Death, HTX, and hospitalizations for HF	23 (37%)	13 (22%)	12 (12%)	2 (3%)	<0.001

HF = heart failure; HTX = heart transplantation; other abbreviations as in Table 1.

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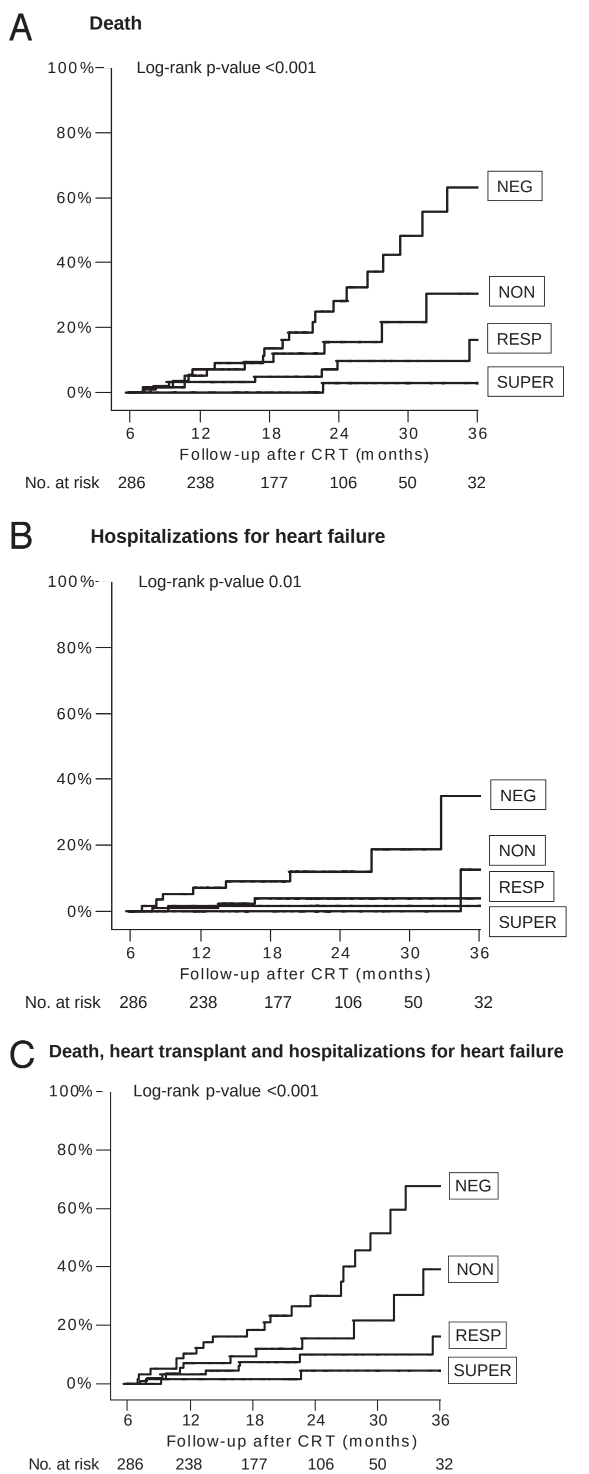

Figure 4 **Long-Term Outcome After CRT According to the Extent in LV Reverse Remodeling**

Event curves for all-cause mortality **(A)**, hospitalizations for heart failure **(B)**, and primary combined end point of death and hospitalizations for heart failure **(C)** for the different CRT response groups. INTER = intermediate responder; LV = left ventricular; other abbreviations as in Figure 3.

an incidence of super-responders of 13% (16). Super-responders showed an increase in LVEF from 25 ± 8% to 60 ± 6% (p = 0.001), whereas the remaining patients showed only a modest improvement in LVEF (from 21 ± 8% to 25 ± 10%, p = 0.004).

However, data on the magnitude of LVESV changes after CRT are lacking. Reverse remodeling may be more important than the increase in LVEF, since reduction in LVESV appeared to be the best predictor for long-term outcome after CRT (8).

