Impact of Ejection Fraction on the Clinical Response to Cardiac Resynchronization Therapy in Mild Heart Failure

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Background—Current guidelines recommend cardiac resynchronization therapy (CRT) in mild heart failure (HF) patients with QRS prolongation and ejection fraction (EF) ≤30%. To assess the effect of CRT in less severe systolic dysfunction, outcomes in the RESynchronization rEVerses Remodeling in Systolic left vEntricular dysfunction (REVERSE) study were evaluated in which patients with left ventricular (LV) ejection fraction (LVEF) >30% were included.

Methods and Results—The results of patients with baseline EF >30% (n=177) and those with EF ≤30% (n=431), as determined by a blinded core laboratory, were compared. In the LVEF >30% subgroup, there was a trend for improvement in the clinical composite response with CRT ON versus CRT OFF (P=0.06) and significant reductions in LV end systolic volume index (−6.7±21.1 versus 2.1±17.6 mL/m²; P=0.01) and LV mass (−20.6±50.5 versus 5.0±42.4 g; P=0.04) after 12 months. Time to death or first HF hospitalization was significantly prolonged with CRT (hazard ratio, 0.26; P=0.012).

In the LVEF <30% subgroup, significant improvements in clinical composite response (P=0.02), reverse remodeling parameters, and time to death or first HF hospitalization (hazard ratio, 0.58; P=0.047) were observed. After adjusting for important covariates, the CRT ON assignment remained independently associated with improved time to death or first HF hospitalization (hazard ratio, 0.54; P=0.035), whereas there was no significant interaction with LVEF.

Conclusions—Among subjects with mild HF, QRS prolongation, and LVEF >30%, CRT produced reverse remodeling and similar clinical benefit compared with subjects with more severe LV systolic dysfunction.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT00271154.

(Circ Heart Fail. 2013;6:1180-1189.)

Key Words: cardiac resynchronization therapy ■ heart failure ■ mortality

Cardiac resynchronization therapy (CRT) is well established for patients with severe left ventricular (LV) systolic dysfunction and ventricular conduction delay in advanced heart failure (HF).1-3 More recently, the benefit of CRT was expanded to patients with mild HF; with improved functional status and reductions in hospitalization and mortality observed.8-12 The most consistent response was noted in subgroups with left bundle-branch block (LBBB) and more prolonged baseline QRS duration.11,14 However, the effect of LV ejection fraction (LVEF) on CRT outcomes is less clear. Based on these results, current guidelines recommend CRT as a Class I indication for subjects with mild HF, LBBB, and LVEF ≤35%.15,16 or 30%17 with LVEF criteria based on the inclusion criteria in the studies.15-17

Clinical Perspective on p 1189

Of the 3 multicenter, randomized trials of CRT in mild HF, only REsynchronization reVerses Remodeling in Systolic left vEntricular dysfunction (REVERSE) included subjects with EF >30%. To determine whether CRT is effective in less severe LV systolic dysfunction, the impact of EF on outcomes in REVERSE was studied. Specifically, we hypothesized that the benefit from CRT would be similar in patients with moderate LV dysfunction (LVEF >30%) as in those with severe LV dysfunction (LVEF ≤30%).

Methods

Study Design and Data Collection

REVERSE was a prospective, randomized, double-blind, parallel-controlled study designed to determine whether CRT limited the
progression of HF compared with optimal medical therapy alone. The study included American College of Cardiology/American Heart Association (ACC/AHA) stage C, New York Heart Association (NYHA) Class I or II HF patients with QRS ≥120 ms and LVEF ≤40% on optimal medical therapy. Patients were implanted with a CRT device with (CRT-D) or without (CRT-P) defibrillator and randomized 2:1 to CRT ON versus CRT OFF. Devices were then programmed as randomized through 12 months in North America and through 24 months in Europe. All centers participating in the study were approved by an institutional review committee, and all participating subjects gave informed consent. The rationale of the REVERSE study has been published previously. For the present analysis, patients were grouped by LVEF >30% or ≤30% by core laboratory evaluation.

