Cardiac Resynchronization Therapy for Patients With Left Ventricular Systolic Dysfunction
A Systematic Review

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Heart failure is the fastest growing cardiovascular diagnosis in the United States, with a community prevalence of 2.5% in adults, and the direct and indirect costs of heart failure exceed $33 billion per year.¹ Despite many advances in diagnosis and pharmacotherapy for heart failure during the past 2 decades, morbidity and mortality remain high and quality of life is poor for many patients. Thus, there is increasing enthusiasm for the therapeutic potential of atrial-synchronized biventricular pacemakers (cardiac resynchronization therapy [CRT]) in patients with heart failure and left ventricular (LV) systolic dysfunction. CRT is designed to eliminate the delay in activation of the LV free wall found in many patients with LV systolic dysfunction and thereby improves me-

Context Left ventricular (LV) systolic dysfunction causes substantial morbidity and mortality, even with optimal pharmacotherapy. Atrial-synchronized biventricular pacemakers (cardiac resynchronization therapy [CRT]) received US Food and Drug Administration (FDA) approval for use in selected patients with LV systolic dysfunction in 2001.

Objective To summarize the current evidence base for the efficacy, effectiveness, and safety of CRT in patients with LV systolic dysfunction.

Evidence Acquisition A search of multiple electronic databases until November 2006 was supplemented by hand searches of reference lists of included studies and review articles, proceedings booklets from meetings, FDA reports, and contact with primary study authors and device manufacturers. A total of 14 randomized trials (4420 patients) were included for the CRT efficacy review, 106 studies (9209 patients) for the CRT effectiveness review, and 89 studies (9677 patients) reported safety outcomes with implantation of a CRT device.

Evidence Synthesis All patients in the CRT studies had LV systolic dysfunction (mean LV ejection fraction [LVEF] range, 21%-30%), prolonged QRS duration (mean range, 155-209 milliseconds), and 91% had New York Heart Association (NYHA) class 3 or 4 heart failure symptoms despite optimal pharmacotherapy. CRT improved LVEF (weighted mean difference, 3.0%; 95% confidence interval [CI], 0.9%-5.1%), quality of life (weighted mean reduction in Minnesota Living With Heart Failure Questionnaire, 8.0 points; 95% CI, 5.6-10.4 points), and functional status (improvements of ≥1 NYHA class were observed in 59% of CRT recipients in the randomized trials). CRT decreased hospitalizations by 37% (95% CI, 21%-51%), prolonged QRS duration (mean range, 155-209 milliseconds), and 91% had New York Heart Association (NYHA) class 3 or 4 heart failure symptoms despite optimal pharmacotherapy. CRT decreased hospitalizations by 37% (95% CI, 7%-57%), and all-cause mortality decreased by 22% (95% CI, 9%-33%). Implant success rate was 93.0% (95% CI, 92.2%-93.7%) and 0.3% of patients died during implantation (95% CI, 0.1%-0.6%). During a median 11-month follow-up, 6.6% (95% CI, 5.6%-7.4%) of CRT devices exhibited lead problems and 5% (95% CI, 4%-7%) malfunctioned.

Conclusions CRT reduces morbidity and mortality in patients with LV systolic dysfunction, prolonged QRS duration, and NYHA class 3 or 4 symptoms when combined with optimal pharmacotherapy. The incremental benefits of combined CRT plus implantable cardioverter-defibrillator devices vs CRT-alone devices in patients with LV systolic dysfunction remain uncertain.

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mechanical synchrony, which in turn increases LV filling time, reduces mitral regurgitation, and reduces septal dyskinesis.

Although previous systematic reviews2–4 have reported morbidity and mortality benefits with CRT therapy in randomized controlled trials (RCTs), there were areas of uncertainty. First, although these earlier systematic reviews focused on randomized efficacy trials, the generalizability of their results to clinical practice were unknown (particularly with respect to response rates, clinical effects, and safety when these devices are used in routine practice outside of clinical trial centers and in less selected patients). Second, none of the earlier reviews was able to clarify the incremental benefits conferred by CRT devices with implantable cardioverter-defibrillator (ICD) capability (combined CRT-ICD devices) over CRT-alone devices, or were these earlier reviews able to define which patient groups would benefit most from these devices. Finally, a number of RCTs have been published since the earlier systematic reviews were performed and their impact on the pooled evidence base was unknown.

Our systematic review summarizes the current evidence regarding the efficacy (outcomes in randomized trial participants), effectiveness (outcomes in clinical settings), safety (in both randomized trial participants and in clinical settings), and cost-effectiveness of CRT with or without an ICD in patients with LV systolic dysfunction.

EVIDENCE ACQUISITION

Search Strategy

We sought studies that (1) reported mortality, hospitalization, changes in functional outcomes (New York Heart Association [NYHA] class, 6-minute walk test, LV ejection fraction [LVEF], and/or quality of life), or peri-implant/postimplant safety with CRT in (2) patients with LV systolic dysfunction (LVEF ≤ 35%, whether or not heart failure symptoms were present) that (3) followed participants for at least 2 weeks, (4) had more than 25 participants, (5) reported original research, and (6) represented the primary report from studies with multiple publications. We searched MEDLINE, Ovid MEDLINE In-Process and other non-indexed citations, Cochrane CENTRAL Register of Controlled Trials, Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects, Health Technology Assessment Database, EMBASE, Science Citation Index Expanded (via Web of Science), International Pharmaceutical Abstracts, PubMed, National Library of Medicine Gateway, OCLC (Online Computer Library Center) Proceedings First and Papers First, CRISP (Computer Retrieval of Information on Scientific Projects), various trial registries (including the National Research Register [UK], Australian Clinical Trials Registry, clinicaltrials.gov, and current controlled trials), and US Food and Drug Administration reports.

