Combined Cardiac Resynchronization and Implantable Cardioversion Defibrillation in Advanced Chronic Heart Failure
The MIRACLE ICD Trial

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An important subset of patients who have chronic heart failure (HF) also have cardiac dyssynchrony. Delays in interventricular or intraventricular electrical activation cause marked abnormalities in the sequence of global and segmental right and left ventricular (LV) activation and impair mechanical performance.1-3 The ability of new methods of cardiac stimulation to resynchronize ventricular function, improve overall cardiac performance, and increase exercise capacity has been shown by the results of several observational and controlled studies.4-10 The Multicenter InSync Randomized Clinical Evaluation (MIRACLE), the first ran-

Context   Cardiac resynchronization therapy (CRT) through biventricular pacing is an effective treatment for heart failure (HF) with a wide QRS; however, the outcomes of patients requiring CRT and implantable cardioverter defibrillator (ICD) therapy are unknown.

Objective   To examine the efficacy and safety of combined CRT and ICD therapy in patients with New York Heart Association (NYHA) class III or IV congestive HF despite appropriate medical management.

Design, Setting, and Participants   Randomized, double-blind, parallel-controlled trial conducted from October 1, 1999, to August 31, 2001, of 369 patients with left ventricular ejection fraction of 35% or less, QRS duration of 130 ms, at high risk of life-threatening ventricular arrhythmias, and in NYHA class III (n=328) or IV (n=41) despite optimized medical treatment.

Interventions   Of 369 randomized patients who received devices with combined CRT and ICD capabilities, 182 were controls (ICD activated, CRT off) and 187 were in the CRT group (ICD activated, CRT on).

Main Outcome Measures   The primary double-blind study end points were changes between baseline and 6 months in quality of life, functional class, and distance covered during a 6-minute walk. Additional outcome measures included changes in exercise capacity, plasma neurohormones, left ventricular function, and overall HF status. Survival, incidence of ventricular arrhythmias, and rates of hospitalization were also compared.

Results   At 6 months, patients assigned to CRT had a greater improvement in median (95% confidence interval) quality of life score (−17.5 [−21 to −14] vs −11.0 [−16 to −7], P=.02) and functional class (−1 [−1 to −1] vs 0 [−1 to 0], P=.007) than controls but were no different in the change in distance walked in 6 minutes (55 m [44-79] vs 53 m [43-75], P=.36). Peak oxygen consumption increased by 1.1 mL/kg per minute (0.7-1.6) in the CRT group vs 0.1 mL/kg per minute (−0.1 to 0.8) in controls (P=.04), although treadmill exercise duration increased by 56 seconds (30-79) in the CRT group and decreased by 11 seconds (−55 to 12) in controls (P=.001). No significant differences were observed in changes in left ventricular size or function, overall HF status, survival, and rates of hospitalization. No proarrhythmia was observed and arrhythmia termination capabilities were not impaired.

Conclusions   Cardiac resynchronization improved quality of life, functional status, and exercise capacity in patients with moderate to severe HF, a wide QRS interval, and life-threatening arrhythmias. These improvements occurred in the context of underlying appropriate medical management without proarrhythmia or compromised ICD function.

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Box. Inclusion and Exclusion Criteria

**Inclusion**
- Age ≥18 years
- Cardiac arrest due to ventricular fibrillation or ventricular tachyarrhythmia, or spontaneously sustained ventricular tachyarrhythmia, or inducible ventricular fibrillation or sustained ventricular tachyarrhythmia
- New York Heart Association functional class III or IV congestive heart failure
- Left ventricular ejection fraction ≤33%
- QRS duration ≥130 ms
- Left ventricular end diastolic diameter ≥55 mm
- Stable drug regimen for ≥1 month

**Exclusion**
- Estimated survival <6 months
- Baseline 6-minute walk test >450 m
- Bradycardia requiring pacemaker
- Unstable angina, myocardial infarction, coronary artery bypass graft, percutaneous transluminal coronary angioplasty, cerebral vascular accident, or transient ischemic attack within previous 3 months
- >2 infusions of inotropic drug per week
- Systolic blood pressure <80 mm Hg or >170 mm Hg
- Resting heart rate >140/min
- Serum creatinine >3 mg/dl (>265 µmol/L)
- Hepatic enzymes >3-fold upper normal values
- Severe lung disease
- Chronic atrial arrhythmias, or cardioversion or paroxysmal atrial fibrillation within previous 1 month
- Heart transplant recipient
- Severe valvular heart disease

We hypothesized that patients with moderate to severe HF symptoms, a wide QRS interval, LV systolic dysfunction, and an established indication for an ICD would benefit from CRT, and that CRT would not be proarrhythmic or compromise ICD therapy.