Outcomes
The primary end point of the REVERSE main study was the percentage of patients at 12 months with a worsened HF clinical composite score (CCS), which scores patients as improved, unchanged, or worsened. The prospectively powered secondary end point was LV end systolic volume index (LVESVi). Other secondary end points were hospitalization for worsening HF and mortality and additional measures of reverse remodeling. Quality of life was measured by the Minnesota Living with Heart Failure Questionnaire (MLHFQ) and the Kansas City Cardiomyopathy Questionnaire (KCCQ). During the blinded period, patients were evaluated every 6 months by blinded staff collecting NYHA class, 6-minute hall walk, quality of life, echocardiographic data, HF-related hospitalizations, and mortality data. HF hospitalizations were adjudicated for HF relatedness by the end point adjudication committee blinded to CRT assignment. This committee also adjudicated causes of death. Likewise, echocardiograms were assessed by 2 core laboratories blinded to CRT assignment, 1 in the United States and 1 in Europe.

Statistical Methods
Statistical analyses followed the intent-to-treat principle. All probability values reported are 2-sided and do not adjust for multiple comparisons. The primary end point was tested with a Fisher exact test that compared the full distribution of CCS at 12 months by randomization group. The primary end point was additionally tested via an exact trend test. An interaction between randomization group and LVEF subgroup was assessed for its effect on the CCS with a proportional odds model. The same testing procedures were used to assess NYHA class at 12 months. Kaplan–Meier curves were estimated for the combined end point of time to death or first HF hospitalization. Time 0 was the date of randomization. Because the length of randomization period in the study differed by geography (12 months in North America and 24 months in Europe), patients without an observed event were censored at the end of their randomization period. Kaplan–Meier curves are truncated when <20 patients are at risk for a time point. A log-rank test compared survival curves between randomization groups. To assess CRT effects on time to death or HF hospitalization modified by LVEF subgroup, a Cox model was fit with main effects for CRT and LVEF subgroup and an interaction effect between them. The Cox model was then adjusted for other potentially confounding variables such as age, intrinsic QRS duration, LVESVi, ischemic heart disease, and blood pressure at baseline. There were 43 patients with missing values for confounding variables.
Factors that were discarded from the multivariable analysis. When comparing clinical and functional baseline characteristics between LVEF subgroups, probability values were calculated using a t test assuming unequal variances for continuous variables and Fisher exact test for categorical variables. Within LVEF subgroup, changes between baseline and 12 months in LV end diastolic volume index (LVEDVi), LVESVi, LVEF, LV end diastolic diameter (LVEDD); LV mass, MLHFQ, KCCQ, and the 6-minute hall walk were compared between randomization groups with a 2-sample t test assuming unequal variances. Interaction effects between randomization group and LVEF subgroup on clinical and echo parameter changes were assessed in an ANOVA model. Finally, regression toward the mean is a concern in subgroup analysis where patients are divided into high and low groups. To examine this potential effect, ANCOVA models were fit for each echo parameter within LVEF subgroups, where the outcome was the difference over 12 months, the independent variable was CRT, and the covariate was the baseline value of the echo parameter. Statistical analyses were conducted in R (http://www.r-project.org) and SAS 9.2 (SAS Institute, Cary, NC).

