Cardiac Resynchronization and Death From Progressive Heart Failure
A Meta-analysis of Randomized Controlled Trials

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Nearly 5 million persons living in the United States have heart failure, with 550,000 new patients diagnosed annually. Despite substantial advances in drug therapy, heart failure was associated with 287,000 deaths and nearly 1 million hospital admissions in the United States in 1999. Heart failure generally leads to death by 1 of 2 mechanisms: sudden death or death from progressive heart failure. The relative proportion of patients dying from these 2 mechanisms varies with severity of heart failure. Patients with mild heart failure most commonly die suddenly from cardiac arrhythmias or vascular events like myocardial infarction. In contrast, patients who survive to the advanced stages of heart failure predominantly die from progressive heart failure, a gradual loss of ventricular function that leads to inadequate systemic perfusion and death.

A common finding in advanced heart failure is abnormal electrical activation. The purpose of this meta-analysis was to determine whether cardiac resynchronization reduces mortality from progressive heart failure.

Context
Progressive heart failure is the most common mechanism of death among patients with advanced heart failure. Cardiac resynchronization, a pacemaker-based therapy for heart failure, enhances cardiac performance and quality of life, but its effect on mortality is uncertain.

Objective
To determine whether cardiac resynchronization reduces mortality from progressive heart failure.

Data Sources

Study Selection
Eligible studies were randomized controlled trials of cardiac resynchronization for the treatment of chronic symptomatic left ventricular dysfunction. Eligible studies reported death, hospitalization for heart failure, or ventricular arrhythmia as outcomes. Of the 683 reports initially identified, 11 reports of 4 randomized trials with 1634 total patients were included in the meta-analysis.

Data Extraction
Trial reports were reviewed independently by 2 investigators in an unblinded standardized manner.

Data Synthesis
Follow-up in the included trials ranged from 3 to 6 months. Pooled data from the 4 selected studies showed that cardiac resynchronization reduced death from progressive heart failure by 51% relative to controls (odds ratio [OR], 0.49; 95% confidence interval [CI], 0.25-0.93). Progressive heart failure mortality was 1.7% for cardiac resynchronization patients and 3.5% for controls. Cardiac resynchronization also reduced heart failure hospitalization by 29% (OR, 0.71; 95% CI, 0.53-0.96) and showed a trend toward reducing all-cause mortality (OR, 0.77; 95% CI, 0.51-1.18). Cardiac resynchronization was not associated with a statistically significant effect on non-heart failure mortality (OR, 1.15; 95% CI, 0.65-2.02). Among patients with implantable cardioverter defibrillators, cardiac resynchronization had no clear impact on ventricular tachycardia or ventricular fibrillation (OR, 0.92; 95% CI, 0.67-1.27).

Conclusions
Cardiac resynchronization reduces mortality from progressive heart failure in patients with symptomatic left ventricular dysfunction. This finding suggests that cardiac resynchronization may have a substantial impact on the most common mechanism of death among patients with advanced heart failure. Cardiac resynchronization also reduces heart failure hospitalization and shows a trend toward reducing all-cause mortality.

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See also pp 712 and 754.
tion of the ventricles or electrical ventricular dyssynchrony.\textsuperscript{10,11} Ventricular dyssynchrony is manifested in an electrocardiogram as prolongation of the QRS interval, often in the pattern of left bundle-branch block. Prolongation of the QRS interval has been associated with diminished cardiac function\textsuperscript{12,13} and increased mortality.\textsuperscript{10} In recent years, cardiac pacemakers have been modified in an effort to correct ventricular dyssynchrony, a treatment referred to as cardiac resynchronization.\textsuperscript{14-16} Unlike traditional right ventricular pacing, cardiac resynchronization uses a left ventricular lead that is usually positioned in a coronary vein.\textsuperscript{15} A left ventricular lead ensures stimulation of the left ventricle at or near the time of right ventricular depolarization. This synchronized activation of the ventricles enhances cardiac function\textsuperscript{17-27} and reduces myocardial oxygen consumption.\textsuperscript{28} Cardiac resynchronization also improves exercise capacity, functional class, and quality of life.\textsuperscript{17,21,23,27,28,35} The effect of cardiac resynchronization on mortality, however, is uncertain.\textsuperscript{17,31,36}

We reasoned that cardiac resynchronization and its associated improvement in cardiac function might lead to decreased mortality from progressive heart failure. Published randomized trials of cardiac resynchronization have been inconclusive in this regard.\textsuperscript{17,31,36} To determine whether cardiac resynchronization decreases mortality from progressive heart failure, we conducted a meta-analysis.

