JACC: HEART FAILURE
VOL. 3, NO. 9, 2015

ISSN 2213-1779/$36.00
PUBLISHED BY ELSEVIER INC.
http://dx.doi.org/10.1016/j.jchf.2015.06.003

EDITORIAL COMMENT

Cardiac Resynchronization Therapy for Mild Heart Failure

Compelling Evidence of Long-Term Benefits*

N.A. Mark Estes III, MD

Multiple prospective, randomized clinical trials evaluating biventricular pacing with cardiac resynchronization therapy (CRT) have demonstrated improved heart failure status, quality of life, exercise capacity, left ventricular (LV) systolic function, mortality, and multiple other outcomes in heart failure patients (1-5). The early observations of clinical improvement in selected patients with advanced New York Heart Association (NYHA) functional class III and IV heart failure patients were followed by assessment of CRT in patients with NYHA functional class I and II heart failure symptoms. Hospitalizations for heart failure and mortality were improved in these patients with less advanced symptoms (1-5).

The heart failure patients with a left bundle branch block (LBBB) derived clinical benefit from CRT with defibrillators (CRT-D) with reductions in heart failure progression, ventricular tachyarrhythmias, and mortality and improved echocardiographic findings with reverse remodeling (1-5). However, no clinical benefit was observed in patients with a non-LBBB QRS pattern (right bundle branch block or intraventricular conduction disturbances). Patients with QRS widths >150 ms consistently demonstrated the greatest decreases in heart failure events and LV volumes and improvement in LV ejection fraction (1-5). Female patients have higher response rates to CRT than male patients. Patients with nonischemic cardiomyopathy demonstrate improved heart failure metrics more frequently than those with ischemic heart disease (1-5). Patients in sinus rhythm demonstrate response rates higher than those in atrial fibrillation. Beyond these clinical benefits, CRT with or without a defibrillator also results in echocardiographic evidence of reverse remodeling of the left ventricle (1-5). On the basis of this evidence, current guidelines recommend CRT for heart failure patients with an LV ejection fraction <35%, NYHA functional class I to III symptoms on optimal medical therapy, and QRS duration >120 ms on the surface electrocardiogram.

Previously, 3 multicenter, prospective, randomized clinical trials evaluated the role of CRT in patients with mild heart failure (1-3). The MADIT-CRT (Multicenter Automatic Implantable Defibrillator Trial with CRT) and the REVERSE (Resynchronization Reverses Remodeling in Systolic Left Ventricular Dysfunction) trial demonstrated that the benefit observed in patients with advanced heart failure can be extended to the prevention of heart failure progression in those with asymptomatic or mildly symptomatic heart failure in the short term (1,2). In these trials, follow-up was limited to 1 to 3 years (1,2). The RAFT (Resynchronization for Ambulatory Heart failure Trial) also demonstrated reduced total mortality among patients with mild to moderate heart failure treated with CRT-D with a mean follow-up of 3.3 years (3). However, the RAFT enrolled patients with more advanced (NYHA functional class III) heart failure (3). Despite important differences in study designs, the results of these trials are complementary, demonstrating the short-term benefit of CRT (1-3).

With the publication of the long-term follow-up of patients in both the MADIT-CRT and REVERSE trial, long-term benefits have been demonstrated with both

*Editorials published in *JACC: Heart Failure* reflect the views of the authors and do not necessarily represent the views of *JACC: Heart Failure* or the American College of Cardiology.

From the Tufts University School of Medicine, New England Cardiac Arrhythmia Center, Tufts Medical Center, Boston, Massachusetts. Dr. Estes is a consultant for Medtronic, Boston Scientific, and St. Jude Medical.

trials (4,5). These benefits have been noted with both CRT with a pacemaker as well as those devices with defibrillator backup (CRT-D) in the REVERSE study (5). After 12 months of CRT, the changes in the clinical composite score, LV end-systolic volume index, 6-min walk time, and quality-of-life indexes were similar between CRT with a pacemaker (CRT-P) and CRT-D patients (3). However, long-term (5 years) follow-up showed lower mortality in the CRT-D group, and CRT-D (hazard ratio: 0.35; $p = 0.003$) was a strong independent predictor of survival (5). Female sex, longer unpaced QRS duration, and smaller baseline LV end-systolic volume index were also associated with better survival (5).

