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Ventricular Reverse Remodeling and 6-Month Outcomes in Patients Receiving Cardiac Resynchronization Therapy: Analysis of the MIRACLE Study

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Abstract. ***Objective:*** **The objective of this analysis was to determine if there were differences in ventricular reverse remodeling and 6-month outcome with cardiac resynchronization therapy (CRT) among specific subgroups enrolled in the Multicenter InSync Randomized Clinical Evaluation (MIRACLE) Study.**

Background: **Analysis of major subgroups receiving CRT is important in determining who may be most likely to benefit, since all patients who receive CRT do not demonstrate improvement.**

Methods: **Differences in response to CRT between subgroups based on baseline echocardiographic parameters, New York Heart Association (NYHA) class, age, gender, beta blocker use, and etiology of heart failure (HF) were analyzed for the clinical end points of the study as well as 6-month HF re-hospitalization or death.**

Results: **The benefit of CRT over control was similar in all subgroups with respect to all clinical endpoints. However, non-ischemic HF patients had greater improvements with CRT compared to ischemic HF patients in left ventricular end diastolic volume ($P < 0.001$) and ejection fraction (EF) (6.7% increase vs. 3.2% [$P < 0.001$]). Greater improvements in EF were also seen in those patients with less severe baseline mitral regurgitation (MR) ($P < 0.001$). Women but not men receiving CRT were more likely to be event-free from first HF hospitalization or death compared to the control group (Hazard Ratio = 0.157).**

Conclusions: **The benefits of CRT with respect to EF and reverse remodeling were greater in patients with non-ischemic HF and less severe MR. Women may also derive more benefit than men with respect to the occurrence of HF hospitalization or death.**

Key Words. **resynchronization, remodeling, subgroups, echocardiography, heart failure, pacing**

Introduction

Cardiac resynchronization therapy (CRT) has been shown to be an effective treatment for patients with heart failure who remain symptomatic despite optimal medical therapy. However, not all patients who receive this therapy have the same response. To date, there have been no large studies to determine if certain subgroups of patients have a better response than others.

The Multicenter InSync Randomized Clinical Evaluation (MIRACLE) was a prospective, randomized, double-blinded study designed to demonstrate the safety and efficacy of CRT in patients with heart failure. A total of 453 patients with moderate-to-severe symptoms of heart failure despite optimal pharmacological therapy, ejection fraction (EF) ≤35%, and QRS duration ≥130 ms were randomized to either CRT or a control group. Patients who received CRT had significant improvements in the primary end-points of New York Heart Association (NYHA) functional class, quality of life and 6-minute walk distance [1]. The goal of this analysis was to examine the homogeneity of response to CRT within various patient subgroups.

Methods

The MIRACLE study design, patient population, methods and results have been published previously [1]. In brief, 453 successfully implanted patients who met inclusion criteria were randomly assigned either to CRT or a control group with the intention of following the patients for at least six months. Primary endpoints included changes from baseline to six months for NYHA functional class, quality of life measured by the Minnesota Living with Heart Failure questionnaire, and distance walked in six minutes.

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Separate subgroup analyses were conducted for each of eight baseline characteristics that were prospectively identified: age (<65, ≥65 years), gender (male, female), heart failure etiology (ischemic, non-ischemic), NYHA classification (III, IV), left ventricular EF (<20%, ≥20%), mitral regurgitation (MR) expressed as MR average jet area (<6 cm^2 *(mild)*, ≥6 cm^2 *(moderate to severe)*), location of implanted left ventricular lead (lateral, other) and baseline beta blocker use (beta blocker, no beta blocker). A nonparametric analysis of variance approach was used to compare treatments (control, CRT) within each of the subgroups for the three primary endpoints and the secondary endpoints of exercise time, relative peak VO_2, QRS width, EF, left ventricular end diastolic volume (LVEDV), and MR after a rank transformation of the data.

Cox regression techniques were used to compare treatments within subgroups with respect to the time of death, time to first hospitalization for worsening heart failure and time of death or first hospitalization for worsening heart failure.