\section*{METHODS}

\subsection*{Study Search}

We searched MEDLINE (1966-2002), EMBASE (1980-2002, week 24), the Cochrane Controlled Trials Register (Second Quarter, 2002), the National Institutes of Health ClinicalTrials.gov database of clinical trials, and the US Food and Drug Administration Web site (http://www.fda.gov) for reports of randomized trials comparing cardiac resynchronization vs control in patients with symptomatic left ventricular dysfunction. Because cardiac resynchronization terminology has not been standardized, searches were performed using multiple terms, including pacemaker; pacing; heart failure; dual-site; multisite; biventricular; resynchronisation; resynchronization; left ventricular preexcitation. We conducted additional searches using 65 author names and 24 trial acronyms frequently cited in narrative reviews of cardiac resynchronization, as well as modified versions of the Cochrane Optimal Search Strategy for randomized trials.\textsuperscript{37} To identify studies reported only at scientific meetings, we performed hand searches or electronic searches of the annual scientific sessions of the American College of Cardiology (1994-2002), the American Heart Association (1994-2001), the European Society of Cardiology (1994-2001), and the North American Society of Pacing and Electrophysiology (1994-2002). The bibliographies of 43 recent narrative review articles were also hand searched. All searches were limited to the years 1994 through 2002 because modern studies of cardiac resynchronization were first reported in 1994.\textsuperscript{34} Searches were performed in May and June of 2002.

\subsection*{Eligibility and Data Abstraction}

Reports of randomized trials of cardiac resynchronization for the treatment of heart failure in humans were eligible for inclusion in the meta-analysis. Randomized controlled trial was defined according to the National Library of Medicine.\textsuperscript{38} We included trials if they reported death, hospitalization because of heart failure, heart transplantation, and ventricular arrhythmia as outcomes. For crossover trials, only data from the first randomized crossover phase were included. Studies were excluded if another report with more complete and/or updated data was available from the same trial or if a report concerned research design only with no available data in our meta-analysis. Randomized controlled trials were both performed independently in an unblinded\textsuperscript{39} standardized manner by 2 reviewers (D.J.B. and E.A.B.). Abstracted data included eligibility criteria, baseline characteristics, interventions, outcomes, and reported methodological quality (internal validity). Outcomes of interest included numbers of patients experiencing death from progressive heart failure, death from any cause, hospitalization because of heart failure, heart transplantation, and ventricular arrhythmia. Trial methodological quality was assessed by abstracting reported use of intention-to-treat analysis and reported allocation generation, allocation concealment, and blinding.\textsuperscript{40} Disagreements between reviewers were resolved by consensus.

\subsection*{Data Analysis}

Odds ratio (OR) was chosen as the principal measure of effect. Because of relatively low event rates, odds closely approximated risk. Odds ratios from each included trial were pooled using random-effects models that used weighting based on inverse variance calculated according to DerSimonian and Laird.\textsuperscript{41} When there were multiple reports from the same trial, we used the most complete and/or recently reported data. To check for quantitative heterogeneity, \textit{X}\textsuperscript{2} tests were used. Quantitative analyses were performed on an
intention-to-treat basis and were confined to data derived from randomized follow-up periods. Sensitivity analyses were performed to assess the importance of different statistical models, baseline heart failure severity, individual trials, and missing data. Statistical analyses were done with Stata 7.0.42

RESULTS

Search Results

Our search for reports is summarized in Figure 1. We initially identified 6883 potentially relevant reports. After excluding 1202 duplicate reports, 5681 were initially screened based on titles and available abstracts. Of these, 5623 reports were excluded for reasons listed in Figure 1. Agreement between the 2 reviewers in the initial stage of screening was 97.6%. Full-text versions of the remaining 58 reports were then retrieved for detailed evaluation. Of these 58 reports, 47 reports were excluded (Figure 1). Among these 47 excluded reports were 3 meeting presentations from a trial with 64 randomized patients (MUSTIC-AF); these 3 meeting presentations were excluded because the reported data were derived, in part, from uncontrolled follow-up periods43,44 or because hospitalizations (1 in the treatment group and 2 in the control group) were not reported separately for the first 3-month crossover period.45 Also among the 47 excluded reports were 7 reports from 2 trials with 66 total randomized patients.20,23,46-50 These 7 reports from 2 trials were excluded from our study because follow-up during the first randomized crossover phases was 1 month. The remaining 11 reports17,31,51-59 of 4 randomized controlled trials were included in the meta-analysis.