**METHODS**

The Multicenter InSync ICD Randomized Clinical Evaluation (MIRACLE ICD) study was a randomized, double-blinded, parallel-controlled clinical trial to evaluate the efficacy of CRT in a large number of patients with moderate to severe systolic HF, ventricular dysynchrony, and an indication for an ICD. More specifically, indications for an ICD at study entry generally were cardiac arrest (manifest by loss of consciousness) due to ventricular tachycardia or ventricular fibrillation without a transient, reversible cause; patients having recurrent, poorly tolerated, and sustained ventricular tachycardia that occurs spontaneously or can be induced. Except for the ICD indication and the timing of baseline tests described later, the patient inclusion criteria and study design were identical to those previously reported for the MIRACLE study. Enrollment began after October 1, 1999, and was completed by August 31, 2001. The investigational review board of each participating institution reviewed and approved the study protocol, and all patients granted their written informed consent before entering the trial.

**Patient Selection and Trial Entry**

The **Box** lists the study inclusion and exclusion criteria. Eligible patients received a stable and appropriate drug regimen, which included an angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker, if tolerated, for at least 1 month. If a patient was taking a β-blocker, it had to have been initiated at least 3 months before enrollment. Initiation of β-blockade was not permitted during the trial period. Patients who met the criteria for entry into the study underwent the following evaluations within 7 days of sys-
system implantation: estimation of NYHA functional class; 6-minute walking test; quality of life evaluation using the Minnesota Living with Heart Failure Questionnaire; 2-dimensional Doppler-flow echocardiography, which included measurement of LV ejection fraction, internal LV diastolic dimensions, end diastolic and systolic volumes, and degree of mitral regurgitation; plasma neurohormonal concentrations; and QRS width on 12-lead surface electrocardiogram. Patients with mild symptoms classified as NYHA.

In patients who agreed to participate, an implant was attempted with the Model 7272 InSync ICD (Medtronic Inc, Minneapolis, Minn), a standard right atrial pacing lead, a standard right ventricular (RV) pacing/defibrillator lead, and a choice of several LV transvenous leads (Medtronic Inc) positioned in a coronary sinus tributary. The InSync ICD delivers atrial-synchronized biventricular pacing for cardiac resynchronization, antitachycardia pacing through RV or RV and LV leads, and cardioversion and defibrillation to treat ventricular tachyarrhythmias delivered through the RV lead only.

Within 7 days of a successful implant, but before randomization, patients underwent a cardiopulmonary exercise test to measure peak oxygen consumption per unit time (V·O₂) and exercise duration. Patients were then randomly assigned, in blocked groups for each center, to active CRT, including optimal medical treatment and active ICD therapy (CRT group), or optimal medical treatment and active ICD therapy (control group) (FIGURE 1). Patients and the physicians from the HF team, who continued to follow patients after implantation of the CRT/ICD system but were not involved in the programming of the device, remained unaware of the randomization assignment until after the 6-month visit.

For patients in the CRT group, the device was programmed to a mode that inhibited atrial or ventricular pacing unless the intrinsic rate was less than 35/min. Implantable cardioverter defibrillator therapy was activated in all patients.

Patients returned at 1, 3, and 6 months for full interrogation of the CRT/ICD system, reassessment of quality of life, follow-up 6-minute walking test, estimation of NYHA functional class, and monitoring of background drug regimen. Echocardiogram, cardiopulmonary exercise testing, and measurements of plasma neurohormones were repeated at the 6-month visit, after which the blinded phase of the study was completed and CRT was activated in patients initially randomized to the control group. Standard protocols were used to perform cardiopulmonary exercise tests and collect plasma neurohormones. Independent core laboratories, unaware of the patient randomization assignment, interpreted the data.