Also of interest are the baseline characteristics of super-responders. In the present study, super-responders more frequently had nonischemic etiology of heart failure, longer QRS duration, more often LBBB configuration, less severe mitral regurgitation, and more extensive LV dyssynchrony (Table 2). Similarly, Castellant et al. (16) suggested that super-response only occurred after CRT in nonischemic patients with LBBB. The study by Blanc et al. (15) reported no differences in baseline characteristics between the super-responders and the remaining patients; however, this particular study included only nonischemic patients with LBBB. In addition, various studies suggested a relationship between LV reverse remodeling after CRT and etiology (17–19). These differences in baseline characteristics help to validate the current patient selection criteria that include a wider QRS complex, particularly with LBBB configuration. Furthermore, patients with more extensive LV damage from ischemic heart disease tend to respond less than patients with nonischemic cardiomyopathy. Additionally, from several studies it has become clear that LV dyssynchrony is important for response to CRT; in the current study, patients with extensive LV dyssynchrony had a high likelihood of response, whereas patients without LV dyssynchrony did not respond to CRT (13,20).

Extent of LV reverse remodeling in CRT—impact on prognosis. Besides clinical end points such as NYHA functional class, quality-of-life score, and 6-min walking distance, echocardiographic end points have been used in heart failure trials (21). Importantly, reversal of LV remodeling in heart failure patients by either pharmacological or interventional therapies is proposed as a surrogate for improved outcome (22).

For instance, in the SOLVD (Studies of Left Ventricular Dysfunction) trial, patients who were randomized to enalapril showed a decrease in LVESV after 1-year follow-up (from 106 ± 42 ml/m^2 to 93 ± 37 ml/m^2, p = 0.01) whereas patients treated with placebo showed an increase in LVESV at 1-year follow-up (from 103 ± 24 ml/m^2 to 116 ± 24 ml/m^2, p = 0.08) (23,24). Since enalapril usage was associated with a 16% reduction in mortality during 33 months of follow-up, it is reasonable to conclude that the LV reverse remodeling effect is associated with favorable outcome. Similar findings on the remodeling process have been reported after the use of carvedilol in patients with chronic LV dysfunction late after myocardial infarction (25,26) as well as metoprolol in patients with mild-to-moderate heart failure and chronic LV dysfunction (27).

These data from pharmacological heart failure trials emphasize the importance of LV reverse remodeling and, consequently, long-term prognosis. Currently, only 1 study related the extent of reverse remodeling after CRT to outcome: Yu et al. (8) evaluated 141 patients and related the extent of reduction in LVESV to long-term clinical outcome (mean follow-up 695 ± 491 days). Receiver-operating characteristic curve analysis showed that a reduction of >10% in LVESV had a sensitivity and specificity of 70% in predicting all-cause mortality. In addition, the change in LVESV was the best predictor for long-term outcome, whereas clinical parameters showed no predictive value.

In the present study, 286 patients were categorized according to reduction in LVESV after 6 months of CRT; 22% were classified as super-responders (decrease in LVESV ≥30%), 35% as responders (decrease in LVESV 15% to 29%), 21% as nonresponders (decrease in LVESV 0% to 14%), and 22% negative responders (increase in LVESV). Expanding the results of Yu et al. (8), an inverse relation between the extent of LV reverse remodeling and outcome was noted. negative responders had a high event rate (37%) for combined death and heart failure hospitalizations, as compared with 22% in nonresponders, 12% in responders, and only 3% in super-responders. Importantly, super-responders exhibited a superior 1- and 2-year hospitalization-free survival of 98% and 96%, respectively.

Conclusions

The extent of LV reverse remodeling after CRT varies significantly among individuals, with 22% considered super-responders to CRT. Importantly, the extent of reverse remodeling after 6 months is related to clinical improvement and survival during long-term follow-up.

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