Qualitative Findings

The 4 trials included in the meta-analysis were the CONTAK CD, InSync ICD, Multicenter InSync Randomized Clinical Evaluation (MIRACLE), and Multisite Stimulation in Cardiomyopathies (MUSTIC) trials (Table 1).17,31,51-59 In the CONTAK CD trial, 490 randomized patients were drawn from 581 enrolled patients of which 248 had planned 3-month follow-up and 333 had planned 6-month follow-up.51 Our mortality analysis of the MIRACLE trial is based on 532 randomized patients.37,58 Of these 532 patients, 71 were followed up for 3 months and 461 were followed up for 6 months;57 outcomes based on patients followed up for 6 months have been published.17

Baseline patient characteristics (Table 1) were similar in the 4 trials with mean ages ranging from 63 to 66 years and mean left ventricular ejection fractions ranging from 21% to 23%.31,51,55,58 In each of the trials, the majority of patients were men with moderate to severe heart failure at baseline (New York Heart Association [NYHA] functional class III and IV).31,51,55,58 In MUSTIC, 37% of patients had heart failure resulting from ischemic cardiomyopathy.31 In contrast, the majority of patients in each of the 3 other trials had ischemic cardiomyopathies.31,55,58 Baseline QRS duration, a measure of ventricular electrical dysynchrony, was similarly prolonged in each of the 4 trials with mean values ranging from 158 to 176 milliseconds.17,31,51,55 Dysynchrony was associated with left bundle-branch block in a majority of patients in each trial.31,51,55,58

Baseline angiotensin-converting enzyme inhibitor or angiotensin receptor blocker use was similarly high in all 4 trials and ranged from 87% to 96% (Table 1).31,51,55,58 In contrast, baseline β-blocker use was variable between the 4 trials and ranged from 28% in MUSTIC31 to 60% in InSync ICD.57 Patients with conventional ICD indications46 were included in CONTAK CD and InSync ICD, but were excluded from MIRACLE and MUSTIC.31,55,58 Both β-blockers and ICDs can improve survival among heart failure patients.51,61-64 Whether treatment interactions exist between cardiac resynchronization and β-blockers or ICDs is uncertain.

Patients with conventional indications for pacemaker implantation,60 such as sinus node dysfunction and

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Figure 1. Reports Evaluated for Inclusion in the Meta-analysis

FDA indicates US Food and Drug Administration.

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atrioventricular block, were excluded from all 4 trials (Table 1). In addition, patients with atrial arrhythmias, such as atrial fibrillation, were excluded from the 3 largest trials. Conventional pacemaker indications and atrial arrhythmias are common among patients with heart failure.

In each of the 4 trials, patients underwent implantation of an ICD or a pacemaker capable of cardiac resynchronization (Table 1). Patients were then randomized to cardiac resynchronization on vs cardiac resynchronization off groups. In CONTAK CD, 54 of 490 randomized patients underwent left ventricular epicardial lead placement via thoracotomy. The remaining patients in CONTAK CD and all patients in InSync ICD, MIRACLE, and MUSTIC received transvenous left ventricular leads. Follow-up during the randomized phase of each trial ranged from 3 to 6 months.

Measures of reported methodological quality (internal validity) were comparable among the 4 trials (Table 1). Method of allocation generation was not reported by the trials, and appropriateness of allocation concealment was either unclear or not reported. Single blinding was used in MUSTIC, and double blinding was used in the remaining 3 trials. Funding for each of the 4 trials was provided, at least in part, by the company whose device was the subject of the study.

Three trials reported the number of patients who underwent unscheduled crossover from one treatment group to another during randomized follow-up (Table 2). The rate of unscheduled crossover in these trials ranged from 0% to 6.9% for patients originally randomized to cardiac resynchronization and from 3.4% to 8.5% for patients originally randomized to no cardiac resynchronization. Assuming that patients who made unscheduled crossovers from one treatment group to another took on the event rates of their new treatment groups, unscheduled crossovers could be expected to