Results

Patient Characteristics

The baseline characteristics of the entire cohort and the main results were reported previously. LVEF was available in 608 of the 610 randomized patients, in 565 subjects by core laboratory measurement, and in 43 by implanting center measurement. Of this cohort, 431 patients (76.3%) had LVEF ≤30% and the remaining 177 patients (23.7%) had LVEF >30%, including 12.2% (n=74) with LVEF >35%, reflecting the LVEF inclusion criterion of REVERSE. The mean center LVEF (26.7±7.0) did not differ from core laboratory LVEF (27.0±6.6). The distribution of LVEF measurements at baseline is shown in Figure 1. Consistent with clinical practice, the centers tended to report LVEF values in multiple of 5 (61.2%) or 10 (33.4%). Baseline characteristics grouped by LVEF are shown in Tables 1 and 2. Patients with LVEF >30% were significantly older and more often had ischemic underlying pathology, worse renal function, and higher systolic blood pressure. Nonetheless, they were more often in NYHA Class I and had smaller LV dimensions and volumes and lower LV mass than those with LVEF ≤30%. Moreover, quality of life both by MLHFQ score and KCCQ and 6-minute hall walk tended to be better in the LVEF >30% group. Although QRS duration was significantly shorter in the LVEF >30% group than in the LVEF <30% group (147±20.4 versus 155.7±22.2 ms; P<0.0001), the presence of LBBB was comparable between subgroups (58% versus 62%, respectively; P=0.31). Both subgroups were well treated medically with most patients receiving both β-blockers and angiotensin-converting enzyme inhibitors or angiotensin receptor blocker agents at baseline.

Echocardiographic Measurements

The echocardiographic results are summarized in Figure 2 and Table 3. Overall, the magnitude of improvement was smaller in the LVEF >30% group than in the LVEF ≤30% group. A significant decrease of LVESVi after 12 months of CRT was observed in both LVEF subgroups compared with CRT OFF. A trend toward significant reduction in LVEDVi by CRT ON was observed in the LVEF >30% group (−11.2±27.0 versus −4.3±22.9 mL/m² in CRT OFF; P=0.12). A statistically significant decrease of LVEDVi was only observed in the LVEF ≤30% group. Adjusting for the potential effect of regression to the mean did not affect the interpretation of the reverse remodeling results (Table 4). A significant interaction effect was detected for LVEDVi and LVESVi but not for other echo parameters. This effect indicates that the difference due to CRT in the change in LVEDVi and LVESVi over time is not as pronounced in the LVEF >30% subgroup.

Table 1. Baseline Clinical Characteristics Divided by LVEF ≤30% and >30%

<table>
<thead>
<tr>
<th>Clinical Characteristics</th>
<th>LVEF ≤30% (n=431)</th>
<th>LVEF &gt;30% (n=177)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>61.8±11.3</td>
<td>64.2±10.0</td>
<td>0.01</td>
</tr>
<tr>
<td>Sex, male, n (%)</td>
<td>336 (78)</td>
<td>142 (80)</td>
<td>0.59</td>
</tr>
<tr>
<td>Ischemic, n (%)</td>
<td>222 (52)</td>
<td>110 (62)</td>
<td>0.02</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>216 (50)</td>
<td>98 (55)</td>
<td>0.25</td>
</tr>
<tr>
<td>Diabetic mellitus, n (%)</td>
<td>93 (22)</td>
<td>43 (24)</td>
<td>0.46</td>
</tr>
<tr>
<td>ACE inhibitors or ARBs, n (%)</td>
<td>416 (97)</td>
<td>172 (97)</td>
<td>0.81</td>
</tr>
<tr>
<td>β-Blockers, n (%)</td>
<td>405 (94)</td>
<td>173 (98)</td>
<td>0.06</td>
</tr>
<tr>
<td>Intrinsic QRS width, ms</td>
<td>155.7±22.2</td>
<td>147.3±20.4</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>QRS morphology</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LBBB,* n (%)</td>
<td>266 (62)</td>
<td>102 (58)</td>
<td>0.31</td>
</tr>
<tr>
<td>IVCD, * n (%)</td>
<td>127 (30)</td>
<td>54 (31)</td>
<td></td>
</tr>
<tr>
<td>RBBB, * n (%)</td>
<td>35 (8)</td>
<td>21 (12)</td>
<td></td>
</tr>
<tr>
<td>Glomerular filtration rate, mL/min</td>
<td>87.6±34.1</td>
<td>82.0±30.3</td>
<td>0.048</td>
</tr>
<tr>
<td>Supine systolic BP, mmHg</td>
<td>122.9±18.1</td>
<td>129.1±19.8</td>
<td>0.0003</td>
</tr>
<tr>
<td>Supine diastolic BP, mmHg</td>
<td>71.7±10.9</td>
<td>73.2±11.8</td>
<td>0.16</td>
</tr>
<tr>
<td>CRT-ICD implanted, n (%)</td>
<td>361 (84)</td>
<td>145 (82)</td>
<td>0.63</td>
</tr>
</tbody>
</table>