For each analysis, factors for treatment group, subgroup, and the interaction between treatment group and subgroup were included in the model. Interactions determined to be significant were further analyzed using a multivariate model adjusting for baseline values of covariates (excluding MR since baseline MR was only available for 346 patients) to determine if the interaction was still significant after adjusting for baseline differences between subgroups. When the interaction was significant in the analysis of variance models, comparisons between treatment groups within subgroups were made using the Wilcoxon rank-sum test. When the interaction term was significant in the Cox regression models, comparisons between treatment groups within subgroups were made using the log-rank test.

Statistical software from SAS, Inc (Cary, NC) was used. P values <0.05 were considered significant. All analyses were conducted retrospectively and no adjustments due to multiplicity were made to any P values.

Results

Baseline demographic data used to define patient subgroups are shown in Table 1. After accounting for missed follow-ups, patient deaths, and other study withdrawals, a total of 416 patients completed the 6-month follow-up visit and were evaluated for at least one of the primary and/or secondary endpoints. However, all 453 patients in the MIRACLE study were included in the time to event analyses.

Table 1. *Baseline demographic data*

Parameter	Control ($N = 225$)	Treatment ($N = 228$)	p-value
Age ≥ 65 years old	52.9%	47.4%	0.280
Sex (% male)	68.0%	68.4%	1.000
Heart failure etiology (% ischemic)	58.2%	50.4%	0.117
NYHA Class III	91.1%	90.4%	0.907
LVEF ≥ 20%	67.6%	69.7%	0.690
MR average Jet Area ≥ 6 cm^2	48.8%	49.4%	0.996
LV lead location (% lateral)	72.3%	76.8%	0.330

NYHA: New York Heart Association; LVEF: left ventricular ejection fraction; MR: mitral regurgitation.

The benefit of CRT over control was similar in all subgroups with respect to all primary endpoints. Specifically there were no significant subgroup differences in response among treatment groups based on NYHA class, EF, lead position or beta blocker use. However, the effect of CRT on changes in echocardiographic parameters demonstrated significantly different results within certain subgroups, as shown in Table 2.

Both non-ischemic and ischemic heart failure patients receiving CRT had statistically significantly greater improvements in EF compared to control patients, but the magnitude of improvement was different. Non-ischemic heart failure

Table 2. *Effect of CRT on efficacy endpoints—significant subgroups*

	N	Median	Range	p-value
Change in EF (%)—Non-ischemic patients				
Control	71	−0.3	−20 to 15	<0.001
CRT	95	6.7	−16 to 41	
Change in EF (%)—Ischemic patients				
Control	99	−0.1	−13 to 26	0.007
CRT	92	3.2	−18 to 17	
Change in LVEDV (cm^3)—Non-ischemic patients				
Control	71	6.6	−8.1 to 19.6	<0.001
CRT	95	−46.7	−69.1 to −30.0	
Change in LVEDV (cm^3)—Ischemic patients				
Control	99	2.5	−4.0 to 15.7	0.013
CRT	92	−16.6	−27.2 to 2.8	
Change in EF (%)—MR average jet area <6 cm^2				
Control	75	0.4	−20 to 15	<0.001
CRT	81	6.0	−16 to 24	
Change in EF (%)—MR average jet area ≥6 cm^2				
Control	75	−0.5	−13 to 26	0.032
CRT	77	1.5	−18 to 27	

EF: ejection fraction; MR: mitral regurgitation; LVEDV: left ventricular end diastolic volume.
The data shown in the table are for all patients who had both baseline and 6-month echocardiograms available for review.

patients in the CRT group had a median absolute increase of 6.7% in EF compared to a median absolute decline of 0.3% in the control arm ($P < 0.001$). On the other hand, ischemic heart failure patients receiving CRT had a median absolute improvement in EF that was approximately half the improvement seen for non-ischemic heart failure patients receiving CRT (3.2%). The improvement was still significantly better than the change seen for ischemic heart failure patients who did not receive CRT ($P = 0.007$).

The effect of CRT on changes in median LVEDV again favored non-ischemic heart failure patients. Both non-ischemic and ischemic heart failure patients who received CRT had significant decreases in LVEDV compared to controls. However, non-ischemic heart failure patients had a greater improvement in LVEDV compared to ischemic heart failure patients.