### Table 1. Characteristics of Trials Included in the Meta-analysis

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>CONTAK CD InSync ICD MIRACLE MUSTIC</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients randomized</td>
<td>490 554 532 58</td>
</tr>
<tr>
<td>Age, mean, y</td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td></td>
</tr>
<tr>
<td>LVEF, mean, %</td>
<td></td>
</tr>
<tr>
<td>NYHA functional class, range</td>
<td></td>
</tr>
<tr>
<td>Ischemic cardiomyopathy</td>
<td></td>
</tr>
<tr>
<td>QRS duration, mean, ms</td>
<td></td>
</tr>
<tr>
<td>LBBB</td>
<td></td>
</tr>
<tr>
<td>ACE inhibitor or ARB</td>
<td></td>
</tr>
<tr>
<td>β-blocker use</td>
<td></td>
</tr>
<tr>
<td>Patients with conventional ICD indication</td>
<td></td>
</tr>
<tr>
<td>Patients with conventional pacemaker indic</td>
<td></td>
</tr>
<tr>
<td>Patients with pacemaker contraindation</td>
<td></td>
</tr>
<tr>
<td>Patients with atrial arrhythmias</td>
<td></td>
</tr>
<tr>
<td>Intervention Cardiac resynchronization on vs off</td>
<td>Yes Yes Yes Yes</td>
</tr>
<tr>
<td>Device</td>
<td>ICD ICD Pacemaker Pacemaker</td>
</tr>
<tr>
<td>Device manufacturer</td>
<td>Guidant Medtronic Medtronic ELA Medical, Medtronic</td>
</tr>
<tr>
<td>Follow-up, randomized, mo</td>
<td>3-6 6 3-6 3 (first crossover period)</td>
</tr>
<tr>
<td>Reported internal validity</td>
<td></td>
</tr>
<tr>
<td>Allocation generation</td>
<td></td>
</tr>
<tr>
<td>Allocation concealment</td>
<td></td>
</tr>
<tr>
<td>Blinding</td>
<td></td>
</tr>
<tr>
<td>Intention-to-treat analysis</td>
<td></td>
</tr>
<tr>
<td>Events committee</td>
<td></td>
</tr>
<tr>
<td>Funding source</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin-receptor blocker; ICD, implantable cardioverter defibrillator; LBBB, left bundle-branch block; LVEF, left ventricular ejection fraction; MIRACLE, Multicenter InSync Randomized Clinical Evaluation; MUSTIC, Multisite Stimulation in Cardiomyopathies; NYHA, New York Heart Association; NR, not reported.

*Data are presented as number (percentage) unless otherwise indicated.
†Baseline characteristics are for 501 patients initially enrolled in trial.
‡Baseline characteristics are for 67 patients initially enrolled in trial.
§QRS duration is from 453 patients.
CARDIAC RESYNCHRONIZATION

decrease the calculated benefit or harm of cardiac resynchronization in the intention-to-treat analysis used in this meta-analysis. The percentage of patients who dropped out of studies prematurely during randomized follow-up for reasons other than death or heart transplantation ranged from 0.4% to 2.7% for patients randomized to cardiac resynchronization and from 0.8% to 2.7% for patients randomized to no cardiac resynchronization (Table 2).\textsuperscript{17,31,51,53}

Total hospitalization was reported by 2 of the 4 trials for patients with planned 6-month follow-up.\textsuperscript{39} In the InSync ICD trial, there were 573 all-cause hospitalization days among 186 cardiac resynchronization patients vs 703 all-cause hospitalization days among 176 control patients. In the MIRACLE trial, there were 275 all-cause hospitalization days among 230 cardiac resynchronization patients vs 664 all-cause hospitalization days among 231 control patients.

Although the 4 trials differ somewhat in terms of patients and interventions, they all focus on the same disorder and they all address the same questions in a substantially similar manner. Qualitative heterogeneity among the 4 trials is modest. Therefore, the results from the 4 trials were pooled, and a quantitative meta-analysis was performed.

Quantitative Findings

In each of the 3 largest trials,\textsuperscript{31,55,57} there was a statistically nonsignificant trend toward reduced death from progressive heart failure among patients treated with cardiac resynchronization vs controls (Figure 2A). When data from all 4 randomized trials (1634 total patients) were pooled using a random-effects model, however, cardiac resynchronization was associated with a statistically significant 51% reduction in death from progressive heart failure relative to controls (OR, 0.49; 95% confidence interval [CI], 0.25-0.93; Figure 2A). Pooled absolute rates of progressive heart failure mortality during 3 to 6 months of follow-up were 1.7% in patients treated with cardiac resynchronization and 3.5% in controls. To test for differences in the odds ratio of progressive heart failure mortality between the 4 trials, we performed a $\chi^2$ test for heterogeneity. By this measure, we did not find evidence of quantitative heterogeneity ($P = .85$).

Based on data from 3 trials and 1080 randomized patients,\textsuperscript{31,55,57} cardiac resynchronization decreased the combined end point of death from progressive heart failure or cardiac transplantation by 59% relative to controls (OR, 0.41; 95% CI, 0.19-0.87). Pooled absolute rates of death from progressive heart failure or cardiac transplantation during 3 to 6 months of follow-up were 1.9% in patients treated with cardiac resynchronization and 4.4% in controls.

In contrast to the beneficial effect of cardiac resynchronization on progressive heart failure mortality, cardiac resynchronization was not associated with a statistically significant effect on non–heart failure mortality (OR, 1.15; 95% CI, 0.65-2.02; Figure 2B). Pooled absolute rates of non–heart failure mortality over 3 to 6 months of follow-up were 3.2% in patients treated with cardiac resynchronization and 2.8% in controls.

