

## Seeking More Time with Synchrony

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Clinical outcomes for patients who have heart failure with reduced ejection fraction continue to improve with the selection of effective therapies and their increasing duration of use. Randomized, controlled trials usually measure the efficacy of a therapy for a limited time, after which its longer-term efficacy is blurred by the crossover of patients to the active treatment after the trial has been completed. If a therapy is tested in patients who have advanced heart failure, its benefits may soon be obvious during the trial. However, earlier initiation of therapy, before symptoms of heart failure have become severe, may have a more profound effect on improving the trajectory years after the trial has ended. The Resynchronization in Ambulatory Heart Failure Trial (RAFT) assessed the clinical benefit of cardiac-resynchronization therapy (CRT), which is used to restore the synchrony of left ventricular contraction that has been impaired by prolonged conduction in patients who have heart failure with reduced ejection fraction. The RAFT results showed the clinical benefit of CRT in patients, most of whom had New York Heart Association (NYHA) class II heart failure, to reduce both mortality and the incidence of hospitalizations for heart failure during a mean of 40 months. Patients at the eight highest-enrolling centers were then followed for a median of nearly 14 years; during that time, as reported by Sapp et al. in this issue of the *Journal*, a sustained survival benefit was seen.<sup>1</sup>

In pivotal trials involving patients with NYHA class III or ambulatory class IV heart failure, CRT reduced symptoms, improved exercise capacity, and decreased hospitalizations.<sup>2,3</sup> Later evidence from the CARE-HF (Cardiac Resynchronization–Heart Failure) trial showed longer survival among patients who received CRT and standard pharmacologic therapy (without implantable cardioverter–defibrillators [ICDs]) than in patients who received pharmacologic therapy alone.<sup>4</sup> These trials showed that CRT reduced mitral regurgitation and cardiac remodeling and improved left ventricular ejection fraction — results that were also shown among patients with

mild heart failure symptoms.<sup>5,6</sup> However, there was controversy regarding the clinical benefit of CRT in patients with NYHA class II heart failure<sup>6</sup> until RAFT showed that more patients who received CRT with an ICD (CRT-D) survived and fewer were hospitalized than those who received an ICD alone. The long-term RAFT outcomes show sustained improvement in survival during a median of nearly 14 years of follow-up,<sup>1</sup> a longer horizon than the 7 years for selected patients in MADIT-CRT (Multicenter Automatic Defibrillator Implantation Trial with Cardiac Resynchronization Therapy), in which a mortality difference between groups was not shown.<sup>5</sup> The benefits of CRT observed in RAFT are additive to the effect of beta-blockers and angiotensin-converting–enzyme (ACE) inhibitors or angiotensin-receptor blockers, which were used by more than 90% of patients at baseline (Fig. 1 in the article). The substantial benefits of CRT were seen despite patient crossover from the ICD group to the CRT-D group and the inclusion of some patients who did not have a left bundle-branch block on electrocardiography and other patients who did not meet the current criteria for CRT.

Enthusiasm for CRT therapy in patients with mild heart failure is likely to increase further with recent data suggesting equal or better clinical outcomes with direct left bundle-branch area pacing instead of placement of the CRT leads through the coronary sinus.<sup>7</sup> A small, randomized trial that used this technique in patients with an indication for CRT and a left ventricular ejection fraction of up to 50% showed a greater likelihood of successful lead implantation and a larger improvement in left ventricular ejection fraction than in those who received traditional CRT.<sup>8</sup> Further advances in the design of pacing leads and delivery sheaths should improve the physiologic response to CRT and reduce procedural complications, which were significantly more prevalent among patients who received CRT-D than in those who received ICDs alone in RAFT.

The improved clinical trajectory for patients with mild heart failure at a median of nearly 14

years after CRT implantation is remarkably similar to the benefits observed in the cohort of asymptomatic patients who received enalapril in the landmark SOLVD (Studies of Left Ventricular Dysfunction) trial.<sup>9</sup> Although survival among patients with heart-failure symptoms was longer with enalapril than with placebo during the initial SOLVD trial period, survival at 12 years among those assigned to receive enalapril had declined to approximately that of patients who were assigned to receive placebo. In contrast, among the patients who were asymptomatic, survival was not longer in the enalapril group than in the placebo group during the 3-year trial period, but survival was significantly longer among these patients for the duration of the 12-year follow-up period, despite the widespread use of ACE inhibitors after the trial period ended.

On the basis of the results of SOLVD and other landmark trials in patients with heart failure, the multiple medications recommended for patients who have symptomatic heart failure with reduced ejection fraction are now recommended also for patients with pre-heart failure (Stage B), before symptom onset. Despite the fact that the patients in RAFT had only mild heart-failure symptoms at the time of their enrollment in the trial, almost 80% had died by 15 years. Because CRT offers remarkable improvements in functional capacity, quality of life, and survival, the principles of providing earlier treatment for heart failure might now include CRT, particularly as technology improves. CRT initiation could be accelerated after a diagnosis of left bundle-branch block is made in patients with a low left ventricular ejection fraction, which is less likely to increase with the use of medical therapy alone.<sup>10</sup> With increasing use of biomarker screening to identify patients with asymptom-

atic left ventricular dysfunction, we should also advance our use of effective therapies, with the hope that we will see more time with good-quality survival.

Disclosure forms provided by the authors are available with the full text of this editorial at NEJM.org.

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DOI: 10.1056/NEJMe2312419

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