In addition, we reviewed all abstracts from the annual Heart Rhythm Society meetings, the reference lists of review articles and included studies, and contacted authors of included studies for additional citations and information. Additional data were also sought from device manufacturers, including Medtronic Inc (Minneapolis, Minn), Boston Scientific (formerly Guidant Corp, Indianapolis, Ind), and St Jude Medical Inc (St Paul, Minn). The search was not limited by language or publication status.

The search terms included biventricular pacing, biventricular pacer, biventricular stimulation, BiV, artificial cardiac pacing, chronic cardiac failure resynchronization therapy, single chamber pacing, dual chamber pacing, cardiac resynchronization, Medtronic, InSync, ELA medical, Guidant, St Jude, congestive heart failure, CHF, chronic heart failure, and heart diseases.

Study Selection

To address the efficacy of CRT in ideal patients and practice settings, we analyzed RCTs that compared CRT or combined CRT-ICD devices with either placebo pacing, right ventricular pacing, or drug therapy alone (or ICD alone for RCTs testing combined CRT-ICD devices). To address the effectiveness of CRT in usual clinical practice, we analyzed observational studies with contemporaneous comparison groups (eg, cohort studies). To address device safety, we included data for CRT recipients from RCTs and observational studies (including those without contemporaneous control groups, such as case series and clinical registry data).

Data Extraction and Analysis

Study selection, quality assessment (using the Jadad scale5 and evaluation of adequacy of allocation concealment for RCTs, and using the Downs and Black checklist6 for observational studies), and data extraction were completed in duplicate and independently. For dichotomous results (congestive heart failure hospitalizations), we calculated relative risks (RRs) and for continuous variables (eg, 6-minute walk test), we calculated weighted mean differences for the pooled estimates. Random-effects models were used for analyses in Review Manager 4.2.5 (The Cochrane Collaboration, Copenhagen, Denmark). All results were reported with 95% confidence intervals (CIs). The I² statistic was used to describe the percentage of total variation across studies that is due to heterogeneity rather than chance (a value of 0% indicates limited heterogeneity, and larger values demonstrate increasing heterogeneity).7 Device efficacy in different patient subgroups was explored using meta-regression analyses.

EVIDENCE SYNTHESIS

Literature Search

From 7110 citations, we identified 14 RCTs8–21 (4420 patients) for determining CRT efficacy, 106 studies (9209 patients from 2 controlled nonrandomized studies, 91 prospective observational studies, and 13 retrospective observational studies) evaluating CRT effectiveness,22–127 and 89 studies (9677...
patients from 14 RCTs, 2 controlled non-randomized studies, 63 prospective observational studies, and 10 retrospective observational studies) reporting success rates and safety outcomes with implantation of a CRT device (Figure 1).* A full list of search strategies, search results, and quality assessments for each included study are available at http://www.ahrq.gov/clinic/tp/defibtp.htm.

Description of Included Patients in the RCTs

All patients in the CRT RCTs had LV systolic dysfunction (mean LVEF range, 21%-30%), prolonged QRS duration (mean QRS range, 155-209 milliseconds), and heart failure symptoms (91% were NYHA class 3 or 4 at baseline and 9% were NYHA class 2). The RCTs attempted to ensure participants were treated with optimal pharmacotherapy (angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers, plus β-blockers, and spironolactone in eligible patients) at baseline, and all comparisons were thus of CRT plus pharmacotherapy vs pharmacotherapy alone. The mean (SD) age of trial participants was 65.4 (10.8) years; 72% were male and 5% had atrial fibrillation (data available upon request). Of the patients in the intervention groups, 1310 (47%) received CRT alone and 1474 (53%) received a combined CRT-ICD device. Eleven of the RCTs (n = 2166)8–14,16–18,21 randomized patients after successful CRT implantation; 3 RCTs (n = 2439)13,19,20 randomized patients before attempted CRT implantation. All 2 of the RCTs14,17 reported industry funding.

Observational Studies

All patients in the CRT observational studies had LV systolic dysfunction (mean LVEF range, 17%-35%) and prolonged QRS duration (mean QRS range, 140–206 milliseconds). Patient demographics were similar to the participants in the CRT RCTs (mean [SD] age, 66 [10] years; 77% were male and virtually all had heart failure symptoms at baseline [8% NYHA class 2 and 91% NYHA class 3 or 4]).

Efficacy of CRT

In the RCTs, 59% of CRT recipients improved by at least 1 NYHA class between baseline and 6 months vs 37% of controls (RR, 1.55; 95% CI, 1.25-1.92 for improving at least 1 NYHA class with CRT). Compared with controls, patients assigned to CRT demonstrated improvements in LVEF (weighted mean difference, 3.0%; 95% CI, 0.9%-5.1%), 6-minute walk test distance (weighted mean difference, 24 m; 95% CI, 13-35 m), and quality of life (weighted mean difference in Minnesota Living With Heart Failure Questionnaire, 8.0 points; 95% CI, 5.6-10.4 points).

