EDITORIAL COMMENT

Is it Time to Expand the Use of Cardiac Resynchronization Therapy to Patients With Mildly Symptomatic Heart Failure?*

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Cardiac resynchronization therapy (CRT) is central to the management of patients with highly symptomatic systolic heart failure and delayed ventricular conduction. Improved survival and reduced rates of hospital stay for heart failure with CRT versus standard medical therapy have been documented in prior trials (1). Thus, CRT combined with a pacemaker or implantable cardioverter-defibrillator (CRT-D) is now routinely recommended for patients with New York Heart Association (NYHA) functional class III or IV limitation, a QRS duration ≥120 ms, and left ventricular (LV) ejection fraction ≤0.35 despite optimal pharmacologic therapy (2–4).

Rationale for CRT earlier in heart failure. Cardiac resynchronization therapy has favorable hemodynamic, energetic, anatomic, and basic cellular effects in advanced heart failure (5–8). Thus, it is both plausible and attractive that early intervention with CRT in heart failure might delay or prevent disease progression. Yet, although CRT is central to the management of patients with highly symptomatic systolic heart failure, its role in patients with mildly symptomatic heart failure is less certain (1).

LV reverse remodeling and clinical outcome. It has been shown that favorable LV reverse remodeling is associated with improved long-term clinical outcomes with CRT (9). However, it is important to recognize that LV reverse remodeling is not a perfect surrogate for clinically important long-term outcomes. For example, the relationship between the degree of LV reverse remodeling and a long-term survival benefit from CRT is far from clear when patients with an ischemic versus nonischemic etiology of heart failure are considered (Table 1) (10–16). For example, in both the MIRACLE (Multicenter InSync Randomized Clinical Evaluation) (10,11) and the CARE HF (Cardiac REsynchronisation in Heart Failure study) (15,16) studies patients with an ischemic etiology of heart failure had less LV reverse remodeling than those with a nonischemic etiology. Yet, the survival benefit from CRT was equivalent in patients with ischemic and nonischemic heart failure. Furthermore, despite the fact that patients with ischemic heart failure typically have less LV reverse remodeling with CRT than patients with nonischemic heart failure (Table 1), the survival benefit with CRT tended to be greater in patients with an ischemic versus nonischemic etiology of heart failure in the COMPANION (Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure) trial (14). Thus, although favorable LV remodeling is desirable with CRT, it does not provide the complete answer with respect to the long-term clinical benefit from CRT.

CRT in patients with mild heart failure symptoms. Until recently, few studies evaluated the efficacy of CRT in patients with mild heart failure (NYHA functional class I or II). These initial studies suggested that CRT had only a minor effect on preventing heart failure hospital stay and was not associated with a significant effect on mortality (1). Table 2 summarizes completed and ongoing trials evaluating the efficacy of CRT in patients with mildly symptomatic heart failure. The CONTAK CD (Guidant Corporation, St. Paul, Minnesota) study represents the earliest of these (12). In that trial, patients with mostly NYHA functional class III or IV limitation underwent CRT-D implantation. During the post-implant period, before randomization, patients had more intensive medical therapy for their heart failure. This resulted in a substantial number of patients having improved NYHA functional class at the time of randomization to active CRT (CRT ON) or usual care (CRT OFF). The CRT did not significantly alter the primary end point of CONTAK CD, progression of heart failure. However, greater LV reverse remodeling was observed with CRT versus control, both in patients with advanced NYHA functional class limitation and those with mildly symptomatic heart failure. The MIRACLE ICD II (Multicenter InSync ICD Randomized Clinical Evaluation II) study (17) included only patients with NYHA functional class II symptoms. The primary efficacy end point for MIRACLE ICD II, change in peak oxygen uptake from baseline to 6 months, was not significantly altered with CRT. However, CRT did favorably alter the secondary outcomes of LV reverse remodeling and clinical response. These early studies were followed by the much larger REVERSE (Resynchronization Reverses Remodeling in Systolic Left Ventricular Dysfunction) trial (18). The REVERSE trial included 610 patients with mostly NYHA functional class II limitation. The primary end point of the REVERSE trial, the percent of
patients who worsened, was not significantly different in the CRT ON versus CRT OFF group over 12 months of follow-up. However, CRT was associated with a significant reduction in the pre-specified secondary end point left ventricular end-systolic volume index (LVESVi). The reduction in LVESVi was particularly prominent in patients with a nonischemic etiology of heart failure, those with larger LV end-systolic volumes, and patients with wider QRS values (≥152 ms) at baseline. The time to first heart failure hospital stay was delayed to a greater extent in patients randomized to CRT ON versus CRT OFF (p = 0.03). The mixed results from the REVERSE study indicate that, although CRT might slow the progression of heart failure, as measured by changes in LV remodeling, its impact on clinical outcomes over the near term seem modest. Thus, larger and longer-term studies are required to better define the role of CRT in less symptomatic patients.