CRT patients had a significant improvement in EF and MR compared to control patients regardless of baseline MR. However, significant differences were observed in the degree of improvement. The improvement in EF after CRT in the group with less MR at baseline was more than twice the improvement in the group with more MR at baseline. Patients with a lower baseline MR average jet area (<6 cm^2) receiving CRT had a median absolute increase in EF of 6% versus 0.4% in the control group ($P < 0.001$). On the other hand, patients with a baseline MR average jet area ≥6 cm^2 in the CRT group had a median absolute increase in EF of 1.5% compared to 0.5% in the control group ($P = 0.032$).

In the analyses of time to clinical events, overall results previously reported showed no difference between treatment groups with respect to death, but there were significant differences between CRT and control groups with respect to the time to first heart failure hospitalization and significant differences between groups with respect to the combined endpoint of time to first heart failure hospitalization or death ($P = 0.03$) [1]. In the current analysis, there were interesting differences in outcome based on gender. Baseline demographic data for men and women are shown in Table 3. Of note, men were older and more often had ischemic HF. In this subgroup analysis, a significant difference in the time to first heart failure hospitalization, and the combined endpoint of first heart failure hospitalization or death, was seen only in women. This difference remained even when controlling for age, etiology of heart failure and other baseline variables. Women receiving CRT show a statistically significant difference in time to first heart failure hospitalization (log-rank chi-square test, $P = 0.002$) and time to first heart failure hospitalization or death

Table 3. *Baseline demographic data comparison, women vs. men*

Parameter	Women ($N = 144$)	Men ($N = 309$)	p-value
Randomization group (% CRT)	50.0	50.5	1.000
Age (% ≥ 65 years old)	42.4	53.7	0.031
Heart failure etiology (% ischemic)	29.2	66.0	<0.001
NYHA functional class (% Class III)	88.9	91.6	0.455
EF (% ≥ 20%)	72.2	67.0	0.313
Baseline MR average jet area (% ≥ 6 cm^2)	41.4	53.0	0.053
LV lead location (% lateral)	78.3	72.8	0.257

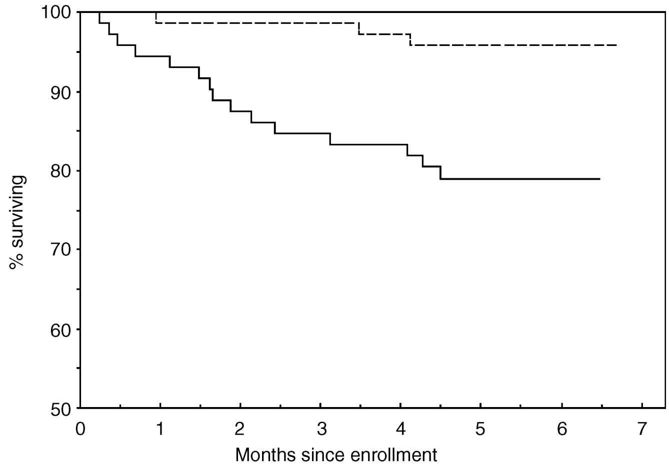
CRT: cardiac resynchronization therapy; EF: ejection fraction; LV: left ventricular; NYHA: New York Heart Association Class; HF: heart failure; LVEDV: left ventricular end diastolic volume; MR: mitral regurgitation; SD: standard deviation.

(log-rank chi-square test, $P < 0.001$) compared to women in the control group. No differences were seen among men for either endpoint. These differences in clinical events between woman and men are clearly demonstrated in the Kaplan-Meier survival curves in Figures 1 and 2.