**Statistical Analysis**

As in the previously reported MIRACLE study, the 3 primary efficacy end points of MIRACLE ICD were NYHA functional class, quality of life score, and distance covered during the 6-minute walking test. In addition, several secondary end points were examined, including peak V·O₂, treadmill exercise duration, LV ejection fraction, LV end-systolic and end-diastolic volumes, LV end-diastolic dimension, severity of mitral regurgitation, QRS duration, neurohormone concentrations, and a clinical composite response that assigned all randomized patients to 1 of 3 response options.

**Figure 1.** Enrollment and Follow-up of Patients in Multicenter InSync Implantable Cardioverter Defibrillator Randomized Clinical Evaluation

![Image of Figure 1](http://jama.jamanetwork.com/pdfaccess.ashx?url=/data/journals/jama/4881/)

639 Patients Enrolled and Consented to Participation

<table>
<thead>
<tr>
<th>182</th>
<th>Assigned to Receive ICD Plus Optimal Medical Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>14</td>
<td>Crossed Over to CRT</td>
</tr>
<tr>
<td>11</td>
<td>Worsening Heart Failure</td>
</tr>
<tr>
<td>2</td>
<td>Bradycardia</td>
</tr>
<tr>
<td>15</td>
<td>Died</td>
</tr>
<tr>
<td>5</td>
<td>Missed 6-Month Follow-up</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>162</th>
<th>Completed 6-Month Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>162</td>
<td>Included in Primary Efficacy Analysis</td>
</tr>
<tr>
<td>182</td>
<td>Included in Adverse Event Analysis</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>187</th>
<th>Assigned to Receive ICD Plus CRT Plus Optimal Medical Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>Crossed Over to ICD Only</td>
</tr>
<tr>
<td>2</td>
<td>Ventricular Lead Dislodgement</td>
</tr>
<tr>
<td>2</td>
<td>Diaphragmatic Stimulation</td>
</tr>
<tr>
<td>6</td>
<td>Programming Errors</td>
</tr>
<tr>
<td>14</td>
<td>Died</td>
</tr>
<tr>
<td>6</td>
<td>Missed 6-Month Follow-up</td>
</tr>
<tr>
<td>2</td>
<td>Cardiac Transplantation</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>165</th>
<th>Completed 6-Month Follow-up</th>
<th>NYHA indicates New York Heart Association; CRT, cardiac resynchronization therapy; ICD, implantable cardioverter defibrillator.</th>
</tr>
</thead>
<tbody>
<tr>
<td>165</td>
<td>Included in Primary Efficacy Analysis</td>
<td></td>
</tr>
<tr>
<td>187</td>
<td>Included in Adverse Event Analysis</td>
<td></td>
</tr>
</tbody>
</table>

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groups (worsened, improved, or unchanged).

A patient was classified as worsened if he or she died, was hospitalized due to worsening HF, permanently discontinued double-blind treatment due to or associated with worsening HF, permanently discontinued double-blind treatment because of withdrawal of consent or other administrative reason, had worsening HF at the time of study discontinuation, demonstrated worsening in NYHA class at last-observation-carried-forward (LOCF) or had moderate to marked worsening of patient global assessment score at LOCF. A patient was said to have improved if he or she had not worsened (as defined above) and demonstrated improvement in NYHA class at LOCF or had a moderate to marked improvement in patient global assessment score at LOCF. Finally, a patient was unchanged if he or she was neither improved nor worsened.21,22 All randomized patients contributed to all analyses with the following exceptions: only patients with data available at both baseline and follow-up were included in efficacy analyses and all patients undergoing an implant attempt were included in the adverse event analysis.

SAS software version 8.2 (SAS Institute, Cary, NC) was used to generate the random allocation sequence. The method of randomization was not disclosed to participating centers and was accomplished in blocked groups of 4 for each to ensure balance of CRT and control assignments at each participating institution. Randomization occurred following a successful implant. The randomization assignment for each patient was provided to the unblinded electrophysiology staff in a consecutively numbered and opaque (folded paper inside an envelope inside a second envelope) sealed envelope that was opened at the time of randomization. The HF staff was blinded to the randomization schedule and each patient’s randomization assignment throughout the 6-month follow-up visit.