**Results in the REVERSE European cohort.** The sub-analysis of European data from the REVERSE trial by Daubert et al. (19) in this issue of the Journal provides important additional insights into the role of CRT in patients with mild symptoms of heart failure. Their analysis included the 262 patients who received CRT devices in Europe. As in the main REVERSE study, European participants were required to have a QRS width ≥120 ms and LV ejection fraction of ≤0.40. Participants were randomly assigned in a 2:1 manner to active therapy (CRT ON, n = 180) or control (CRT OFF, n = 82). European patients were followed for 24 months, twice the duration of the North American cohort. Over 24 months, 19% of the CRT ON versus 34% of the CRT OFF patients worsened (p = 0.01). Furthermore, LVESVi decreased by a mean of 27.5 ± 31.8 ml/m² in the CRT ON versus only 2.7 ± 25.8 ml/m² in the CRT OFF group (p < 0.0001). The time to first heart failure hospital stay or death was also significantly delayed with CRT ON versus CRT OFF (p = 0.003). Thus, these results provide additional data to support the use of CRT in delaying heart failure progression.

**The REVERSE European cohort data in perspective.** Although the data from Daubert et al. (19) are interesting, they should not be considered definitive. First, it is important to recognize that few patients were truly asymptomatic and the results are mostly applicable to patients with mildly symptomatic heart failure. Furthermore, as with any sub-analysis, there is the distinct possibility of overestimating or underestimating the true effect size by chance alone. This is particularly relevant, given that only 13 deaths were observed in the entire European cohort.

As acknowledged by the authors, important differences in demographic characteristics were apparent between the European and North American patients. Furthermore, these might in part explain the apparent differences in CRT efficacy in this subanalysis. European patients were less likely to have an ischemic etiology of heart failure, had longer average QRS

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### Table 1

**Key Randomized Trials Assessing the Efficacy of CRT: Ischemic Versus Nonischemic Etiology of Heart Failure**

<table>
<thead>
<tr>
<th>Study (Ref. #)</th>
<th>Year</th>
<th>n</th>
<th>Ischemic Etiology</th>
<th>LV Reverse Remodelling</th>
<th>Survival</th>
<th>Differences by Etiology of Heart Failure</th>
</tr>
</thead>
<tbody>
<tr>
<td>MIRACLE (10,11)</td>
<td>2002</td>
<td>453</td>
<td>54%</td>
<td>+</td>
<td>+</td>
<td>Less remodeling among patients with ischemic etiology. No reported differences in survival.</td>
</tr>
<tr>
<td>CONTAK CD (12)</td>
<td>2003</td>
<td>490</td>
<td>69%</td>
<td>+</td>
<td>±</td>
<td>No reported differences in remodeling or survival.</td>
</tr>
<tr>
<td>MIRACLE ICD (13)</td>
<td>2003</td>
<td>369</td>
<td>70%</td>
<td>±</td>
<td>±</td>
<td>No reported differences in remodeling or survival.</td>
</tr>
<tr>
<td>COMPANION (14)</td>
<td>2004</td>
<td>1,520</td>
<td>55%</td>
<td>—</td>
<td>+</td>
<td>Statistical trend (p = 0.06) toward a greater reduction in mortality in patients with an ischemic versus a nonischemic etiology.</td>
</tr>
<tr>
<td>CARE HF (15,16)</td>
<td>2005</td>
<td>812</td>
<td>42%</td>
<td>+</td>
<td>+</td>
<td>Less remodeling among patients with ischemic etiology but similar survival benefit.</td>
</tr>
</tbody>
</table>

CRT = Cardiac Resynchronization Therapy; LV = left ventricular; — = not reported; ± = no improvement; + = small improvement; ++ = large improvement.