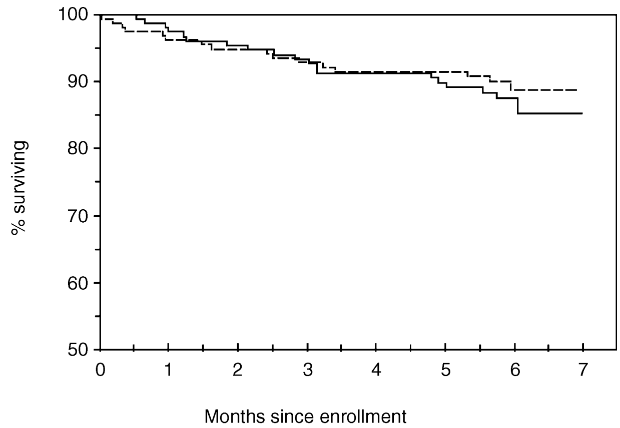
Discussion

The MIRACLE study showed that CRT improved a number of measures of cardiac function and clinical status in patients with moderate to severe heart failure [1]. In the present analysis, significant differences in the primary endpoints were consistent within all subgroups examined. However, there were differences in response within certain subgroups with respect to reverse ventricular remodeling and LV function.

In our analysis of patients receiving CRT, both non-ischemic and ischemic heart failure patients had statistically significant improvements in EF, as reported recently [2]. This is consistent with other reports of improvement in EF with CRT [3–6]. However, non-ischemic heart failure patients had a greater improvement in EF than ischemic heart failure patients. This finding is consistent with previous studies that showed greater increases in EF in patients with non-ischemic heart failure than ischemic heart failure, although both groups improved clinically with CRT [2,7]. Non-ischemic heart failure patients may respond better to CRT than ischemic heart failure patients because ischemic heart failure patients tend to have areas of regional rather than global dyssynchrony from areas of ischemia or scar that may be unresponsive to pacing and resynchronization.



(A)



(B)

Fig. 1. *(A) Kaplan-Meier estimates of time to first HF hospitalization for women. (B) Kaplan-Meier estimates of time to first HF hospitalization for men.*

Regardless of the severity of MR, patients receiving CRT had statistically significant improvements in EF compared to the controls within each subgroup. However, EF increased more from CRT in patients with less baseline MR, than patients with more baseline MR compared to their respective controls. Patients with less MR have been shown to improve hemodynamics, systolic function and LV dimensions with CRT [8–10]. There is one study, however, suggesting that patients with less MR did not have clinical improvement from CRT [11].

It is important to note that improvement in EF does not necessarily correlate with an improved clinical response. However, lower EFs are known to be associated with increased mortality [12–14]. Therefore, though mortality benefits from CRT have recently been reported [15], specific implications of EF and mortality risk in this CRT population have not been elucidated. As with lower EFs, ventricular dilatation has prognostic value. Studies of post infarct as well as non-ischemic heart failure patients with LV dysfunction have demonstrated

