

## EDITORIALS



## MADIT-CRT — Breathtaking or Time to Catch Our Breath?

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Cardiac-resynchronization therapy (CRT) received Food and Drug Administration approval for use in selected patients with left ventricular systolic dysfunction in 2001. Since that time, CRT has been embraced as a recommended approach to achieve meaningful clinical improvement in patients who have heart failure with a reduced left ventricular ejection fraction (LVEF) and who continue to have symptoms despite optimal medical therapy.<sup>1</sup> A number of pivotal randomized trials and scores of additional safety and effectiveness trials have consistently shown that CRT improves the LVEF, quality of life, and functional status in symptomatic patients with an LVEF of less than 35% and a prolonged QRS duration (mean range, 155 to 209 msec).<sup>2</sup> In addition, a systematic 2007 review calculated that CRT decreased the rate of hospitalization by 37% and lowered the rate of death from any cause by 22% in such patients.<sup>3</sup>

Despite the consistent and salutary benefits of CRT, at least 30% of patients who were selected for therapy according to the aforementioned criteria did not benefit from CRT.<sup>4</sup> Moreover, many patients had a clinical response (e.g., an increase in exercise capacity or in quality-of-life measures) in the absence of improved left ventricular systolic function. Likewise, some patients had major evidence of reverse ventricular remodeling on echocardiography but had no enhanced functional tolerance.

These observations have led to two related areas of investigation: alternative measures to detect mechanical dyssynchrony (disparity in the timing of regional ventricular contraction) apart from the electrical delay that is manifested by a wide QRS duration and the selection of patients who are likely to have more consistent benefit from CRT. Evidence of mechanical dyssynchrony

has been shown to be an independent predictor of clinical events and worsened survival in patients with heart failure and has correlated better than the QRS duration with the long-term benefit of CRT.<sup>4</sup> Accordingly, multiple noninvasive techniques have been used to identify mechanical dyssynchrony in patients with heart failure, and the results seem to suggest that dyssynchrony is extraordinarily common in all forms of heart failure.<sup>5</sup> However, attempts to translate these observations into an expanded indication for CRT or a greater response rate after device implantation have not been forthcoming.

For example, the randomized, controlled Cardiac Resynchronization Therapy in Patients with Heart Failure and Narrow QRS (RethinQ) trial (ClinicalTrials.gov number, NCT00132977) investigated the role of CRT in patients with heart failure who had mechanical dyssynchrony but a narrow QRS duration.<sup>6</sup> At 6 months, there was no benefit from CRT on the primary end point of peak oxygen capacity or on heart-failure events. Similarly, the observational Predictors of Response to Cardiac Resynchronization Therapy (PROSPECT) trial (NCT00253357), which was designed to identify echocardiographic predictors of response to CRT, revealed a low predictive accuracy for various measures of mechanical dyssynchrony.<sup>7</sup>

An argument that CRT might delay disease progression in patients with less severe symptoms through left ventricular reverse remodeling has led to a number of trials enrolling patients with New York Heart Association (NYHA) functional class I or II heart failure, including the Resynchronization Reverses Remodeling in Systolic Left Ventricular Dysfunction (REVERSE) trial (NCT00271154)<sup>8</sup> and the Resynchroniza-

tion/Defibrillation for Ambulatory Heart Failure Trial (RAFT) (NCT00251251).<sup>9</sup> The results of the REVERSE trial and other smaller CRT trials involving patients with mild-to-moderate heart failure are strikingly consistent, although all the studies had a relatively short follow-up period (6 to 12 months). The trials did not show any significant improvement in functional capacity, as assessed by the 6-minute walk test or NYHA classification, and there was no improvement in quality of life.<sup>9</sup> However, there was a concordant and significant reduction in the left ventricular volume and an increase in the LVEF across the trials. In addition, the REVERSE trial showed a significant reduction (53%) in the relative risk of first hospitalization for heart failure in patients receiving CRT, although there was no difference in mortality between patients who received CRT and those who received optimal medical therapy.<sup>8</sup>