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### Table 2

**Key Randomized Trials Assessing the Efficacy of CRT in Patients With Less Symptomatic Heart Failure**

<table>
<thead>
<tr>
<th>Study (Ref. #)</th>
<th>Year</th>
<th>n</th>
<th>NYHA Functional Class</th>
<th>Mean Walk Distance, m</th>
<th>Mean LVEF</th>
<th>LV Reverse Remodelling</th>
<th>Morbidity</th>
<th>Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>CONTAK CD (12)</td>
<td>2003</td>
<td>490</td>
<td>II: 14% III: 71% IV: 15%</td>
<td>—</td>
<td>263</td>
<td>69%</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>MIRACLE ICD II (17)</td>
<td>2004</td>
<td>186</td>
<td>II: 100%</td>
<td>370</td>
<td>0.25</td>
<td>+</td>
<td>—</td>
<td>+</td>
</tr>
<tr>
<td>REVERSE (18)</td>
<td>2008</td>
<td>610</td>
<td>I: 18% II: 82%</td>
<td>399</td>
<td>0.27</td>
<td>++</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>MADIT CRT (20)</td>
<td>2009</td>
<td>1,820</td>
<td>I: 15% II: 85%</td>
<td>361</td>
<td>0.24</td>
<td>+++</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>RAFT (21)</td>
<td>2010</td>
<td>1,800</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

LVEF = left ventricular ejection fraction; NYHA = New York Heart Association; other abbreviations as in Table 1.
durations, and less comorbid illness as compared with the non-European participants in the REVERSE study. Thus, the author’s conclusion, “these observations suggest that CRT prevents the progression of disease in patients with asymptomatic or mildly symptomatic LV dysfunction,” is generally reasonable. However, it is important to acknowledge that additional evidence is required before more wide-scale use of CRT in patients with mildly symptomatic heart failure.

**Ongoing and recently completed trials.** Two large trials will provide important additional evidence of the efficacy of CRT in a broader group of patients with mildly symptomatic heart failure. The MADIT CRT (Multi-center Automatic Defibrillator Implantation with Cardiac Resynchronization Therapy) study compared usual implantable cardioverter-defibrillator therapy with CRT-D in 1,820 subjects in sinus rhythm with LV ejection fraction values \( \leq 0.30 \), QRS durations \( \geq 130 \) ms, and mild heart failure. This trial demonstrated a 29% reduction in the risk of the combined end point of death or heart failure events (\( p = 0.003 \)) (20). This outcome was purely driven by a reduction in heart failure events. The proportion of these events that were actual hospitalizations for heart failure is unclear. Further, the average 6-min walk test distance of \( 361 \pm 108 \) m suggests that many of these patients would have been categorized as NYHA functional class III in past trials, based on a walk distance of \(<450\) m (10). Nonetheless, clear improvements in LV mechanical indexes and corresponding reductions in heart failure events were demonstrated in MADIT-CRT. The RAFT (Resynchronization/Defibrillation in Advanced Heart Failure Trial) is another large ongoing study comparing implantable cardioverter-defibrillator therapy with CRT-D among 1,800 subjects in sinus rhythm or with atrial fibrillation, LV ejection fractions \( \leq 0.30 \), QRS durations \( \geq 120 \) ms, and mostly mildly symptomatic heart failure (21). The REVERSE study and other trials will provide clearer answers as to the role of CRT in patients with mildly symptomatic heart failure. Given the growing evidence for CRT as a means to delay heart failure progression, it is tempting to recommend it beyond present guidelines (2-4). However, it is premature to recommend CRT as a routine intervention to patients with asymptomatic LV dysfunction or those with mildly symptomatic heart failure today.

**REFERENCES**


**Key Words:** cardiac resynchronization therapy • heart failure • mortality • randomized trial • remodeling • subgroup.