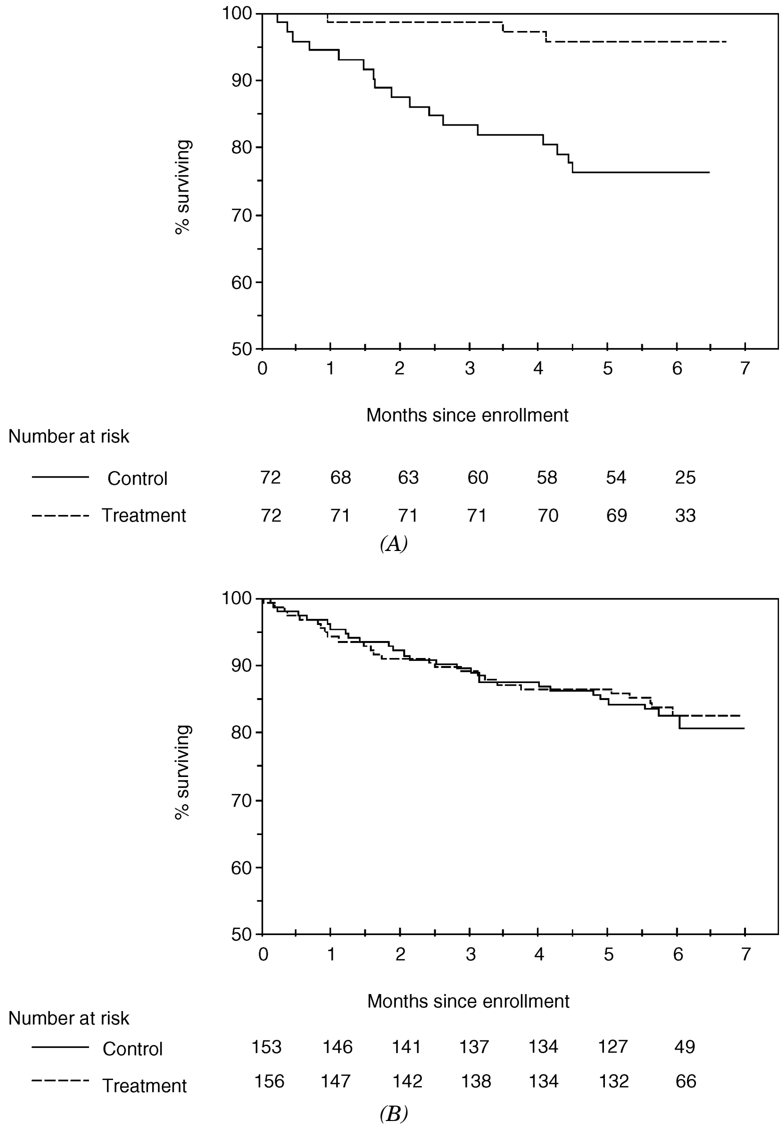


Fig. 2. *(A) Kaplan-Meier estimates of time to first HF hospitalization or death for women. (B) Kaplan-Meier estimates of time to first HF hospitalization or death for men.*

an association between increased ventricular size and cardiovascular events and mortality [16–18]. Cardiac resynchronization therapy leads to reverse ventricular remodeling as indicated by decreased left ventricular end-diastolic dimensions (LVEDD) and left ventricular end-diastolic volumes (LVEDV) [2,9,19,20]. Our analysis showed that non-ischemic heart failure patients had greater reductions in LVEDV after CRT. Some have suggested patients with higher baseline LVEDV are less likely to demonstrate reverse remodeling from CRT [10]. Others have shown that patients with significant LV enlargement may be unresponsive to the remodeling benefits of pharmacologic therapy [21]. One could, therefore, argue that CRT should be implanted earlier in the course of heart failure before remodeling becomes too severe.

The presence of MR can significantly impact morbidity, limit exercise capacity and cause deterioration in cardiac hemodynamics [22–24]. Functional MR has been associated with cardiac dilatation and is likely a result of the loss of coordination between the closing and tethering forces that act on the mitral valve [25,26]. Reductions in MR from CRT are likely due to the direct mechanical effects of optimization of the AV delay and improved inter- and intra-ventricular dyssynchrony [3,27] as well as reverse remodeling with reductions in LV dimensions chronically [28]. In the original MIRACLE analysis, there was a significant reduction in MR in those who received CRT vs. control, suggesting that patients with significant valvular disease on the basis of ventricular dilatation might benefit from CRT.

Recently, a meta-analysis of the CRT trials as well as the Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure (COMPANION) study, suggested that CRT significantly reduces all cause mortality and all cause hospitalization [15,29]. Our subgroup analysis shows that the clinical endpoint of time to first heart failure hospitalization or the combined clinical endpoints of time to first heart failure hospitalization or death within six months of implant were significantly different in women, but no such difference was seen in men, even when accounting for baseline differences in demographics and etiology of heart failure. This is a unique finding that bears further exploration in future clinical trials.

Limitations

The major limitation of this analysis was its retrospective nature. Therefore, it is difficult to declare definitively that patients who fit into certain subgroups will respond better to CRT than others. While our analysis suggests some differences, the initial study was not designed or powered to detect differences within subgroups. Second, although the sample size of the original study was large, dividing the study population into subgroups reduces sample size. Third, with multiple subgroup analyses involving many comparisons, there is a high chance of "false positives." Fourth, not all patients had data available for all analyses. Fifth, improved echocardiographic parameters do not necessarily correlate with improved clinical effects or events, making it difficult to definitively draw conclusions about symptomatic improvement or morbidity.

Conclusions

Our analysis suggests that there are subgroup differences in response to CRT as manifested by improvements in echocardiographic parameters of LV function and reverse remodeling. Although most patients receive benefit from CRT, non-ischemic heart failure patients and women may derive even more benefit. Based on our analysis, further large-scale studies of subgroups based on heart failure etiology and gender are warranted.

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