ACE indicates angiotensin-converting enzyme; ARB, angiotensin receptor blocker; BP, blood pressure; CRT, cardiac resynchronization therapy; ICD, implantable cardioverter defibrillator; IVCD, intraventricular conduction delay; LBBB, left bundle-branch block; LVEF, left ventricular ejection fraction; and RBBB, right bundle-branch block.

*Sample sizes for QRS morphology are n=428 (LVEF ≤30%) and n=177 (LVEF >30%).
Clinical Measurements

The clinical results at 12 months are shown in Table 3 and Figure 3. In the LVEF >30% group, the distribution of CCS was better in CRT ON compared with OFF but did not reach statistical significance (Fisher exact test, \( P = 0.06 \); trend test, \( P = 0.13 \)). A statistically significant improvement was observed in the LVEF ≤30% group and in the full study group. In the overall group, there was a significant improvement in NYHA class with CRT ON (Fisher exact test, \( P = 0.003 \); trend test, \( P = 0.03 \)). A statistically significant improvement was also observed in the LVEF >30% group. Although the numeric trends in the EF subgroups were in the same direction, it did not reach statistical significance in either group. There was no statistically significant interaction between CRT and LVEF, indicating that there was no evidence that the benefit of CRT varied with LVEF.

Effect of CRT on Time to First HF Hospitalization or Death in EF ≤30% Versus >30%

Time to first HF hospitalization or death was tracked through 12 months (North America) or 24 months (Europe) and is shown in Figure 4. There were 16 deaths, 41 HF hospitalizations, and 51 total composite end points in the LVEF ≤30% group; and 3 deaths, 9 HF hospitalizations, and 12 total composite end points in the LVEF >30% group. Overall, the composite morbidity and mortality rate was nearly twice as high in the LVEF ≤30% group; death occurred in 3.7% of patients and 11.8% experienced the composite end point of HF hospitalization or death during the randomization period. Comparatively, in the LVEF >30% group, 1.7% of patients died and 6.8% of patients experienced a HF hospitalization or death during the randomization period. There were significant prolonged time to first hospitalization for HF or death for CRT ON versus CRT OFF in both the LVEF ≤30% (hazard ratio, 0.58; \( P = 0.047 \)) and >30% groups (hazard ratio, 0.26; \( P = 0.012 \)) with curves for CRT ON and OFF separating early within the first months (Figure 4).

In the LVEF ≤30% group, there were 16 deaths: 6 of 141 patients in CRT OFF because of progressive HF, arrhythmia, stroke, electromechanical dissociation, renal cancer, and by unknown cause; and 10 of 290 patients in CRT ON because of progressive HF (n=3), arrhythmia, bradyarrhythmia, pulmonary fibrosis, stroke, prostate cancer, and by unknown cause (n=2). In the LVEF >30% group, there were 3 deaths: 1 of 50 patients in CRT OFF (gastrointestinal bleeding) and 2 of 127 patients in CRT ON (gastrointestinal bleeding and pulmonary fibrosis). The effect of the interaction between CRT and LVEF subgroup on time to death or HF hospitalization was also assessed.

