

CORRESPONDENCE



Cardiac-Resynchronization Therapy

TO THE EDITOR: In the Multicenter Automatic Defibrillator Implantation Trial with Cardiac Resynchronization Therapy (MADIT-CRT), Moss and colleagues (Oct. 1 issue)¹ enrolled minimally symptomatic patients with severe left ventricular dysfunction, who had an annual rate of death from any cause of 2.9%. The primary end point was therefore driven by a 41% reduction in heart-failure events among patients in the group receiving cardiac-resynchronization therapy plus an implantable cardioverter-defibrillator (CRT-ICD), as compared with the group that received an ICD only.

The clinical significance of these results merits further clarification. Since treatment assignments were not blinded, it would be helpful if the authors could provide information regarding the decision to augment decongestive therapy. Specifically, were the majority of patients with heart-failure events treated in the context of a primary hospitalization for heart failure, or were medications titrated after admission for other reasons? If the latter is true, the reasons for hospitalization should be provided. When a broader indication for CRT is considered, a more precise understanding of the potential benefits in minimally symptomatic patients is of paramount importance, given the associated costs and the invasive nature of this therapy.

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No potential conflict of interest relevant to this letter was reported.

1. 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.

TO THE EDITOR: Moss et al. describe an unusual end point consisting of “heart-failure events,” which are defined as the need for outpatient intravenous decongestive therapy or inpatient admission with intensification of the heart-failure regimen. Because the treating physician was not blinded to the study-group assignment, the choice of outpatient intravenous diuresis would be subject to bias. Would it be possible for the authors to break down the components of “heart-failure events”? Could it be that outpatient treatment was the primary driver of the end point of heart failure? We are also interested to find out which events were referred for adjudication by the heart-failure events committee. Was each outpatient visit adjudicated by the committee or only cases in which intravenous diuretics were used?

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TO THE EDITOR: The original pivotal trials that established the effectiveness of CRT were blinded studies in which all patients received a left ven-

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tricular pacing lead, and biventricular pacing was then programmed on or off, depending on randomization.¹⁻³ In some cases, patients were even allowed to serve as their own blinded control by changing the programmed settings after some period of time.⁴

In this study, however, the assignment to left ventricular pacing was not blinded to either the patients or their treating physicians. In our center, both groups (patients and physicians) expressed excitement and optimism when randomization to the ventricular-pacing group occurred and disappointment when it did not. These sentiments often persisted into follow-up visits. Given such strong positive feelings by the patients and the similar reinforcement that they often received from their primary treating cardiologists, it would have been somewhat surprising if the results showed anything other than improved outcomes from biventricular pacing. Unfortunately, a truly blinded study is still needed to address this clinically important question.

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No potential conflict of interest relevant to this letter was reported.

1. Auricchio A, Stellbrink C, Sack S, et al. The Pacing Therapies for Congestive Heart Failure (PATH-CHF) study: rationale, design, and endpoints of a prospective randomized multicenter study. *Am J Cardiol* 1999;83:5B:130D-135D.
2. Abraham WT, Fischer WG, Smith AL, et al. Cardiac resynchronization in chronic heart failure. *N Engl J Med* 2002;346:1845-53.
3. Saxon LA, Boehmer JP, Hummel J, et al. Biventricular pacing in patients with congestive heart failure: two prospective trials. *Am J Cardiol* 1999;83:5B:120D-130D.
4. Cazeau S, Leclercq C, Lavergne T, et al. Effects of multisite biventricular pacing in patients with heart failure and intraventricular conduction delay. *N Engl J Med* 2001;344:873-80.

TO THE EDITOR: Moss et al. seem to unduly accentuate the benefits of CRT in patients with heart failure and mild symptoms. The authors report a 41% reduction in the risk of heart-failure events, an impressive outcome. However, over the average 2.4 years of follow-up in the study, heart-failure events occurred in 17.2% of patients in the CRT-ICD group, as compared with 25.3% of patients in the ICD-only group, which suggests that CRT prevented heart-failure events in only 8.1% of patients over 2.4 years. Moreover, 7.5% of patients who were assigned to receive CRT-ICD ther-

apy had unsuccessful placement of CRT leads, 1% could not receive an implant at all, and 1.3% had to have the devices removed during the trial. Overall, 9.8% of patients had device-related problems. Taken together, these observations suggest that patients with heart failure and mild cardiac symptoms who undergo CRT are more likely to have device-related problems than to benefit from the therapy.