The percentage of patients hospitalized for heart failure was 27% in controls and 19% in patients assigned to CRT (RR, 0.63; 95% CI, 0.43-0.93) (Figure 2), and all-cause mortality was 13.2% in patients assigned to CRT vs 15.5% in controls (RR, 0.78; 95% CI, 0.67-0.91) (Figure 3). The survival benefit was driven largely by reductions in progressive heart failure deaths (RR, 0.64; 95% CI, 0.49-0.84). Although the mortality reduction with CRT was evident by 6 months in these trials, the mortality reduction was larger in those RCTs with the longest follow-up. For example, a long-term extension of the CARE-HF trial137 confirmed that the relative survival benefits of CRT were stable (constant hazard ratio), and as such the absolute magnitude of benefit increased substantially over time. Consequently, although our meta-analysis demonstrated a number needed to treat to prevent 1 death of 29 patients at 6 months, the CARE-HF trial follow-up data demonstrated the numbers needed to treat to prevent 1 death of 13 patients at 2 years and 9 patients at 3 years.137 The long-term impact of


Figure 1. Study Flow
Figure 2. Effect of CRT on Proportion of Patients Hospitalized for Heart Failure (Randomized Trial Data)

<table>
<thead>
<tr>
<th>Source</th>
<th>CRT</th>
<th>Control</th>
<th>Relative Risk (95% Confidence Interval)</th>
<th>Favors</th>
<th>Favors</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRT Alone vs Medical Therapy</td>
<td>CRT</td>
<td>Control</td>
<td>0.33 (0.10-1.11)</td>
<td>Favors CRT</td>
<td>Favors Control</td>
</tr>
<tr>
<td>MUSTIC-SR,14 2001</td>
<td>3/29</td>
<td>9/29</td>
<td>0.33 (0.10-1.11)</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>MIRACLE,15 2002</td>
<td>19/228</td>
<td>34/225</td>
<td>0.52 (0.30-0.90)</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>MUSTIC-AF,11 2002</td>
<td>1/25</td>
<td>2/18</td>
<td>0.90 (0.04-3.67)</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>FD-CHF,9 2003</td>
<td>1/22</td>
<td>7/22</td>
<td>0.14 (0.02-1.07)</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>CARE-HF,19 2005</td>
<td>72/409</td>
<td>133/404</td>
<td>0.53 (0.42-0.69)</td>
<td>□</td>
<td>□</td>
</tr>
</tbody>
</table>

Subtotal | 95/713 | 185/698 | 0.51 (0.41-0.64) | □ | □ |

Test for Heterogeneity: $\chi^2 = 3.72$; $P = .93$; $I^2 = 0$
Test for Overall Effect: $Z = 3.16$; $P = .002$

CRT + ICD vs ICD Alone

<table>
<thead>
<tr>
<th>Source</th>
<th>CRT</th>
<th>Control</th>
<th>Relative Risk (95% Confidence Interval)</th>
<th>Favors</th>
<th>Favors</th>
</tr>
</thead>
<tbody>
<tr>
<td>CONTAK-CD,13 2003</td>
<td>32/245</td>
<td>39/245</td>
<td>0.82 (0.53-1.26)</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>MIRACLE-ICD,10 2003</td>
<td>85/187</td>
<td>78/182</td>
<td>1.06 (0.84-1.33)</td>
<td>□</td>
<td>□</td>
</tr>
</tbody>
</table>

Subtotal | 117/432 | 117/427 | 1.00 (0.80-1.24) | □ | □ |

Test for Heterogeneity: $\chi^2 = 11.0$; $P = .29$; $I^2 = 8.8$
Test for Overall Effect: $Z = 0.04$; $P = .97$

Total | 212/1145 | 302/1125 | 0.63 (0.43-0.93) | □ | □ |

Test for Heterogeneity: $\chi^2 = 23.08$; $P < .001$; $I^2 = 74.0$
Test for Overall Effect: $Z = 2.34$; $P = .02$

Figure 3. Effect of CRT on All-Cause Mortality (Randomized Trial Data)

<table>
<thead>
<tr>
<th>Source</th>
<th>CRT</th>
<th>Control</th>
<th>Relative Risk (95% Confidence Interval)</th>
<th>Favors</th>
<th>Favors</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRT Alone vs Medical Therapy</td>
<td>CRT</td>
<td>Control</td>
<td>3.00 (0.13-70.74)</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>MUSTIC-SR,14 2001</td>
<td>1/29</td>
<td>0/29</td>
<td>3.00 (0.13-70.74)</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>MIRACLE,15 2002</td>
<td>12/228</td>
<td>16/225</td>
<td>0.74 (0.36-1.53)</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>MUSTIC-AF,11 2002</td>
<td>1/25</td>
<td>0/18</td>
<td>2.19 (0.08-50.85)</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>PATH-CHF II,16 2003</td>
<td>2/24</td>
<td>0/17</td>
<td>3.69 (0.18-70.54)</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>PATH-CHF I,16 2003</td>
<td>2/43</td>
<td>3/43</td>
<td>0.67 (0.12-3.79)</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>FD-CHF,9 2003</td>
<td>2/22</td>
<td>4/22</td>
<td>0.50 (0.10-2.45)</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>COMPANION,17 2004</td>
<td>131/617</td>
<td>77/308</td>
<td>0.86 (0.66-1.09)</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>CARE-HF,19 2005</td>
<td>90/409</td>
<td>124/404</td>
<td>0.70 (0.56-0.98)</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>VECTOR,20 2005</td>
<td>1/59</td>
<td>1/47</td>
<td>0.80 (0.05-12.40)</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>HOBIPLACE,17 2006</td>
<td>1/16</td>
<td>1/16</td>
<td>1.00 (0.07-14.64)</td>
<td>□</td>
<td>□</td>
</tr>
</tbody>
</table>