As there were some baseline differences between the 2 LVEF subgroups, a multivariable analysis was performed to adjust for potential confounding factors (Table 5). After adjusting for important covariates, the main effect for CRT assignment remained independently associated (hazard ratio, 0.54; \( P = 0.035 \)) with improved outcomes among patients assigned to CRT ON. There was no statistically significant interaction between CRT and LVEF, indicating that there was no evidence that the benefit of CRT varied with LVEF. Baseline LVESVi \( (P = 0.0002 \) ) and QRS duration \( (P = 0.003 \) ) were also independently associated with hospitalization for HF or death with better outcome in subjects with smaller LV size and longer QRS duration. The cause of heart disease (ie, ischemic versus nonischemic) was not associated with outcome in this analysis.

Discussion

The primary results of the present analysis show that the beneficial effect of CRT ON on ventricular function and time to
death or first hospitalization occurs across the full spectrum of LVEF studied in REVERSE, with indications of a similar benefit in patients with LVEF >30% and those with LVEF ≤30%. These findings are strengthened by the randomized design of the study, the blinded comparison against CRT-OFF, and the rigorous examination of the potential effect of regression to the mean on the reverse remodeling results.

Substudies of CRT Results by Different Ejection Fractions

In previous substudies of randomized controlled studies, no apparent difference in CRT benefit was observed in patients with LVEF >20% or <20% in moderate to severe and mild HF. Similar observations were made in a retrospective analysis of the Predictors of Response to CRT (PROSPECT) study evaluating less severe LV dysfunction and an analysis of single-center data. PROSPECT was an open-label study, which included patients with NYHA Class III to IV, QRS ≤130 ms, and LVEF ≤35%. CRT induced similar benefit among patients with LVEF ≤35% or >35% with regard to reverse remodeling and the percentage improved by CCS. Importantly, a recently published post hoc analysis of Multicenter Automatic Defibrillator Implantation Trial–Cardiac Resynchronization Therapy (MADIT-CRT) of NYHA I to II patients also indicated a benefit of CRT in the subjects with LVEF >30%. As in our study and in PROSPECT, core
laboratory evaluation resulted in some subjects with higher LVEF than allowed by the study inclusion criteria. In agreement with our findings, the clinical benefit for time to HF hospitalizations or death was greater for patients with LVEF >30% compared with other LVEF groups.27 However, in contrast to our findings, the extent of reverse remodeling defined as decrease of LVESVi was higher for the LVEF >30% group27 than for the other groups in spite of smaller baseline LV. The reason for this discrepancy is not clear, although subjects with less severe LV dysfunction were included in REVERSE.

Results in the Present Study With Regard to LVEF

To our knowledge, only REVERSE included patients with LVEF ≤40%. In fact, 12.2% (n=74) of our patients had LVEF >35%, that is, with LVEFs beyond the current guideline recommendations in the United States.15,16 In contrast, a smaller fraction of patients in the MADIT-CRT substudy had LVEF >35%. Our results show some signs of significant reverse remodeling benefits by CRT at 12 months regardless of whether baseline LVEF was below or above 30%. In this study, the patients with higher LVEF were older and had more ischemic heart disease and worse renal function, implying...
negative prognostic impact. However, they were more often in NYHA I functional class and had smaller baseline LV volumes than patients with LVEF <30%.

Moreover, multivariate analysis indicated that a smaller LVESVi at baseline was linked to greater magnitude of response to CRT, which also suggests earlier intervention with CRT than indicated in present guidelines.\(^{15-17}\) The magnitude of reverse remodeling in the higher LVEF group was less than that observed in patients with severe HF and with worse LV function in the post hoc analysis of PROSPECT.\(^{24}\) One contributing factor for this observation may be that patients in this group often had underlying ischemic heart disease and shorter QRS duration, which is known to be linked to less extensive reverse remodeling.\(^{6,14,28,29}\) In the Multicenter InSync Randomized Clinical Evaluation (MIRACLE) trial, the extent of reverse remodeling was half the magnitude in patients with ischemic underlying pathology as in those with dilated cardiomyopathy.\(^{28}\) Similar findings were made in the Cardiac Resynchronization–Heart Failure (CARE-HF) trial despite similar clinical benefit.\(^{29}\) We have previously reported that ischemic HF patients in REVERSE had 3 times less reverse remodeling than patients with dilated cardiomyopathy\(^{30}\) and that the magnitude of QRS duration is an independent predictor of the extent of reverse remodeling.\(^{14}\) The effect of QRS duration and cause of HF on reverse remodeling has also been noted in studies of advanced HF.\(^{31}\) Thus, the greater proportion