Cardiac resynchronization was associated with a trend toward reduced all-cause mortality (OR, 0.77; 95% CI, 0.51-1.18; Figure 2C). Pooled absolute rates of all-cause mortality over 3 to 6 months of follow-up were 4.9% in patients treated with cardiac resynchronization and 6.3% in controls. As with death from progressive heart failure, we did not find evidence of quantitative heterogeneity for all-cause mortality between the 4 trials ($\chi^2$ test for heterogeneity; $P = .83$).

Cardiac resynchronization reduced hospitalization for heart failure by 29% (OR, 0.71; 95% CI, 0.53-0.96; Figure 3). Pooled absolute rates of hospitalization for heart failure during 3 to 6 months of follow-up were 13% in patients treated with cardiac resynchronization and 17.4% in controls. These results are based on 1497 randomized

| Table 2. Unscheduled Treatment Crossovers and Dropouts* |

<table>
<thead>
<tr>
<th>Study</th>
<th>Randomized to CR</th>
<th>Randomized to No CR</th>
<th>Randomized to CR</th>
<th>Randomized to No CR</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. (%) of Dropouts</td>
<td>No. (%) of Crossovers</td>
<td>No. of Patients</td>
<td>No. of Patients</td>
</tr>
<tr>
<td>CONTAK CD\textsuperscript{31}</td>
<td>NR</td>
<td>NR</td>
<td>245</td>
<td>1 (0.4)</td>
</tr>
<tr>
<td>InSync ICD\textsuperscript{31,55}†</td>
<td>186</td>
<td>10 (5.4)</td>
<td>176</td>
<td>15 (8.5)</td>
</tr>
<tr>
<td>MIRACLE\textsuperscript{4}</td>
<td>228</td>
<td>0</td>
<td>225</td>
<td>10 (4.4)</td>
</tr>
<tr>
<td>MUSTIC\textsuperscript{31,57}§</td>
<td>29</td>
<td>2 (6.9)</td>
<td>29</td>
<td>1 (3.4)</td>
</tr>
<tr>
<td>Total</td>
<td>443</td>
<td>12 (2.7)</td>
<td>430</td>
<td>26 (6.0)</td>
</tr>
</tbody>
</table>

Abbreviations: CR, cardiac resynchronization; MIRACLE, Multicenter InSync Randomized Clinical Evaluation; MUSTIC, Multisite Stimulation in Cardiomyopathies; NR, not reported.

*Unscheduled treatment crossovers refers to the number of randomized patients who switched treatments during randomized follow-up. Dropouts refers to the number of randomized patients who left a study prematurely during randomized follow-up for reasons other than heart transplantation or death.

†New York Heart Association Class III and IV patients.

§Six-month follow-up patients.

First randomized crossover phase of trial.
Figure 2. Death Among Patients Randomized to Cardiac Resynchronization vs No Resynchronization

### A. Progressive Heart Failure Mortality

<table>
<thead>
<tr>
<th>Study</th>
<th>No. of Patients</th>
<th>No. (%) of Heart Failure Deaths</th>
<th>Weight, %</th>
<th>Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CONTAK CD51</td>
<td>245</td>
<td>4 (1.6)</td>
<td>29.6</td>
<td>0.44 (0.13-1.43)</td>
</tr>
<tr>
<td>InSync ICD55</td>
<td>272</td>
<td>6 (2.2)</td>
<td>39.9</td>
<td>0.61 (0.22-1.71)</td>
</tr>
<tr>
<td>MIRACLE57</td>
<td>263</td>
<td>4 (1.5)</td>
<td>30.6</td>
<td>0.40 (0.12-1.29)</td>
</tr>
<tr>
<td>MUSTIC31</td>
<td>29</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>809</td>
<td>14 (1.7)</td>
<td></td>
<td>0.49 (0.25-0.93)</td>
</tr>
</tbody>
</table>

### B. Non-Heart Failure Mortality

<table>
<thead>
<tr>
<th>Study</th>
<th>No. of Patients</th>
<th>No. (%) of Non-Heart Failure Deaths</th>
<th>Weight, %</th>
<th>Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CONTAK CD51</td>
<td>245</td>
<td>7 (2.9)</td>
<td>28.4</td>
<td>1.00 (0.35-2.89)</td>
</tr>
<tr>
<td>InSync ICD55</td>
<td>272</td>
<td>8 (2.9)</td>
<td>30.4</td>
<td>1.19 (0.43-3.33)</td>
</tr>
<tr>
<td>MIRACLE57</td>
<td>263</td>
<td>10 (3.8)</td>
<td>38.2</td>
<td>1.14 (0.46-2.86)</td>
</tr>
<tr>
<td>MUSTIC31</td>
<td>29</td>
<td>1 (3.4)</td>
<td>3.1</td>
<td>3.11 (0.12-79.4)</td>
</tr>
<tr>
<td>Overall</td>
<td>809</td>
<td>26 (3.2)</td>
<td>1.15</td>
<td>0.65-2.02</td>
</tr>
</tbody>
</table>

