Cardiac Resynchronization Therapy for Mild Heart Failure
Compelling Evidence of Long-Term Benefits*

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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 volume 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...
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.

**REFERENCES**


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