Subtotal | 245/1472 | 231/1129 | 0.77 (0.66-0.91) | □ | □ |

Test for Heterogeneity: $\chi^2 = 3.72$; $P = .93$; $I^2 = 0$
Test for Overall Effect: $Z = 3.16$; $P = .002$

CRT + ICD vs ICD Alone

<table>
<thead>
<tr>
<th>Source</th>
<th>CRT</th>
<th>Control</th>
<th>Relative Risk (95% Confidence Interval)</th>
<th>Favors</th>
<th>Favors</th>
</tr>
</thead>
<tbody>
<tr>
<td>CONTAK-CD,13 2003</td>
<td>11/245</td>
<td>16/245</td>
<td>0.69 (0.33-1.45)</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>MIRACLE-ICD,10 2003</td>
<td>14/187</td>
<td>15/182</td>
<td>0.91 (0.45-1.83)</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>MIRACLE ICD II,16 2004</td>
<td>2/85</td>
<td>2/101</td>
<td>1.19 (0.17-8.26)</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>RHYTHM-ICD,21 2005</td>
<td>6/119</td>
<td>2/60</td>
<td>1.51 (0.31-7.27)</td>
<td>□</td>
<td>□</td>
</tr>
</tbody>
</table>

Subtotal | 33/636 | 35/688 | 0.86 (0.54-1.39) | □ | □ |

Test for Heterogeneity: $\chi^2 = 0.97$; $P = .81$; $I^2 = 0$
Test for Overall Effect: $Z = 0.60$; $P = .55$

Total | 278/2108 | 266/1717 | 0.78 (0.67-0.91) | □ | □ |

Test for Heterogeneity: $\chi^2 = 4.90$; $P = .88$; $I^2 = 0$
Test for Overall Effect: $Z = 3.18$; $P = .001$

CRT indicates cardiac resynchronization therapy; ICD, implantable cardioverter-defibrillator. Size of data markers indicates the weight of the study.
CARDIAC RESYNCHRONIZATION THERAPY AND LEFT VENTRICULAR SYSTOLIC DYSFUNCTION

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CRT on hospitalizations and functional outcomes is uncertain due to a paucity of data at this time.

No definitive subgroup effects were apparent in the CRT RCTs, although it should be recognized that these RCTs were not powered to detect subgroup effects of small to moderate magnitude. For example, although the PATH CHF II Investigators14 reported significantly greater improvements in exercise capacity in their 16 patients with QRS duration of more than 150 milliseconds at baseline than in those with shorter QRS width, the 5 other RCTs8,10,13,15,19 that evaluated this subgroup did not find such a relationship. Furthermore, although a post hoc analysis of the MIRACLE trial138 suggested that patients with an ischemic etiology demonstrated less improvement in LVEF and LV volumes with CRT than those patients with nonischemic disease, the effect of CRT on mortality did not differ between patients with and without ischemia in the CONTAK CD,13 COMPANION,15 or CARE-HF19 studies (3 RCTs that specifically tested for this interaction in a priori specified subgroup analyses).

Univariate meta-regressions found no significant modification of the effect of CRT on all-cause mortality by presence or absence of ICD, ischemic etiology, duration of follow-up, whether randomization was predevice or postdevice implantation, whether the RCT was industry funded, the Jadad score for the RCT, or various patient characteristics (including NYHA class, age, or LVEF, within the narrow range enrolled in these RCTs). However, these meta-regression analyses were based on aggregate data from a small number of relatively homogeneous trials and thus were underpowered to detect subgroup effects. In contrast, several factors were found to be associated with a reduced benefit from CRT on heart failure hospitalizations (presence of an ICD in both controls and patients assigned to CRT [P<.001], NYHA class 2 at baseline [P=.003], and higher LVEF [P=.004]). Although CRT markedly reduced the proportion of patients hospitalized with heart failure when compared with medical therapy alone (RR, 0.51; 95% CI, 0.41-0.64; in the 5 RCTs reporting this outcome [280 of 1411 patients hospitalized]), CRT had no effect on heart failure hospitalizations in those trials in which combined CRT-ICD devices were compared with ICD-alone devices (RR, 1.00; 95% CI, 0.80-1.24; in 2 trials [234 of 859 patients hospitalized]).

The COMPANION trial13 performed the only direct comparison between combined CRT-ICD devices and medical therapy alone, and confirmed that combined CRT-ICD devices reduced all-cause mortality (hazard ratio, 0.64; 95% CI, 0.48-0.86) and improved 6-minute walk test distance (weighted mean difference, 45 m; 95% CI, 27-63 m), NYHA class (RR, 1.49; 95% CI, 1.23-1.81; for improving at least 1 NYHA class), and quality of life (weighted mean difference in Minnesota Living With Heart Failure Questionnaire, 14 points; 95% CI, 10-18 points) compared with medical therapy alone.

The COMPANION trial13 also permits a secondary comparison of combined CRT-ICD devices vs CRT-alone devices within the same trial. Although this latter comparison is underpowered and was not prespecified in the protocol, there was a statistically nonsignificant reduction in all-cause mortality (P=.13) and in time to death or heart failure hospitalization in those patients receiving the combined CRT-ICD device compared with those receiving the CRT-alone device. This is consistent with our meta-regression of aggregate trial data, which suggested that combined CRT-ICD devices and CRT-alone devices demonstrated similar effects, but is also not definitive.