All end points were analyzed according to the intention-to-treat principle. Data are presented as median changes between baseline and 6 months. Confidence limits for medians were computed using a distribution-free approach.23 Mean values are presented as mean (SD). For continuous variables, including NYHA, changes from baseline to the 1, 3, or 6-month visit in the control group vs the CRT group and demographic characteristics were compared with the Wilcoxon rank sum test. For categorical end points, differences in the distribution of responses to treatment at 6 months in the 2 groups were compared by using the Fisher exact test. Survival curves were constructed according to the Kaplan-Meier method with time zero being the date of implant, and differences between curves were examined by the log-rank test statistic. Confidence intervals (CIs) for survival were computed on the log-log survival scale.

For the primary efficacy variables, prespecified objectives were considered reached if differences between the groups in all 3 end points had P ≤ .05, if 2 had P ≤ .025, or if 1 had P ≤ .017, by using the Hochberg criterion.25 The sample size (112 patients per treatment group) was estimated on the basis of the assump-

<table>
<thead>
<tr>
<th>Table 1. Baseline Characteristics of MIRACLE ICD Study Groups*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Characteristic</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Men, No. (%)</td>
</tr>
<tr>
<td>Age, y</td>
</tr>
<tr>
<td>NYHA functional class, No. (%)</td>
</tr>
<tr>
<td>III</td>
</tr>
<tr>
<td>IV</td>
</tr>
<tr>
<td>Resting heart rate/min</td>
</tr>
<tr>
<td>Blood pressure, mm Hg</td>
</tr>
<tr>
<td>Systolic</td>
</tr>
<tr>
<td>Diastolic</td>
</tr>
<tr>
<td>QRS duration, ms</td>
</tr>
<tr>
<td>Isolated right bundle branch block, No. (%)</td>
</tr>
<tr>
<td>Left ventricular ejection fraction, %</td>
</tr>
<tr>
<td>Left ventricular end diastolic diameter, mm</td>
</tr>
<tr>
<td>Left ventricular end systolic diameter, mm</td>
</tr>
<tr>
<td>Left ventricular end diastolic volume, mL</td>
</tr>
<tr>
<td>Mitral regurgitation, average jet area, cm²</td>
</tr>
<tr>
<td>Quality of life score</td>
</tr>
<tr>
<td>6-Minute walk, m</td>
</tr>
<tr>
<td>Peak VO₂, mL/kg per minute</td>
</tr>
<tr>
<td>Exercise duration, s</td>
</tr>
<tr>
<td>Underlying heart disease, No. (%)</td>
</tr>
<tr>
<td>Ischemic</td>
</tr>
<tr>
<td>Nonischemic</td>
</tr>
<tr>
<td>Indication for ICD, No. (%)</td>
</tr>
<tr>
<td>Cardiac arrest</td>
</tr>
<tr>
<td>Sustained ventricular tachycardia</td>
</tr>
<tr>
<td>Induced ventricular fibrillation and sustained ventricular tachycardia</td>
</tr>
<tr>
<td>Baseline medications, No. (%)</td>
</tr>
<tr>
<td>ACE inhibitor or ACE inhibitor substitute</td>
</tr>
<tr>
<td>Antiarrhythmic</td>
</tr>
<tr>
<td>β-Blocker</td>
</tr>
</tbody>
</table>

Abbreviations: ACE, angiotensin-converting enzyme; CRT, cardiac resynchronization therapy; ICD, implantable cardioverter defibrillator; MIRACLE ICD, Multicenter InSync ICD Randomized Clinical Evaluation; NYHA, New York Heart Association; VO₂, oxygen consumption per unit time.

*All differences between control and CRT groups are not statistically significant, except for ischemic vs nonischemic underlying heart disease (P = .02).
tion that the study would have 80% power (2-sided \( \alpha = .017 \)) to detect a difference in NYHA class of 0.75, quality of life of 13 points, or distance walked in 6 minutes of 50 m. For secondary end points, \( P = .05 \) was considered statistically significant. All \( P \) values were calculated using 2-sided tests. In an analysis that was not prespecified, potential clinically relevant covariates were analyzed by using analysis of variance with randomization assignment, the covariates, and the interactions between the covariates and randomization assignment as independent variables.

A complication was defined as a sign, symptom, illness, or other medical event that was resolved invasively or that resolved.