### C. All-Cause Mortality

<table>
<thead>
<tr>
<th>Study</th>
<th>No. of Patients</th>
<th>No. (%) of All-Cause Deaths</th>
<th>Weight, %</th>
<th>Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CONTAK CD51</td>
<td>245</td>
<td>11 (4.5)</td>
<td>28.9</td>
<td>0.67 (0.31-1.48)</td>
</tr>
<tr>
<td>InSync ICD55</td>
<td>272</td>
<td>14 (5.1)</td>
<td>34.0</td>
<td>0.85 (0.41-1.75)</td>
</tr>
<tr>
<td>MIRACLE57</td>
<td>263</td>
<td>14 (5.3)</td>
<td>35.4</td>
<td>0.74 (0.36-1.51)</td>
</tr>
<tr>
<td>MUSTIC31</td>
<td>29</td>
<td>1 (3.4)</td>
<td>1.7</td>
<td>3.11 (0.12-79.4)</td>
</tr>
<tr>
<td>Overall</td>
<td>809</td>
<td>40 (4.9)</td>
<td>0.77</td>
<td>0.51-1.18</td>
</tr>
</tbody>
</table>

CI indicates confidence interval; CR, cardiac resynchronization; MIRACLE, Multicenter InSync Randomized Clinical Evaluation; MUSTIC, Multisite Stimulation in Cardiomyopathies. Odds ratio less than 1.0 favors CR. Weight refers to weight given to each trial in statistical model. Boxed area is proportional to weight. A, odds ratio refers to odds ratio of death from progressive heart failure among patients randomized to CR vs no CR. Heterogeneity $\chi^2=0.34$ ($P=85$). B, Odds ratio refers to the odds ratio of non–heart failure death among patients randomized to CR vs no CR. Heterogeneity $\chi^2=0.43$ ($P=93$). C, Odds ratio refers to the odds ratio of death from all causes among patients randomized to CR vs no CR. Heterogeneity $\chi^2=0.90$ ($P=83$).
patients and include all randomized patients in CONTAK CD and InSync ICD, as well as 453 six-month follow-up patients in MIRACLE.\textsuperscript{17} We did not include heart failure hospitalization results from MUSTIC because these data were reported as numbers of hospitalizations (9 in the control group and 3 in the cardiac resynchronization group) as opposed to numbers of different patients hospitalized.\textsuperscript{31}

Among 1044 patients with ICDs,\textsuperscript{51,55} cardiac resynchronization was not associated with a statistically significant reduction in patients experiencing ventricular tachycardia or ventricular fibrillation (OR, 0.92; 95% CI, 0.67-1.27). Overall, 17.2% of ICD patients treated with cardiac resynchronization had ventricular tachycardia or ventricular fibrillation during 3 to 6 months of follow-up vs 18.4% of controls.

**Sensitivity Analyses**

We performed sensitivity analyses to determine the effect of plausible changes in assumptions on the association between cardiac resynchronization and reduced mortality from progressive heart failure (Table 3). First, we compared fixed effects and random effects statistical models. The 2 types of models yielded identical results.

Second, we excluded NYHA functional class II patients (mild heart failure) and analyzed data only from class III and class IV patients (moderate to severe heart failure). We performed this subgroup analysis because the US Food and Drug Administration has approved cardiac resynchronization devices for class III and IV patients. As shown in Table 3, the point estimate of the OR of death from progressive heart failure for 1179 class III and IV patients (0.51) was very similar to the OR for all 1634 combined class II, III, and IV patients (0.49).

Third, we compared outcomes among patients who received pacemakers vs those who received ICDs (Table 3). Both classes of devices, pacemakers and ICDs, were capable of cardiac resynchronization. The point estimate of the OR of death from progressive heart failure for 1044 ICD patients (0.53)\textsuperscript{31,35} was similar to the OR for 590 pacemaker patients (0.40).\textsuperscript{31,57}

Fourth, we assessed the influence of individual trials on the pooled OR of death from progressive heart failure. With exclusion of individual trials, the

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**Table 3.** Sensitivity Analysis of the Effect of Cardiac Resynchronization on Death From Progressive Heart Failure