Effectiveness of CRT

Survival over time in recipients of CRT or combined CRT-ICD devices was similar in the 95 observational studies that reported this outcome as in the 14 RCTs. Only 1 observational study139 compared outcomes in patients with CRT with outcomes in contemporaneous controls without CRT; their findings of improved LVEF (weighted mean difference, 4.6%; 95% CI, 2.9%-6.3%) and lower mortality rates (RR, 0.64; 95% CI, 0.26-1.56) in the CRT group were consistent in magnitude to the findings from our meta-analysis of the CRT trials.

The pooled effectiveness estimates from the observational studies for functional outcomes were consistent with those estimates from the efficacy RCTs. For example, in the RCTs, 59% of patients implanted with a CRT device improved by at least 1 NYHA class, and in the observational studies between 63% and 82% of patients improved by at least 1 NYHA class (TABLE 1). Determining the true response rate with CRT is hampered by the lack of a universally accepted definition for response140 and the fact that patients may demonstrate a response clinically but not echocardiographically or vice versa (with only 76% agreement in the classification of responder/nonresponder between definitions).140 No covariates were consistently shown across studies to predict CRT response.

Safety of CRT

In 54 studies (6123 patients) of CRT-alone devices, implant success rate was 93.0% (95% CI, 92.2%-93.7%), periimplantation mechanical complications occurred in 4.3% (95% CI, 3.6%-5.1%) of procedures, and periimplant deaths occurred in 0.3% of patients (95% CI, 0.1%-0.6%). During a median 6-month follow-up, 5% (95% CI, 4%-7%) of CRT devices malfunctioned and 1.8% (95% CI, 1.3%-2.5%) of patients were hospitalized for infections in the implant site; and during a median 11-month follow-up, lead problems occurred in 6.6% (95% CI, 5.6%-7.4%) of CRT devices. Although earlier studies raised concerns about a potentially higher risk of non–heart failure outcomes in patients with CRT (particularly an excess of ventricular arrhythmias),141 pooling the data from all of the RCTs did not reveal any excess risk of sudden death (RR, 1.07; 95% CI,
0.79-1.46) or noncardiac death (RR, 0.81; 95% CI, 0.43-1.52) in recipients of a CRT device.

In 36 studies (5199 patients) of combined CRT-ICD devices, safety outcomes were similar to CRT-alone devices (implant success rate was 93.7% [95% CI, 92.9%-94.4%]; peri-implantation mechanical complica-

| Table 1. Response Rates Reported in Observational Studies: CRT Alone or Combined CRT-ICD Devices |
|---|---|---|---|---|
| **Source** | **Follow-up, mo** | **Sample Size** | **Definition of Responder** | **Proportion of Responders, %** | **Independent Predictors of Positive Response** |
| **Functional definition of response** | | | | | |
| CRT alone | | | | | |
| Bleeker et al,34 2005 | 6 | 170 | Improved ≥1 NYHA class | 78 | Analysis by age <70 vs ≥70 years* |
| Chan et al,40 2003 | 3 | 63 | 6-min walk test increased 10% | 67 | Not performed |
| Lecoq et al,72 2005 | 6 | 139 | Alive, no CHF hospitalizations, improved ≥1 NYHA class or >10% increase V˙O₂max during 6-min walk test | 72 | Δ QRS (step of 20 milliseconds) |
| Lenom et al,73 2005 | 6 | 36 | Improved NYHA class | 71 | Not performed |
| Molhoek et al,86 2005 | 6 | 74 | Improved ≥1 NYHA class | 68 | Analysis by etiology* |
| Sawinney et al,104 2004 | 3 | 40 | Improved ≥1 NYHA class | 63 | Acute response to CRT by aortic Doppler VTI |
| Stählberg et al,110 2005 | 6 | 35 | Alive, no CHF hospitalizations, improved ≥1 NYHA class and/or 10% increase in 6-min walk test distance | 66 | Not performed |
| Combined CRT-ICD | | | | | |
| Alonso et al,25 1999 | 6 | 26 | Alive, improved ≥1 NYHA class, 10% increase in peak V˙O₂max | 73 | Not performed |
| Bax et al,33 2004 | 6 | 85 | Improved ≥1 NYHA class, improved 6-min walk test ≥25% | 74 | Baseline LV dysynchrony of ≥65 milliseconds |
| Díaz-Infante et al,53 2005 | 6 | 143 | Alive, no heart transplant, 10% increase in 6-min walk test | 80 | Etiology, mitral regurgitation, LVEDD <75 mm |
| Hernández et al,63 2004 | 6 | 28 | Improved 6-min walk test ≥10% | 79 | BNP level, etiology, baseline NYHA |
| Kiès et al,65 2005 | 6 | 97 | Improved ≥1 NYHA class | 74 | Analysis by diabetes mellitus vs no diabetes mellitus* |
| Molhoek et al,82 2004 | 6 | 60 | Improved ≥1 NYHA class | 72 | Not performed |
| Molhoek et al,84 2004 | 6 | 117 | Improved ≥1 NYHA class | 78 | NYHA class 3 vs 4 |
| Molhoek et al,85 2004 | 6 | 61 | Improved ≥1 NYHA class | 74 | Analysis by baseline QRS* |
| Reuter et al,104 2002 | 12 | 102 | Improved NYHA class associated with improved quality of life score | 82 | Etiology, cardiac output |
| **Echocardiographic definition of response** | | | | | |
| CRT alone | | | | | |
| Bax et al,32 2003 | 6 | 25 | Absolute increase in LVEF ≥5% | 68 | Septal to lateral delay |
| Penicka et al,97 2004 | 6 | 49 | Relative increase in LVEF ≥25% | 55 | Tissue doppler imaging derived indices of asynchrony |
| Yu et al,122 2002 | 3-6 | 141 | Reduction in LV end-systolic volume >10% | 62 | None |
| **Multiple definitions of response** | | | | | |
| CRT alone | | | | | |
| Mascioli et al,90 2002 | 6 | 68 | Improved ≥1 NYHA class, LVEF increased by ≥10% | 69 | Analysis performed but none found |
| Yu et al,124 2004 | 3 | 30 | Reduction in LV end-systolic volume >15% | 57 | Systolic dysynchrony by tissue doppler imaging |
| Combined CRT-ICD | | | | | |
| Notabartolo et al,92 2004 | 3 | 49 | Clinical: any 2 of (1) improved ≥1 NYHA class, (2) >50 m increase in 6-min walk test, or (3) decrease in quality of life score = 15 points | 75 (clinical) | PVD predicted echocardiographic response; no significant predictors of clinical response |
| | | | | | |
| Echocardiographic definition of response | | | | | |
| CRT alone | | | | | |
| Bax et al,32 2003 | 6 | 25 | Absolute increase in LVEF ≥5% | 68 | Septal to lateral delay |
| Penicka et al,97 2004 | 6 | 49 | Relative increase in LVEF ≥25% | 55 | Tissue doppler imaging derived indices of asynchrony |
| Yu et al,122 2002 | 3-6 | 141 | Reduction in LV end-systolic volume >10% | 62 | None |

