Why We Have to Use Cardiac Resynchronization Therapy–Pacemaker More

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KEYWORDS

• Cardiac resynchronization therapy • Pacemaker • Chronic heart failure

KEY POINTS

- Cardiac resynchronization therapy (CRT) may use either a pacemaker (CRT-P) or a biventricular implantable cardioverter-defibrillator (CRT-D). Both are electrical treatment modalities that have been validated for the management of chronic heart failure (CHF).
- There is currently no strong scientific evidence indicating that a CRT-D must be offered to all candidates for CRT.
- The preferential choice of CRT-P in the remainder of patients is currently an acceptable one.
- Another direction to explore is downgrading from CRT-D to CRT-P at the time of battery depletion in patients with large reverse remodeling and no ventricular tachycardia and ventricular fibrillation detected.

Supported by extensive clinical evidence, electrical device therapy for heart failure has had impressive development during the last 15 years. Patients with chronic heart failure (CHF) may benefit from implantable electrical cardiac devices with a view to (1) resynchronize the failing discoordinated heart to improve mechanical performance or (2) prevent the risk of arrhythmic death by automatic cardioversion-defibrillation. These 2 therapies can be applied separately with dedicated devices. Cardiac resynchronization therapy (CRT) may use specific pacemakers (CRT-P) or an implantable cardioverter defibrillator (ICD). Or these can be applied together with a combined device, the biventricular implantable cardioverter-defibrillator (CRT-D). Today, the proportion of CRT-D devices among all CRT devices implanted worldwide is about 75%, reaching 90% or more in the United States and in some European countries such as Germany and Italy.[1] By contrast, other European countries are still implanting a significant number of CRT-P devices: 39% in France, 44% in Sweden, 46% in and Belgium in 2013. Why are there such different practices in highly developed countries with common scientific guidelines and similar or nearly similar levels of health expenditure? The response to this intriguing question remains unclear. This article attempts to answer these important questions for clinical practice: Is the growing use of CRT-D devices supported by solid clinical evidence? Is the risk-benefit and cost-benefit profile of CRT-D better than CRT-P in CHF patients?

DO ALL HEART FAILURE PATIENTS WITH EJECTION FRACTION LESS THAN 35% NEED AN IMPLANTABLE CARDIOVERTER DEFIBRILLATOR?

The widespread use of CRT-D is justified because all patient candidates for CRT are theoretically indicated for an ICD. The use of ICDs for primary prevention in heart failure is based on the high

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proportion of sudden death in total mortality in CHF patients with reduced left ventricular ejection fraction (LVEF). Data from large drug trials with events adjudication committees show a range between 35% to 58% in the Metoprolol Randomized Intervention Trial in Congestive Heart Failure (MERIT-HF),[2] which is probably explained by the inclusion of 41% of subjects in New York Heart Association (NYHA) functional class II. As the severity of CHF increases, the proportion of sudden death relative to overall mortality decreases and, conversely, the percentage of deaths attributed to worsening heart failure increases.[2] In MERIT-HF, the relative proportion of sudden death was 84% in NYHA class II subjects, 51% in class III, and 33% in class IV when the total 1-year mortality rate was 6.3%, 10.5%, and 18.6%, respectively. Therefore, the greatest benefit of ICDs is likely to be for patients with mild-to-moderate heart failure. The Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT) is, thus far, the only trial showing a reduction of all-cause mortality by ICD therapy in subjects with mild-to-moderate heart failure and LVEF less than 35%.[3] In that study, which enrolled subjects optimally treated for CHF, ICD therapy was compared with amiodarone or placebo. Although amiodarone conferred no benefit compared with placebo, a significant 23% relative reduction in the risk of overall mortality was observed among the ICD recipients. However, these apparently spectacular results must be interpreted cautiously. The demographic characteristics of the SCD-HeFT population were quite peculiar (see later discussion). In addition, the trial had to include more than 2500 subjects followed up for a median of 45.5 months and be extended for another year to show a statistically significant, albeit modest, absolute risk reduction (ARR) of 7.2% at 5 years. Finally, in agreement with the epidemiologic data mentioned earlier, a subgroup analysis showed that the risk reduction was confined to NYHA class II subjects (hazard ratio [HR] 0.54 [0.40–0.74], probability [*P*]<.001, ARR 11.9% at 5 years). No treatment benefit was observed among the 30% more severely affected subjects (HR 1.16 [0.84–1.61], $P = .30$). Finally, the clinical benefit by the ICD was similar in subjects with ischemic cardiomyopathy (HR 0.79 [0.60–1.04]) and nonischemic cardiomyopathy (HR 0.73 [0.50–1.07]). These findings were incorporated in recent guidelines on heart failure[4] with recommendation to implant an ICD in subjects with symptomatic heart failure (NYHA class II-III) and an ejection fraction less than or equal to 35%, despite greater than or equal to 3 months of treatment with optimal pharmacologic therapy, who are expected to survive for greater than 1 year with good functional status, irrespective of the cause. The recommendation is class IA for ischemic and IB for nonischemic due to the wider evidence in ischemic patients.

The Real World and the Individual Patient

Randomized trials are often criticized because they enroll highly selected subjects, unlike those encountered in the real life. This criticism is particularly applicable in the treatment of CHF. Considering the large randomized studies of drugs or devices in CHF conducted in recent times, the mean age of the populations was relatively young, between 60 and 67 years, and the proportion of women was small, between 20% and 32%. The most striking example is the SCD-HeFT, with a population 60.1 years old on average and 23% women.[3] These demographic characteristics are largely different from the real life in which the mean ages are more than 70 years and the proportion of women approaches 50%.[5] It is, therefore, problematic to apply recommendations issued from randomized trials to the general population of patients with CHF. Common sense dictates that these recommendations would have to be applied to similar or identical patient populations as the studies used to validate the clinical indication. In the case of the SCD-HeFT, the treatment should be logically offered to young or relatively young patients without serious comorbidities. However, most patients with moderate to severe CHF are older and have various concomitant disorders.[5]

IS THE CLINICAL SUPERIORITY OF CARDIAC RESYNCHRONIZATION THERAPY–DEFIBRILLATOR COMPARED WITH CARDIAC RESYNCHRONIZATION THERAPY–PACEMAKER CLEARLY ESTABLISHED?

Current clinical evidence is based on the results of randomized controlled trials, principally the Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure (COMPANION) trial, a post hoc analysis from REsynchronization reVErses Remodeling in Systolic left vEntricular dysfunction (REVERSE) study in subjects with mild CHF, meta-analyses, or extensive reviews and some large-scale registries.

New York Heart Association Functional Class III-IV

Several randomized trials have been conducted to ascertain the clinical impact of CRT in subjects with moderate-to-severe CHF using CRT-P, CRT-D, or both.[6–12] Meta-analyses have also