In this issue of the *Journal*, the results of the Multicenter Automatic Defibrillator Implantation Trial with Cardiac Resynchronization Therapy (MADIT-CRT) (NCT00180271)<sup>10</sup> confirm the earlier findings. The investigators followed 1820 patients with NYHA class I or II heart failure for an average of 2.4 years. The primary end point, a composite of death from any cause or nonfatal heart failure (which was defined as the need for intravenous decongestant therapy in an outpatient regimen or an augmented heart-failure regimen during hospitalization), was significantly reduced when CRT was added to an implantable cardioverter-defibrillator (ICD), as compared with an ICD alone. Patients in the CRT-ICD group also had significant improvement in cardiac function at 1 year. The superiority of CRT was driven solely by a 41% reduction in the risk of a first heart-failure event, since mortality was not influenced by the choice of device, even with an increased trial duration. In CRT trials enrolling symptomatic patients, the reduction in mortality among those receiving CRT has been evident by 6 months but has been larger in trials with the longest follow-up. In their meta-analysis of CRT trials, McAlister et al.<sup>3</sup> calculated that 29 patients would need to be treated for 6 months to prevent one death. In the longer follow-up in the Cardiac Resynchronization in Heart Failure (CARE-HF) trial (NCT00318357), another CRT trial enrolling symptomatic patients with NYHA class III or IV heart failure, in order to prevent one death, 13 patients would need to be treated for 2 years and

9 patients for 3 years.<sup>11</sup> It is unlikely that less symptomatic patients receiving CRT would have a significant reduction in mortality unless a large number of patients underwent prolonged follow-up.

Should the guideline indications for CRT change as a result of MADIT-CRT? It is not completely clear how the enrolled patients differ from those in earlier CRT trials, since no objective criteria were used to classify functional status at baseline and the treatment of patients and their subsequent functional status were determined by clinicians who were aware of study-group assignments. Moreover, at least 10% of patients had NYHA class III or IV symptoms at least 3 months before randomization. We know from several cohort studies that the transition from stage B heart failure (i.e., patients with substantial ventricular structural abnormalities in the absence of symptoms) to symptomatic stage C is associated with an increase in the risk of death by a factor of five.<sup>12,13</sup> It appears that MADIT-CRT enrolled patients with stage C heart failure and not patients who had always been asymptomatic (e.g., stage B). This is a critical point and would argue against the use of CRT in patients solely on the basis of a wide QRS duration. In addition, both the REVERSE trial and MADIT-CRT showed that the observed clinical benefit with respect to nonfatal heart failure occurred primarily in the prespecified subgroup of patients with a QRS duration of 150 msec or more.<sup>8,10</sup>

In 2007, it was estimated that 1 to 3% of all patients who were discharged after the index hospitalization for heart failure and 15 to 20% of patients who were observed in specialized heart-failure clinics met current CRT eligibility criteria: an LVEF of less than 35%, a QRS duration of more than 120 msec, sinus rhythm, and NYHA class III or IV heart failure despite optimal medical management.<sup>3</sup> An analysis that was based on data from the five longest CRT randomized trials revealed that the incremental cost per quality-adjusted life-year gained was \$32,822. The incremental cost-effectiveness of combined CRT with ICD devices, as compared with CRT devices alone, has been markedly higher in most analyses.<sup>3</sup>

In MADIT-CRT, 12 patients would need to be treated to prevent a single heart-failure event, whereas in the REVERSE trial, 20 patients would need to be treated to delay a heart-failure hospi-

talization. Is this money that could be spent more wisely? If the indication for CRT is expanded to all stage C patients with a low LVEF and a QRS duration of more than 120 msec, regardless of current symptoms or the duration of medical therapy, the potential “indication creep” in patients who are unlikely to derive a mortality benefit will alter the benefit-to-safety ratio and tip the score on cost-effectiveness even further in the wrong direction. Given the sobering facts about the costs of health care confronting us now and in the future, it appears prudent that any expanded indication for CRT in less symptomatic patients should be confined to patients with a QRS duration of more than 150 msec and in whom previous marked symptoms have been controlled with optimal medical therapy.

Dr. Jessup reports serving on an advisory board for Medtronic. No other potential conflict of interest relevant to this article was reported.

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This article (10.1056/NEJMe0907335) was published on September 1, 2009, at NEJM.org.