Abbreviations: BNP, brain natriuretic peptide; CHF, congestive heart failure; CRT, cardiac resynchronization therapy; ICD, implantable cardioverter-defibrillator; LV, left ventricular; LVEDD, LV end-diastolic diameter; LVEF, LV ejection fraction; NYHA, New York Heart Association class; PVD, pulmonary vein doppler; V˙O₂max, maximum oxygen consumption; VTI, velocity time integral.

*Not significant (P>0.05).
tions occurred in 4.6% [95% CI, 3.7%-5.6%] of procedures; peri-implant deaths occurred in 0.5% [95% CI, 0.2%-0.8%] of patients; and during a median 12-month follow-up, 5% [95% CI, 4.0%-6.3%] of combined CRT-ICD devices malfunctioned, 1.1% [95% CI, 0.7%-1.7%] of patients developed site infection, and lead problems were detected in 7.2% [95% CI, 6.3%-8.1%] of patients). There were no appreciable differences between implant success rates or frequency of adverse events in the RCTs or the observational studies for CRT-alone or combined CRT-ICD devices.

Cost-effectiveness of CRT

Five published decision analyses142-146 have explored the cost-effectiveness of CRT therapy. Although 1 study142 estimated the median incremental cost of CRT plus medical therapy over medical therapy alone to be as high as $107 800 per quality-adjusted life-year, this was based on outcome data from the early CRT RCTs (most of which reported outcome data only within the first 3 months after CRT activation). Four subsequent cost-effectiveness analyses,143-146 which incorporated more recently published trials with substantially longer follow-up durations, reported lower incremental costs per quality-adjusted life-year gained with CRT devices: €19 600 in an analysis of the COMPANION trial data,143 £19 319 (US $24 360) per quality-adjusted life-year gained, but the cost-effectiveness ratios were less favorable in older patients (€15 805 [US $21 370] in 55-year-old patients vs €22 490 [US $30 408] in 75-year-old patients).145 The incremental cost-effectiveness of combined CRT-ICD devices vs CRT-alone devices, however, was markedly higher in all of these analyses ($171 538 per quality-adjusted life-year in the United States, £34 664 [US $68 547] in the United Kingdom, and €47 909 [US $64 777] in Europe). Thus, although CRT-alone devices are clearly cost-effective compared with medical therapy alone in trial eligible patients, the cost-effectiveness ratios when these devices are used in clinical practice are uncertain, as is the incremental cost-effectiveness of combined CRT-ICD devices vs CRT-alone devices remains uncertain pending further research.

Proportion of Patients With Heart Failure Likely to Be Eligible for CRT

Approximately 1% to 3% of all patients discharged alive after their index hospitalization for heart failure and 15% to 20% of patients observed in specialized heart failure clinics met CRT trial eligibility criteria (LVEF ≤35%, QRS ≥120 milliseconds, sinus rhythm, and NYHA class 3 or 4 symptoms despite optimal medical management).147 Of these patients, approximately 50% also met trial eligibility criteria for an ICD.148

Controversies and Areas for Future Research

Despite consistent evidence across published studies, a number of areas of uncertainty remain. Some of these gray areas result from the underrepresentation of patients with particular characteristics, such as bradyarrhythmias, atrial fibrillation, less severe heart failure symptoms, chronic kidney disease, or right-bundle branch blocks, in the RCTs conducted thus far and should be resolved by ongoing trials (TABLE 2). However, a number of other caveats should be raised when considering the CRT data presented herein.