<table>
<thead>
<tr>
<th>Study</th>
<th>No. of Trials</th>
<th>No. of Patients Analyzed</th>
<th>Death From Progressive Heart Failure, Odds Ratio (95% Confidence Interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Statistical model</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Random effects</td>
<td>4</td>
<td>1634</td>
<td>0.49 (0.25-0.93)</td>
</tr>
<tr>
<td>Fixed effects</td>
<td>4</td>
<td>1634</td>
<td>0.49 (0.25-0.93)</td>
</tr>
<tr>
<td>NYHA baseline functional class</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>II-IV</td>
<td>4</td>
<td>1634</td>
<td>0.49 (0.25-0.93)</td>
</tr>
<tr>
<td>III-IV</td>
<td>4</td>
<td>1179</td>
<td>0.51 (0.26-1.0)</td>
</tr>
<tr>
<td>Pacemaker vs ICD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ICD trials</td>
<td>2</td>
<td>1044</td>
<td>0.53 (0.24-1.15)</td>
</tr>
<tr>
<td>Pacemaker trials</td>
<td>2</td>
<td>590</td>
<td>0.40 (0.12-1.20)</td>
</tr>
<tr>
<td>Analysis with all studies except CONTAK CD</td>
<td>3</td>
<td>1144</td>
<td>0.51 (0.24-1.1)</td>
</tr>
<tr>
<td>InSync ICD</td>
<td>3</td>
<td>1080</td>
<td>0.42 (0.18-0.96)</td>
</tr>
<tr>
<td>MIRACLE</td>
<td>3</td>
<td>1102</td>
<td>0.53 (0.24-1.15)</td>
</tr>
<tr>
<td>MUSTIC</td>
<td>3</td>
<td>1576</td>
<td>0.49 (0.25-0.93)</td>
</tr>
</tbody>
</table>

Abbreviations: ICD, implantable cardioverter defibrillator; MIRACLE, Multicenter InSync Randomized Clinical Evaluation; MUSTIC, Multisite Stimulation in Cardiomyopathies; NYHA, New York Heart Association.

Odds ratio, pooled odds ratio of death from progressive heart failure among patients treated with cardiac resynchronization vs no cardiac resynchronization. Odds ratio less than 1.0 favors cardiac resynchronization.
cardiac resynchronization vs control. Cardiac resynchronization has previously been shown to improve exercise capacity, functional class, and quality of life.17,21,23,27,29,35 By pooling data from randomized trials in a meta-analysis, we now show that the benefits of cardiac resynchronization can be extended to include reduced death from progressive heart failure. This finding is important because approximately one half of all deaths among patients with severe heart failure results from progressive cardiac dysfunction.5,8,9

Several lines of supportive evidence65 strengthen the conclusion that cardiac resynchronization reduces mortality from progressive heart failure. First, such a conclusion is biologically plausible given the improvement in cardiac function associated with cardiac resynchronization.17-27 Second, a reduction in progressive heart failure mortality is concordant with other known benefits of cardiac resynchronization such as improved exercise capacity, functional class, and quality of life.17,21,23,27,29-35 Third, the favorable effect of cardiac resynchronization on progressive heart failure mortality is consistent with other related outcomes from our meta-analysis including decreased heart failure hospitalization and a trend toward decreased all-cause mortality. Fourth, the magnitude of the effect, a 51% relative reduction in progressive heart failure mortality, is large. Lastly, sensitivity analyses showed that the estimated effect of cardiac resynchronization on death from progressive heart failure was consistent under a plausible range of assumptions.

Both long-term β-blocker therapy and cardiac resynchronization improve cardiac function.17,66 β-Blockers and cardiac resynchronization might therefore be expected to produce comparable reductions in death from progressive heart failure compared with controls. In fact, long-term treatment with metoprolol CR/XL was associated with a 49% relative reduction in death from worsening heart failure in the Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure (MERIT-HF) trial,2 an effect very similar to the 51% reduction observed in our study. Unlike β-blockers, cardiac resynchronization does not require dose titration or daily patient compliance. Cardiac resynchronization does, however, require an invasive procedure. Cardiac resynchronization may allow enhancement of β-blocker therapy in patients with heart failure by prevention of bradycardia.

We found an encouraging, but statistically nonsignificant, 23% relative

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reduction in all-cause mortality among patients treated with cardiac resynchronization vs controls. This trend in reduced all-cause mortality largely reflects a reduction in death from progressive heart failure. Cardiac resynchronization had no statistically significant effect on non–heart failure mortality. We speculate that several factors, including sample size, severity of heart failure, and length of follow-up, may explain why reduced death from progressive heart failure did not translate into a statistically significant improvement in survival. In addition, the relatively wide CI around the OR of non–heart failure death (OR, 1.15; 95% CI, 0.65-2.02) leaves open the possibility that cardiac resynchronization may increase non–heart failure mortality, thereby offsetting some of the favorable effect cardiac resynchronization has on death from progressive heart failure. Assuming average follow-up of 1 year, type I error rate of 5%, and power of 90%, we estimate that a future meta-analysis will require outcomes derived from approximately 2000 to 3000 additional patients (beyond the 1634 included in our study) in order to detect a statistically significant reduction in all-cause mortality among patients treated with cardiac resynchronization vs controls. 