1. Jessup M, Abraham WT, Casey DE, et al. 2009 Focused update: ACCF/AHA Guidelines for the Diagnosis and Management of Heart Failure in Adults: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines: developed in collaboration with the International Society for Heart and Lung Transplantation. *Circulation* 2009;119:1977-2016.
2. Bax JJ, Abraham T, Barold SS, et al. Cardiac resynchronization

therapy: part 1 — issues before device implantation. *J Am Coll Cardiol* 2005;46:2153-67.

3. McAlister FA, Ezekowitz J, Hooton N, et al. Cardiac resynchronization therapy for patients with left ventricular systolic dysfunction: a systematic review. *JAMA* 2007;297:2502-14.
4. Bax JJ, Gorcsan J III. Echocardiography and noninvasive imaging in cardiac resynchronization therapy: results of the PROSPECT (Predictors of Response to Cardiac Resynchronization Therapy) study in perspective. *J Am Coll Cardiol* 2009;53:1933-43.
5. Kass DA. An epidemic of dyssynchrony: but what does it mean? *J Am Coll Cardiol* 2008;51:12-7.
6. Beshai JF, Grimm RA, Nagueh SF, et al. Cardiac-resynchronization therapy in heart failure with narrow QRS complexes. *N Engl J Med* 2007;357:2461-71.
7. Chung ES, Leon AR, Tavazzi L, et al. Results of the Predictors of Response to CRT (PROSPECT) trial. *Circulation* 2008;117:2608-16.
8. Linde C, Abraham WT, Gold MR, St John Sutton M, Ghio S, Daubert C. Randomized trial of cardiac resynchronization in mildly symptomatic heart failure patients and in asymptomatic patients with left ventricular dysfunction and previous heart failure symptoms. *J Am Coll Cardiol* 2008;52:1834-43.
9. Tang AS, Wells GA, Arnold M, et al. Resynchronization/defibrillation for ambulatory heart failure trial: rationale and trial design. *Curr Opin Cardiol* 2009;24:1-8.
10. Moss AJ, Hall WJ, Cannom DS, et al. Cardiac-resynchronization therapy for the prevention of heart-failure events. *N Engl J Med* 2009;361:1329-38.
11. Cleland JG, Daubert JC, Erdmann E, et al. Longer-term effects of cardiac resynchronization therapy on mortality in heart failure. *Eur Heart J* 2006;27:1928-32.
12. Ammar KA, Jacobsen SJ, Mahoney DW, et al. Prevalence and prognostic significance of heart failure stages: application of the American College of Cardiology/American Heart Association heart failure staging criteria in the community. *Circulation* 2007;115:1563-70.
13. Wang TJ, Evans JC, Benjamin EJ, Levy D, LeRoy EC, Vasan RS. Natural history of asymptomatic left ventricular systolic dysfunction in the community. *Circulation* 2003;108:977-82.

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## Gestational Diabetes — Whom Do We Treat?

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In 1964, O’Sullivan and Mahan<sup>1</sup> proposed glucose-tolerance-test criteria to define gestational diabetes mellitus — that is, any degree of glucose intolerance that first occurs or is first identified during pregnancy. Women whose glucose levels exceeded these thresholds during an index pregnancy were recognized to be at increased risk for developing nongestational diabetes 8 years later. Subsequently, considerable data indicated that lowering glucose levels in women who were diagnosed with gestational diabetes mellitus was associated with reduced rates of perinatal complications and death. However, many considered these data to be insufficient evidence to support treatment for gestational diabetes<sup>2,3</sup>; most of the studies were ob-

servational,<sup>4</sup> few were prospective, and, until fairly recently, blinded, randomized trials were lacking to guide management recommendations.

The results of the first of two multi-institutional, double-blind, randomized, controlled trials that showed benefits to the baby and to the mother of treating gestational diabetes mellitus — the Australian Carbohydrate Intolerance Study in Pregnant Women (ACHOIS) trial — were published in the *Journal* in 2005.<sup>5</sup> Among women with gestational diabetes, those who received dietary counseling and insulin as needed to reduce glycemia, as compared with those who did not receive treatment, had a reduced rate of serious perinatal complications (including death, shoulder dystocia,