First, an important question about CRT, as with any new therapy, is whether the efficacy demonstrated in RCTs translates into effectiveness when applied in clinical practice. This is of particular concern for device therapies such as CRT that have been tested in a selected spectrum of patients and depend on specialized technical expertise. Thus, although the trials proving the efficacy of CRT enrolled relatively young patients and a high proportion of men, population-based cohort data147 demonstrate that patients with heart failure in clinical practice are almost a decade older than trial participants and have a substantially greater burden of comorbid illnesses. Recent analyses of Medicare ICD recipients confirmed that these devices are being implanted in older patients with more comorbidities152 than trial participants, and are being implanted by less experienced health care practitioners working in lower volume hospitals153 than those health care practitioners and hospitals that participated in the RCTs. It seems likely that such trends exist in CRT implants as well.

Second, approximately half of the patients in our efficacy analysis were participants in RCTs that randomized patients only after successful device implantation; as a result, patients who could not tolerate the procedure or in whom implantation was unsuccessful were not included in the final trial data. Although our meta-regression did not demonstrate this factor to be statistically significantly related to magnitude of demonstrated benefits, this analysis was underpowered due to the small number of studies, and it is still possible that these RCTs may overestimate the potential benefits from CRT and underestimate the risks.

And third, our estimates of implant success and peri-implant vs postimplant safety are based on only a few thousand patients and thus should not
be considered definitive (particularly in light of the recent experiences with ICD device recalls).

These points serve to emphasize the importance of establishing a prospective CRT registry—akin to the Heart Rhythm Society and American College of Cardiology National Cardiovascular Data Registry for ICD devices—to provide real world estimates of benefits and risks with CRT or combined CRT-ICD devices. Such a registry would also provide much needed data on the long-term functional and morbidity outcomes with CRT and combined CRT-ICD devices, and would permit the tracking of complication rates as device implanters, the tools for implantation, and the sophistication of the devices change over time.

### Table 2. Summary of Evidence for CRT Alone or Combined CRT-ICD Devices in Patients With Left Ventricular Systolic Dysfunction (LVEF ≤35%) *

<table>
<thead>
<tr>
<th>Device</th>
<th>NYHA Status</th>
<th>Electrocardiogram Criteria</th>
<th>Quality of Evidence</th>
<th>Magnitude of Effect</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRT alone</td>
<td>NYHA class 3 or 4</td>
<td>QRS &gt;120 milliseconds and sinus rhythm</td>
<td>High (multiple RCTs with homogeneous results)</td>
<td>Reduced mortality: RR, 0.78; 95% CI, 0.67-0.91 Reduced heart failure hospitalizations: RR, 0.51; 95% CI, 0.41-0.64</td>
<td>Definite benefit</td>
</tr>
<tr>
<td></td>
<td>NYHA class 2</td>
<td>QRS &gt;120 milliseconds and sinus rhythm</td>
<td>Moderate (1 small RCT plus post hoc meta-regression of aggregate trial data from 14 RCTs, but few patients had NYHA class 2) Ongoing RCTs: REVERSE,144 RAFT†</td>
<td>No significant effect on mortality (in 1 RCT: RR, 1.19; 95% CI, 0.17-8.26); in meta-regression, patients with class 2 symptoms not significantly associated with reduction in mortality (P = .76) Effect on hospitalization smaller in NYHA class 2 vs class 3 or 4 heart failure; in meta-regression, patients with class 2 symptoms significantly associated with reduction in hospitalization (P = .003)</td>
<td>Inconclusive</td>
</tr>
<tr>
<td>CRT-ICD</td>
<td>NYHA class 3 or 4</td>
<td>QRS &gt;120 milliseconds and bradycardia or atrial fibrillation</td>
<td>Low (post hoc meta-regression of aggregate trial data from 14 RCTs) Ongoing RCTs: Trip HF, RAFT,† APAF, BLOCK HF</td>
<td>No significant association in meta-regression between patients with atrial fibrillation and reduction in mortality or hospitalizations (P = .73 and P = .58, respectively)</td>
<td>Inconclusive</td>
</tr>
<tr>
<td>Combined</td>
<td>NYHA class 3 or 4</td>
<td>QRS &lt;120 milliseconds Any rhythm</td>
<td>Low (secondary analyses of small observational studies)</td>
<td>Improvements in symptoms and LV remodelling not significantly different between patients with narrow QRS and patients with wide QRS in any of the studies</td>
<td>Inconclusive</td>
</tr>
<tr>
<td>CRT-ICD</td>
<td>NYHA class 1</td>
<td>Any QRS duration Any rhythm</td>
<td>None</td>
<td>No published evidence Ongoing RCT: REVERSE49</td>
<td>Not applicable Inconclusive</td>
</tr>
<tr>
<td>All other patient subgroups</td>
<td>None</td>
<td>QRS &gt;120 milliseconds and sinus rhythm</td>
<td>Moderate (1 large RCT) Ongoing RCTs: DECREASE-HF,150 RAFT†</td>
<td>Reduced mortality: HR, 0.64; 95% CI, 0.48-0.86 Reduced mortality or all-cause hospitalization: HR, 0.80; 95% CI, 0.68-0.95</td>
<td>Definite benefit</td>
</tr>
<tr>
<td>Combined</td>
<td>NYHA class 3 or 4</td>
<td>QRS &gt;120 milliseconds and sinus rhythm</td>
<td>Moderate (1 large RCT, but comparison was not a priori specified or adequately powered)</td>
<td>No significant effect on mortality (RR, 0.83; 95% CI, 0.66-1.05) and no significant effect on time to death in NYHA class 4 subgroup (HR, 1.27; 95% CI, 0.68-2.37)</td>
<td>Inconclusive</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; CRT, cardiac resynchronization therapy; ICD, implantable cardioverter-defibrillator; HR, hazard ratio; LV, left ventricular; LVEF, LV ejection fraction; NYHA, New York Heart Association class; RCT, randomized controlled trial; RR, risk ratio.