![Figure 3](image1.png)  
**Figure 3.** Clinical composite response distribution in patients with baseline left ventricular ejection fraction ≤30% or >30% in relation to cardiac resynchronization therapy ON and OFF assignments.

![Figure 4](image2.png)  
**Figure 4.** Time to death or hospitalization for heart failure in patients with baseline left ventricular ejection fraction ≤30% or >30% in relation to cardiac resynchronization therapy ON and OFF assignments.
of patients with ischemic underlying pathology and shorter mean QRS duration in the LVEF >30% group may partly explain the smaller reverse remodeling.

Nonetheless, CRT in LVEF >30% was associated with significant clinical improvement as assessed by the time to mortality or hospitalizations for HF as in the LVEF ≤30% group over a follow-up period of 12 to 24 months. In fact, the relative risk reduction was 74% in the LVEF >30% group compared with 42% in the LVEF <30% group, suggesting a greater benefit. CRT was independently associated with outcome independent of LVEF. Age or baseline ischemic heart disease and diabetes mellitus were not independent predictors of clinical outcome.

Electric dyssynchrony is critical for CRT-induced improvements, with previous studies suggesting that response increases with longer intrinsic QRS duration or left bundle branch morphology.13,14 Our patients all had wide QRS (155.7±22.2 ms in the LVEF <30% group and 147±20.4 ms in the LVEF >30% group), and LBBB was present in about 60% of patients within each subgroup. QRS duration, but not LBBB, was found to be an independent predictor of response in our study. Coinciding with our findings, a recent meta-analysis showed that increasing QRS duration was an independent predictor for response and not LBBB.32 These study results indicate that the benefits of CRT may be present for patients with QRS prolongation and mild HF with less severe LV dysfunction than previously studied.

Limitations
The study should be interpreted in light of certain methodological limitations. This was a post hoc subgroup analysis that was not powered during study design, and randomization was not stratified based on EF. There were also some important clinical differences between subgroups, although multivariate analysis indicated that EF was not an independent predictor of response.

Conclusions
In this analysis of REVERSE study patients with LVEF >30%, CRT produced improvements in time to death or HF-related hospitalizations and was associated with significant reduction in LVESVi and LV mass consistent with reverse remodeling. These findings warrant further prospective validation.

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**CLINICAL PERSPECTIVE**

Current guidelines recommend cardiac resynchronization therapy (CRT) in mild heart failure (HF) patients with QRS prolongation and ejection fraction (EF) <30%. We compared outcomes of CRT in patients with left ventricular ejection fraction (LVEF) >30% (n=177) to those with LVEF <30% (n=431) in a REsynchronization reVerSes Remodeling in Systolic left vEntricular dysfunction (REVERSE) substudy. In the LVEF >30% subgroup, there was a trend for improvement in the clinical composite response with CRT ON versus CRT OFF and significant reductions in LV end systolic volume index and LV mass after 12 months. The time to death or first HF hospitalization was significantly prolonged with CRT. In the LVEF <30% subgroup, significant improvements in clinical composite response, reverse remodeling parameters, and time to death or first HF hospitalization were observed. After adjusting for important covariates, the CRT ON assignment remained independently associated with improved time to death or first HF hospitalization, whereas there was no significant interaction with LVEF. In summary, among subjects with mild HF, QRS prolongation, and LVEF >30%, CRT produced reverse remodeling and similar clinical benefit compared with subjects with more severe LV systolic dysfunction.
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