SEE PAGE 691

In this issue of *JACC: Heart Failure*, Gold et al. (6) extend the long-term observations in the REVERSE trial, reporting the results of a novel technique of assessment of the lifelong extrapolated patient outcomes with CRT in mild heart failure. The investigators used data from the 5-year follow-up of the REVERSE trial to extrapolate survival and heart failure hospitalizations. It should be noted that advanced statistical modeling techniques, known as the rank-preserving structural failure time model, were used to adjust for protocol-mandated crossover in the survival analysis to extrapolate clinical outcomes to patient lifetime (6). CRT-ON was predicted to increase survival 22.8%, leading to a projected survival of 9.76 years (CRT-ON vs. CRT-OFF) (6). CRT-D was projected to demonstrate a significant improvement in survival compared with CRT-P (hazard ratio: 0.47; $p = 0.02$). Their analysis demonstrates a projected clinically significant long-term benefit of CRT in mild heart failure (6). On the basis of their analysis, CRT was predicted to reduce mortality, with CRT-D prolonging life more than CRT-P (6). Additionally, NYHA functional class I/II patients were shown to have a significantly reduced risk of heart failure hospitalization compared with functional class III patients, leading to CRT reducing heart failure hospitalization rates (6).

These findings extend the previous observations related to long-term benefits of patients with NYHA functional class I and II heart failure receiving CRT, reduced ejection fraction, and LBBB (4,5). The use of statistical modeling of long-term outcomes is novel in cardiovascular medicine. As noted by the authors, the statistical techniques used are commonly accepted for such analyses of long-term survival benefits in oncology. This analytic technique allowing lifetime extrapolation of outcomes with statistical adjustments for changes in treatment provides the capability to assess the economic impacts of therapy beyond the duration of the trial (6). In this respect, further economic analyses of these data using these analytic techniques and projecting the lifetime cost and cost-effectiveness of CRT are clearly warranted. With these additional data on the long-term impact of CRT, clinicians involved in the care of patients with heart failure should recognize that the data are compelling. Routinely providing both optimal medical therapy and early intervention with CRT in patients similar to those demonstrating short- and long-term benefits in these trials is supported by the highest standards of evidence-based medicine.

REPRINT REQUESTS AND CORRESPONDENCE: Dr. N.A. Mark Estes III, Tufts University School of Medicine, New England Cardiac Arrhythmia Center, Tufts Medical Center, 750 Washington Street, Boston, Massachusetts 02111. E-mail: nestes@tuftsmedicalcenter.org.

REFERENCES

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.

2. 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.

3. Tang AS, Wells GA, Talajic M, et al. Cardiac-resynchronization therapy for mild-to moderate heart failure. N Engl J Med 2010;363:2385–95.

4. Goldenberg I, Kutyifa V, Klein HU, et al. Survival with cardiac-resynchronization therapy in mild heart failure. N Engl J Med 2014;370:1694–701.

5. Gold MR, Daubert JC, Abraham WT, et al. Implantable defibrillators improve survival in patients with mildly symptomatic heart failure receiving cardiac resynchronization therapy: analysis of the long-term follow-up of remodeling in systolic left ventricular dysfunction (REVERSE). Circ Arrhythm Electrophysiol 2013;6:1163–8.

6. Gold MR, Padhiar A, Mealing S, Sidhu MK, Tsintzos SI, Abraham WT. Long-term extrapolation of clinical benefits among patients with mild heart failure receiving cardiac resynchronization therapy: analysis of the 5-year follow-up from the REVERSE study. J Am Coll Cardiol HF 2015;3:691–700.

KEY WORDS biventricular pacing, cardiac resynchronization therapy, chronic remodeling, heart failure