*Note that other considerations may outweigh the trial evidence in some situations (for example, the patient who wishes to be “do not resuscitate”), and there is no data on the effects of either CRT or ICD in patients with advanced age or severe comorbidities, such as end-stage renal disease.

†Resynchronization/Defibrillation for Advanced Heart Failure Trial (http://www.clinicaltrials.gov: NCT00251251).
†Protocols can be found at http://www.clinicaltrials.gov (Trip HF: NCT00187265; APAF: NCT00111527; BLOCK HF: NCT00267098).
ICD devices should be considered in patients who are CRT eligible who would otherwise be candidates for ICD (those patients with a history of, or at increased risk for, sudden cardiac death who do not have significant comorbidities), this should not be extrapolated to endorse the implantation of combined CRT-ICD devices in all patients who are CRT eligible or all patients who are ICD eligible. We believe there is a need for device manufacturers and trialists to design studies that compare the effect of combined CRT-ICD devices with CRT-alone devices.

CONCLUSIONS

CRT is an efficacious and cost-effective therapy for patients with NYHA class 3 or 4 heart failure despite optimal medical management, an LVEF of 35% or less, sinus rhythm, and ventricular dyssynchrony (currently identified by prolonged QRS duration). CRT improves ventricular function and remodelling, symptoms, and exercise capacity, while also reducing frequency of heart failure hospitalizations by 37% and death by 22%. The magnitude of these benefits are similar to those reported for angiotensin-converting enzyme inhibitors or β-blockers and are additive to the benefit of such medical therapy. Although the periprocedural risks of CRT appear modest and are similar to the frequency reported for patients undergoing implantation of conventional dual-chamber pacemakers, there is a 5% risk of device or lead failure and a 2% risk of infection in the first 6 months after CRT implantation, and these risks should be factored into clinical decisions about whether to refer a patient for device implantation.

However, implantation of a CRT pacemaker (in particular the LV lead) can be technically challenging, and device malfunctions or lead problems (most frequently with the LV lead) are not infrequent. Even when lead placement is thought to be successful, CRT does not always restore mechanical synchrony. Studies to define which patients are most likely to benefit from CRT, such as the ongoing Predictors of Response to Cardiac Resynchronization Therapy Study, and which positions in the ventricular wall are most appropriate for implantation of the pacing leads are clear research priorities, as are studies to better define which patients who are CRT eligible are at highest risk for ventricular arrhythmias and thus most likely to benefit from a combined CRT-ICD device.

Second, although we were unable to detect any differential subgroup effects in the efficacy of CRT, the RCT subgroup analyses and our meta-regressions were post hoc and underpowered. Individual patient data from the RCTs conducted thus far would be needed to appropriately examine this issue, and we believe the compilation and analysis of this data should be an urgent research priority in this field. Indeed, relying on RCT eligibility criteria to define those patients most likely to benefit is imperfect, particularly since more than one third of CRT recipients do not exhibit any functional or echo-cardiographic improvements after activation of their CRT.

In particular, QRS duration has been used to select patients for CRT in the RCTs conducted thus far and it is uncertain whether, and to what extent, the use of newer techniques to detect electromechanical dyssynchrony, such as tissue doppler imaging, or to detect those patients at increased risk for ventricular arrhythmias, such as the microvolt T-wave alternans test, will impact the effectiveness and safety of these devices.

Although the incremental benefit of combined CRT-ICD devices vs ICD alone is uncertain, this issue should be resolved after the ongoing RAFT (Resynchronization/Defibrillation for Advanced Heart Failure Trial; http://www.clinicaltrial.gov: NCT00251251) and DECREASE-HF150 trials are completed. However, we are not aware of any ongoing randomized trials exploring the incremental benefit of combined CRT-ICD devices vs CRT alone, which we believe is a key area of residual uncertainty for patients with LV systolic dysfunction. Because CRT alone appears to reduce the frequency of ventricular arrhythmias153 and the long-term risk of sudden death,137 the incremental benefits of a combined CRT-ICD device in patients who are CRT eligible may be less than anticipated by those clinicians extrapolating from RCTs comparing ICD with drug therapy. Although we believe that combined CRT-ICD devices should be considered in patients who are CRT eligible who would otherwise be candidates for ICD (those patients with a history of, or at increased risk for, sudden cardiac death who do not have significant comorbidities), this should not be extrapolated to endorse the implantation of combined CRT-ICD devices in all patients who are CRT eligible or all patients who are ICD eligible. We believe there is a need for device manufacturers and trialists to design studies that compare the effect of combined CRT-ICD devices with CRT-alone devices.
cCARDIAC RESYNCHRONIZATION THERAPY AND LEFT VENTRICULAR SYSTOLIC DYSFUNCTION

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CARDIAC RESYNCHRONIZATION THERAPY AND LEFT VENTRICULAR SYSTOLIC DYSFUNCTION


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Let me advise you not to aim too high. The big prizes in our profession are only for the few, and they do not always bring much happiness when gained. “Seekest thou great things? Seek them not,” as the wise man said. If you have earned enough for your needs and been able to put a little aside for your old age, and if, at the same time, you have won the esteem of your colleagues and the affection of your patients, you have done well enough, and that measure of success should be within the reach of most of you.

—Sir Robert Hutchison (1871-1960)