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### Table 2. Efficacy End Points Analysis Between Baseline and 6 Months

<table>
<thead>
<tr>
<th>End Point</th>
<th>Control Group</th>
<th>CRT Group</th>
<th>Control vs CRT ( P ) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Change in quality of life score</td>
<td>157 (−11 (−16 to −7))</td>
<td>162 (−17.5 (−21 to −14))</td>
<td>.02</td>
</tr>
<tr>
<td>Change in NYHA functional class</td>
<td>162 (0 (−1 to 0))</td>
<td>165 (−1 (−1 to −1))</td>
<td>.007</td>
</tr>
<tr>
<td>Change in 6-minute walk distance, m</td>
<td>153 (53 (43 to 75))</td>
<td>152 (55 (44 to 79))</td>
<td>.36</td>
</tr>
<tr>
<td>Change in quality of life score</td>
<td>163 (−11 (−16 to −6))</td>
<td>170 (−17 (−21 to −13))</td>
<td>.01</td>
</tr>
<tr>
<td>Change in NYHA functional class</td>
<td>166 (0 (−1 to 0))</td>
<td>171 (−1 (−1 to −1))</td>
<td>.006</td>
</tr>
<tr>
<td>Change in 6-minute walk distance, m</td>
<td>163 (52 (40 to 74))</td>
<td>166 (54.5 (40 to 75))</td>
<td>.32</td>
</tr>
</tbody>
</table>

#### Secondary

<table>
<thead>
<tr>
<th>Cardiopulmonary exercise</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Change in peak ( V\cdot O_2 ) (mL/kg per minute)</td>
<td>121 (0.1 (−0.1 to 0.8))</td>
<td>120 (1.1 (0.7 to 1.6))</td>
<td>.04</td>
</tr>
<tr>
<td>Change in exercise duration, s</td>
<td>123 (−11 (−55 to 12))</td>
<td>120 (55.5 (30 to 79))</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Echocardiographic LV size and function</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Change in end diastolic volume, mL</td>
<td>133 (−5.7 (−16.2 to 1.8))</td>
<td>132 (−19.9 (−39.7 to −6.3))</td>
<td>.06</td>
</tr>
<tr>
<td>Change in end systolic volume, mL</td>
<td>133 (−8.2 (−19.1 to 0.6))</td>
<td>132 (−22.2 (−32.8 to −10.7))</td>
<td>.06</td>
</tr>
<tr>
<td>Change in ejection fraction, absolute %</td>
<td>133 (1.7 (0.7 to 2.4))</td>
<td>132 (2.1 (1.2 to 4.1))</td>
<td>.12</td>
</tr>
<tr>
<td>Change in end diastolic diameter, mm</td>
<td>67 (−0.2 (−0.3 to 0))</td>
<td>70 (−0.1 (−0.3 to 0.1))</td>
<td>.81</td>
</tr>
<tr>
<td>Change in end systolic diameter, mm</td>
<td>65 (−0.3 (−0.5 to −0.1))</td>
<td>69 (−0.1 (−0.4 to 0.1))</td>
<td>.53</td>
</tr>
<tr>
<td>Change in mitral regurgitant jet area, mm</td>
<td>126 (−0.33 (−0.85 to 0))</td>
<td>130 (−0.55 (−2.00 to 0))</td>
<td>.58</td>
</tr>
</tbody>
</table>

#### Change in overall clinical status, No. (%)

<table>
<thead>
<tr>
<th>Improved</th>
<th>Unchanged</th>
<th>Worsened</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>78 (42.9)</td>
<td>43 (23.6)</td>
<td>61 (33.5)</td>
<td>98 (52.4)</td>
<td>.07</td>
</tr>
</tbody>
</table>

| Change in QRS duration, ms | 160 | 162 | .001 |

| Changes in plasma neurohormones, pg/mL |      |      |         |
| Brain natriuretic peptide | 121 (−68 (−133 to −6)) | 119 (−50 (−163 to −6)) | .77                         |
| Dopamine | 117 | 112 | 0 | .37 |
| Noradrenaline, ng/dL | 117 (−17 (−54 to 49)) | 113 (4 (−12 to 68)) | .58                         |
| Epinephrine | 115 (−3 (−8 to 0)) | 112 (0 (−4 to 0)) | .05                         |
| Big endothelin | 119 (−1.8 (−3.7 to 0.9)) | 110 (−2.5 (−6.0 to 1.3)) | .98                         |

Abbreviations: CI, confidence interval; CRT, cardiac resynchronization therapy; LV, left ventricular; NYHA, New York Heart Association; \( V\cdot O_2 \), oxygen consumption per unit time.