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TO THE EDITOR: The substantial and significant increase in the ejection fraction in patients undergoing CRT in MADIT-CRT appears to be a real phenomenon and has been shown in previous studies of CRT involving patients with New York Heart Association (NYHA) class II heart failure.^{1,2} An important issue to address is why this factor did not translate into an improvement in mortality. The study may have been underpowered to identify a modest decrease in the low mortality of 2.5% in the ICD-only group. A possibility that should also be considered is that the expected benefit of CRT could have been offset by harm. In the early CRT studies, there was a concern that CRT may have been proarrhythmogenic. For patients with NYHA class III disease, this concern has not been realized, with any such effect being swamped by the benefit. For patients with class II disease, there are currently no data available to enable us to draw a similar conclusion. Until such data become available (a noninferiority study would be sufficient), guideline committees should resist the clamor to make NYHA class II disease an indication for CRT.

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No potential conflict of interest relevant to this letter was reported.

1. 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.
2. Abraham WT, Young JB, Leon AR, et al. Effects of cardiac resynchronization on disease progression in patients with left

ventricular systolic dysfunction, an indication for an implantable cardioverter-defibrillator, and mildly symptomatic chronic heart failure. *Circulation* 2004;110:2864-8.

THE AUTHORS REPLY: Several of the correspondents express concern that patients and their attending physicians were aware of treatment assignments in our study. Before the start of the trial, we realized that full blinding would be nearly impossible, since results on electrocardiography for patients during follow-up would allow differentiation between those with and those without biventricular pacing. However, all heart-failure events were adjudicated in a blinded fashion.

Regarding the heart-failure end point: this event occurred during in-hospital admission in 87% of the adjudicated cases (as pointed out in our article), with 78% of these patients having heart failure as the primary diagnosis. Outpatient treatment for heart failure occurred in only 13% of the adjudicated heart-failure end points. All hospitalizations and all potential heart-failure events that were categorized as such by study physicians were reviewed and independently adjudicated by the blinded end-point committee. The echocardiographic findings that patients in the CRT-ICD group had significantly greater reductions in left ventricular volumes and greater increases in ejection fraction from baseline to 1 year than patients in the ICD-only group provide a physiological explanation for the reduced rate of heart-failure events with biventricular pacing.

We understand Wilson's concern regarding device problems. Of note, the absolute reduction

of 8.1 percentage points in end-point events between the CRT-ICD group and the ICD-only group was found in the intention-to-treat analysis, which took into account unsuccessful lead placement and device removal.

Owen's concern about the lack of reduction in mortality with CRT-ICD therapy relates to the low annual mortality of 3% or less in each of the study groups. Our findings are similar to those in the Studies of Left Ventricular Dysfunction (SOLVD)–Prevention trial that were reported in 1992, in which the use of enalapril in at-risk, asymptomatic patients with cardiac disease reduced heart-failure events but had a negligible effect on the low death rate among patients.¹ However, in SOLVD, a reduction in mortality occurred during long-term follow-up.² In our trial, we carried out prospective device interrogations, and no proarrhythmic effects were associated with biventricular pacing.

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Since publication of their article, the authors report no further potential conflict of interest.

1. The SOLVD Investigators. Effect of enalapril on mortality and the development of heart failure in asymptomatic patients with reduced left ventricular ejection fractions. *N Engl J Med* 1992;327:685-91. [Erratum, *N Engl J Med* 1992;327:1768.]

2. Jong P, Yusuf S, Rousseau MF, Ahn SA, Bangdiwala SI. Effect of enalapril on 12-year survival and life expectancy in patients with left ventricular systolic dysfunction: a follow-up study. *Lancet* 2003;361:1843-8.

Comparative Efficacy of Influenza Vaccines

TO THE EDITOR: In their study comparing the efficacy of two vaccines against influenza types A and B, Monto et al. (Sept. 24 issue)¹ report that the absolute efficacy against both types of influenza was 68% for the trivalent inactivated vaccine and 36% for the live attenuated vaccine. The term "absolute" is misleading, since the authors used it to mean the relative reduction in incidence in the vaccinated group, as compared with placebo. In the placebo group, the baseline risk, which was 9.5% for influenza A and 1.2% for influenza B, should have been reported in an ac-

cessible manner, along with the relative risks. Without this information, the absolute risk is not easily accessible, and the reader's perception of benefit or harm may be exaggerated.² Since the trial included a diverse population in terms of age, sex, and ethnic background, results on heterogeneity of effect across these variables and the presence or absence of coexisting illnesses (e.g., diabetes and renal and cardiovascular disease) would be helpful to know. This is especially important because the cost-effectiveness of influenza vaccination for various subgroups remains uncer-