Randomized trials have produced variable results regarding the effect of cardiac resynchronization on heart failure hospitalization. Two of the trials we analyzed showed a statistically significant reduction in heart failure hospitalization associated with cardiac resynchronization, whereas 2 trials did not. By pooling randomized trial data, however, we found that cardiac resynchronization was associated with a statistically significant 29% relative reduction in heart failure hospitalization. This finding has potentially important economic implications because, in 2000, aggregate charges for heart failure hospitalizations in the United States exceeded $14 billion. Determining whether the up-front costs of cardiac resynchronization are subsequently offset by reduced expenditures for hospitalization will require further study.

Published studies, with a combined total of 93 patients, have reported that cardiac resynchronization reduces the occurrence of ventricular arrhythmias. Based on pooled data from 2 trials with 1044 patients with ICDs, we were unable to confirm these findings. We found no statistically significant reduction in ventricular arrhythmias among patients treated with cardiac resynchronization (OR, 0.92; 95% CI, 0.67-1.27). This discrepancy may be the result of differences in patient populations, definitions of ventricular arrhythmias, or methods for detection of arrhythmias. Our analysis suggests that if cardiac resynchronization does have a favorable effect on ventricular arrhythmias, the magnitude of the effect is small. Our results also suggest that a cardiac resynchronization-mediated reduction in death from progressive heart failure does not appear to be offset by a large increase in the incidence of ventricular arrhythmias.

Patients enrolled in the trials that we analyzed had moderate to severe heart failure symptoms, prolonged QRS intervals, and moderate to severe left ventricular systolic dysfunction. These characteristics are typical of approximately 10% of heart failure patients. Thus, the results of our study are potentially generalizable to approximately 500,000 patients in the United States. Patients with atrial arrhythmias or conventional pacemaker indications were excluded from the trials that we analyzed. Results from our meta-analysis therefore cannot be generalized to these important subsets of heart failure patients. Our study has potential limitations. First, our results may have been influenced by publication bias, the publication or non-publication of research findings, depending on the nature and direction of the results. We minimized the possible influence of publication bias by performing an extensive search. This search yielded 6883 potentially relevant reports, 1355 of which were not in the form of published journal articles. Although we generated funnel plots to check for publication bias, their utility is probably limited because of the relatively small number of trials included in our study. A second potential limitation is our use of data from trials reported in formats other than journal articles. Of the 4 trials included in the meta-analysis, only 2 were reported in the form of journal articles. Some have suggested that inclusion of unpublished studies in meta-analyses is inappropriate because such studies have not undergone peer review. However, in an analysis of 135 systematic reviews, McAuley and colleagues found that failure to include unpublished data in meta-analyses was associated with exaggerated claims of treatment efficacy. Therefore, our inclusion of nonjournal article reports likely enhances the validity of our results. Furthermore, the nonjournal article reports we included had previously undergone scrutiny by the US Food and Drug Administration. A third potential limitation of our study is the relatively short 3- to 6-month patient follow-up periods of the trials we analyzed. Although we cannot conclude that cardiac resynchronization confers long-term reductions in death and hospitalization from worsening heart failure, the large relative reductions in these end points after 3 to 6 months of follow-up are encouraging. A reversal of the benefits of cardiac resynchronization after 6 months would be unexpected because uncontrolled evidence shows that cardiac resynchronization is well tolerated after 2 years of ongoing treatment. A final potential limitation of our study is that determination of mechanism of death may not always be straightforward, even in well-organized trials like the ones we analyzed. Difficulty in classifying the mechanism of death usually arises when a patient dies suddenly or in an unwitnessed manner, and assignment of arrhythmia as mode of death is often gradual, and because patients with end-stage heart failure are frequently hospitalized and closely monitored. Therefore, it is unlikely that misclassification of deaths from progres-
sive heart failure accounts for all of the observed treatment effect.

In summary, cardiac resynchronization reduces mortality from progressive heart failure in patients with symptomatic left ventricular dysfunction and ventricular dyssynchrony. Cardiac resynchronization may have a substantial impact on the most common mechanism of death among patients with advanced heart failure. Cardiac resynchronization also reduces heart failure hospitalization and shows a trend toward reducing all-cause mortality. Ongoing and future trials will not only more precisely measure the effect of cardiac resynchronization on all-cause mortality, but also will assess the economic impact of cardiac resynchronization and better define those patients who will derive greatest benefit from this promising treatment.

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