*Including all patients with data.
†Last-observation-carried-forward analysis, excluding patients who died and those with either no baseline data or no follow-up data at 1, 3, and 6 months.
sulted in the death of or serious injury to a patient. The termination of a significant device function was also considered a complication. An invasive procedure was one that penetrated the skin, including the administration of parenteral fluids or drugs. The clinical events review committee reviewed and classified adverse events without knowledge of the randomization assignment. Investigators had full access to all data and performed analyses without restrictions or limitations from the sponsor.

RESULTS

Through August 31, 2001, 639 patients were enrolled in the MIRACLE ICD study program as detailed in Figure 1. Of those, 210 patients had mild HF symptoms (NYHA functional class II) and, by a priori protocol design, had a separate primary end point and are not included in this analysis. Sixty NYHA class III or IV patients underwent an implant attempt but did not proceed to the randomized therapy phase. A total of 369 patients included in the MIRACLE ICD study underwent successful implantation and were randomized (control group, n = 182; CRT group, n = 187). The baseline characteristics of the randomized patients, summarized in Table 1, were consistent with patients with moderate to severe HF and candidates for ICD therapy. Except for a higher percentage of patients with ischemic heart disease in the control group, the baseline clinical characteristics of the 2 groups were similar.

Crossovers From Randomized to Alternate Treatment

In the control group, 14 patients (8%) crossed over to CRT before the end of the randomized phase of the study. Biventricular pacing was activated early because of worsening symptoms of HF in 11 patients, bradycardia in 2 patients, and programming errors in 1 patient. In the CRT group, 10 patients (5%) crossed over from active biventricular pacing to no pacing before the end of the randomized phase. Biventricular pacing was deactivated due to LV lead dislodgement in 2 patients, diaphragmatic stimulation in 2 patients, and programming errors in 6 patients.

Primary Efficacy End Points

The results of the efficacy end points analyses are summarized in Table 2. An improvement in quality of life was observed in both study groups (Figure 2). However, the median decrease (improvement) in quality of life score between baseline and the 6-month visit was significantly higher in the CRT group compared with the control group (P = .02). Similarly, a significantly greater median decrease in NYHA functional class was measured in the CRT group compared with the control group (P = .007) (Figure 3). A similar increase between baseline and 6 months in median distance covered during 6-minute walking test was measured in both groups (Figure 2). When a LOCF analysis for surviving patients was performed, both the magnitude of changes in the primary end points and the P values for comparison between groups were nearly identical to those previously described in the analysis of paired data at 6 months (Table 2).

The treatment effect on quality of life score and NYHA functional class was not influenced by the use of a β-blocker, underlying heart disease (ischemic vs nonischemic), morphology of the QRS complex (left vs right bundle branch block), or the baseline duration of the QRS interval (P > .10 for all interactions

Table 3. Appropriate and Inappropriate ICD Treatment by Randomization Assignment and by CRT Treatment Received During 6-Month Randomization Period

<table>
<thead>
<tr>
<th>Category</th>
<th>Randomization Assignment</th>
<th>CRT Treatment Received</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control (n = 182)</td>
<td>CRT (n = 187)</td>
</tr>
<tr>
<td>No. of Patients</td>
<td>No. (%) of Patients</td>
<td>No. of Patients</td>
</tr>
<tr>
<td>Appropriate ICD shocks</td>
<td>154 (26)</td>
<td>155 (26)</td>
</tr>
<tr>
<td>Inappropriate ICD shocks</td>
<td>59 (13)</td>
<td>49 (13)</td>
</tr>
<tr>
<td>Appropriate: only ATP used</td>
<td>229 (37)</td>
<td>618 (32)</td>
</tr>
<tr>
<td>Inappropriate: only ATP used</td>
<td>32 (4)</td>
<td>21 (4)</td>
</tr>
</tbody>
</table>

Abbreviations: ATP, antitachycardia pacing; CRT, cardiac resynchronization therapy; ICD, implantable cardioverter defibrillator.

*Note that the difference in numbers between the randomized to CRT and CRT treatment received is due to crossovers. Furthermore, the analysis was for the treatment received and was performed on 180 patients having no CRT and 189 patients having CRT the majority of the time.
with randomization assignment). This analysis was not preplanned, however, and may have been underpowered.

Secondary Efficacy End Points
At 6 months, patients randomized to treatment with CRT exercised on the treadmill for a longer duration than at baseline, whereas treadmill exercise duration decreased in the control group (P < .001) (Table 2). A higher median increase in peak VO₂ was measured in the CRT than in the control group (P = .04). By echocardiographic analysis, there was a trend toward greater reductions in LV systolic and diastolic volumes in the CRT group (P = .06 for both), although changes in other measures of LV size and function were similar in both groups. Median changes in plasma neurohormones were similar in both groups, except for a greater decrease in epinephrine in the control group than the CRT group, a difference of borderline statistical significance (P = .05). A larger proportion of patients with CRT improved in their composite clinical response than in the control group and a smaller proportion worsened during the study period, but this was only a statistical trend (P = .07) (FIGURE 4).

Arrhythmic Events and Survival
During the 6-month randomization period, 47 patients (26%) in the control group and 42 patients (22%) in the CRT group experienced at least 1 spontaneous episode of ventricular tachycardia or fibrillation (P = .47). Of the spontaneous and treated episodes, outcomes of ICD therapy were recorded for 233 episodes in the control group and 678 episodes in the CRT group. Four episodes (1.7%) were not successfully terminated within the interval determined by device criteria in the control group vs 1 episode (0.1%) in the CRT group. These 5 episodes all eventually terminated spontaneously. There was no difference between the study groups in the detection times of ventricular fibrillation episodes. Furthermore, there was no difference in the number of patients receiving either appropriate or inappropriate ICD treatment, when comparisons are made by randomization assignment and by whether CRT was activated (TABLE 3). A total of 15 patients in the control group and 14 patients in the CRT group died during the 6-month follow-up. In each group, 3 of these deaths were characterized as sudden deaths. Cumulative survival at 6 months was 92.2% in the control group (95% CI, 87.2%-95.3%) vs 92.4% (95% CI, 87.5%-95.4%) in the CRT group (log rank P = .96). Of the 429 enrolled patients with at least 1 implant attempt, 5 (1.2%) died within 30 days of their latest implant attempt. Of the 429 patients undergoing an implant attempt, 120 patients (28%) experienced 159 complications from implant to hospital discharge. Of these 159 complications, 37 (23%) were related to the LV lead, including 15 coronary sinus dissections and 4 cardiac perforations. Other perioperative complications included HF decompensation in 6 patients, all treated with intravenous medications; heart block in 3 patients, all requiring bradycardia pacing support; muscle stimulation in 4 patients, treated by either a lead repositioning or lead replacement; pericardial effusion in
2 patients treated with a pericardioten-
tesis; pericarditis in 1 patient treated with
intravenous medications; hemo/ pneu-
mothorax in 3 patients treated with the
placement of a chest tube; ven-
tricular tachycardia and ventricular fi-
brillation in 5 patients, in which 3 pa-
tients were treated with external
defibrillation and 2 patients were treated
with intravenous medications; and el-
evated pacing thresholds or loss of cap-
ture in 7 patients, in which 6 patients
were treated with a lead repositioning
or lead replacement and 1 patient had a set
screw tightened in the connector block.

Fifty patients had an unsuccessful
cRT system implant but a successful
placement of an ICD-only system. Of
those 50 patients, 20 experienced a total
of 35 complications from the time of
hospital discharge through 6 months.
Heart failure decompensation was the
most common complication, account-
ing for 19 events (Table 4).

From hospital discharge to the end of
the 6-month randomization period, 175
(46%) of the 379 patients with success-
ful implants experienced 398 complica-
tions. The rate of device-related events
was substantially lower than the rates antici-
pated in the prespecified criteria of the
original study protocol. The frequency of
adverse events unrelated to the de-
vice or to HF did not differ significantly
between the 2 groups.

COMMENT
The improvements in quality of life and
NYHA functional class in patients with
moderate to severe HF, LV systolic dys-
function, wide QRS interval, and indica-
tions for an ICD were similar to those
observed in comparable patient popu-
lations without indications for ICDs.9,10,11
However, the absence of a positive treat-
ment effect on the 6-minute walking test
contrasts with these earlier trials and with the
improvements observed in this study with
the more objective measurements of
peak VO2 and treadmill exercise dura-
tion. Whether these discrepancies are
due to differences between patient
populations or to the different timing of
the 6-minute walking test (per-
formed before, instead of after, CRT sys-
tem implantation) remains uncertain.
Furthermore, although there was a
trend of decreased LV volumes and in-
creased ejection fraction in MIRACLE
ICD (Table 2), these observations were
not as compelling as those in the
MIRACLE study.11 Perhaps this is re-
lated to the fact that MIRACLE ICD pa-
tients, on the whole, were more ill (ie,
having an ICD indication) with less
chance for morphometric remodeling
benefits that might be associated with
cardiac resynchronization.

Although complications associated
with biventricular pacemaker and ICD
insertion were not trivial, the proce-
dure was generally well tolerated with ac-
ceptable morbidity. Of particular inter-
est was the incremental risk associated
with the placement of the LV electrode
and the impact of biventricular pacing
on the incidence of ventricular arrhyth-
mas and ICD functions, because all pa-
tients in this study were a priori candi-
dates for an ICD. Of the 19 patients
(4.4%) with either coronary sinus dis-
section or cardiac perforation, 11 ulti-
mately underwent a successful CRT sys-
tem implantation procedure, suggesting
that the incremental risk was quite low.
After successful CRT system implanta-
tion, 47 patients (12%) underwent LV
lead repositioning or replacement dur-
ing follow-up, which is comparable with
the rates observed in previously com-
mercialized LV lead models.11,26

In the control group, crossovers to
CRT were prompted by an inability to
medically manage congestive HF in 11
of 14 patients, whereas in the CRT group,
al crossovers to the alternate treatment
were due to programming errors, lead
dislodgment, or diaphragmatic pacing.
This low incidence of crossovers had no
effect on the results of the analyses, which
were performed on an intention-to-
treat basis.

Small uncontrolled studies have sug-
gested that CRT may prevent ventricu-
lar arrhythmias.27-29 However, a larger
randomized crossover study found no
survival benefit conferred by biven-
tricular pacing in HF patients with a
preexistent indication for an ICD.30 In
this study, the number of patients ex-
periencing ventricular arrhythmias was
similar in both treatment groups (Table
3). Perhaps the 6-month duration of the
randomization phase was too brief to
allow expression of the full therapeu-
tic effects of CRT. Considerably longer
follow-up has often been required to
demonstrate the benefits in pharma-
ceutical trials in HF. Another impor-
tant observation in this trial was that
detection of ventricular arrhythmias and
their successful treatment by the ICD
were unimpeded by the presence of bi-
ventricular pacing.

There were no differences in survival
or rates of hospitalization between the
control and the CRT groups. However,
this study was not designed with the
power to detect differences in survival
and the 6-month randomization period
may have been too brief to detect differ-
ences in hospitalization rates between the
treatment groups. A meta-analysis of ran-
domized controlled trials of cardiac re-
synchronization in symptomatic pa-
tients has suggested a reduction in
mortality from congestive HF with bi-
ventricular pacing strategies.31

Right ventricular pacing was infre-
quent in the control group, whereas the
CRT group was predominately biven-
tricular paced. The Dual Chamber and
VVI Implantable Defibrillator (DAVID)
trial32 showed that, in patients with life-
threatening ventricular arrhythmias, the
combined risk of death and hospital-
ization for worsening failure was higher
in patients exposed to dual-chamber
pacing with RV apical stimulation than
in patients left unpaced in their spon-
taneous rhythm. Although patients in
the control groups of both studies were
treated similarly, only approximately
one third of the patients in the DAVID
trial had a QRS duration of 130 ms or
more and only 12% were in NYHA
functional class III or IV HF and there-
fore were not eligible for randomiza-
tion in the MIRACLE ICD trial. Also,
differences in rates of hospitalizations
for HF in the DAVID trial became ap-
parent at 6 months, corresponding with
the duration of the randomized phase
of this study. These results raise the
question of a treatment-limiting effect of RV added to LV stimulation vs a dual-chamber or CRT group.

The major limitation of the MIRACLE ICD trial is that it was not designed or powered to detect a mortality or morbidity difference between control and CRT groups and the follow-up was relatively short.

In conclusion, CRT without interventional ICD functions improved the quality of life, functional capacity, and cardiopulmonary exercise test performance of patients with moderate to severe HF, a wide QRS interval, and life-threatening ventricular arrhythmias. These therapeutic effects were observed in the context of appropriate pre-existing and continuous vigorous medical management of these patients.

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