EDITORIAL COMMENTARY

Cardiac resynchronization in pacing-associated cardiomyopathy: Is it time to upgrade?

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Cardiac resynchronization therapy (CRT) is a potent weapon in the armamentarium for chronic systolic heart failure. Although numerous randomized clinical trials have shown improvement in morbidity and mortality in appropriately selected patients, there remains substantial controversy regarding the role of CRT in certain populations, including patients with atrial fibrillation (AF) and mid-range ejection fraction. Many patients with conventional device implant indications develop worsening atrioventricular (AV) conduction disease over time, often based on heart failure progression, and undergo upgrade of their existing devices to CRT. Such patients were excluded from early randomized clinical trials for CRT therapy. Considering the substantial risk of procedure-related complications in patients undergoing CRT upgrade procedures, further data regarding the clinical benefit return of the procedure are required for patients to make an informed decision regarding such procedures.

A new study reported by Brandão and colleagues[1] in this issue of *Heart Rhythm O*^{2} provides important insights into both the clinical decision-making and outcomes in patients undergoing CRT upgrades for standard indications. The purpose of their study was to compare clinical outcomes in patients undergoing upgrade to cardiac resynchronization therapy to those receiving de novo implants. They analyzed 295 patients treated at their single institution over an 11-year period; 56 of these patients received upgrade of an existing pacemaker or implantable cardioverter-defibrillator system. At a median follow-up of 3 years the following outcome variables were analyzed: objective and subjective CRT response, all-cause mortality, and major adverse cardiac events (MACE). Demographics and outcomes were reported for the entire cohort, as well as a propensity-matched cohort of 106 patients. It is worthwhile noting that the patients represented in the trial have a high prevalence of features associated with improved CRT response: nonischemic cardiomyopathy (73%), high NYHA class (77% classes III and IV), and wide QRS duration (mean 171 ms).

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The authors report no difference in either clinical or echocardiographic response to CRT between the de novo and upgrade cohorts. The rates of CRT response are also in keeping with those reported in other trials. Importantly, however, major adverse cardiac events were 45% less common in the de novo patients compared to upgrades. This finding seems to be primarily driven by heart failure hospitalization in the upgrade cohort. In the propensity-matched cohorts, the MACE curves are nearly superimposable between the 2 groups.

The reported difference in MACE bears further discussion. Compared to patients undergoing a de novo CRT implant, the upgrade patients were older and had a substantially higher burden of medical comorbidities, renal insufficiency, valvular heart disease, and AF. Although the use of propensity matching in the study design is useful to minimize bias with respect to the primary analysis, the decisions regarding whether to upgrade and to which system (ie, CRT-P vs CRT-D) were inherently subjective. Thus, although the propensity schema would suggest that well-matched de novo and upgrade patients have similar outcomes, the design is less useful in informing the clinical decision regarding which patient to upgrade.

When one considers the original implant indication and clinical characteristics of the upgrade cohort, several important points should be made. First, 44 of 56 (79%) upgrade patients had pacemakers implanted originally. Of these 44 patients, only 15% were originally implanted for sinus node dysfunction. Thus, one would anticipate a substantial burden of right ventricular pacing in most of these pacemaker patients. Furthermore, 20 of 44 patients implanted with pacemakers had a reduced left ventricular ejection fraction (mean 42.5%) and 13 of 44 had a clinical heart failure diagnosis at the time. Considering the results from the BLOCK-HF trial, the majority of these upgrade patients would likely receive de novo CRT devices in contemporary practice.[2] Given that the majority of the upgraded patients had right ventricular pacing–induced left ventricular dysfunction, and that these patients tend to respond well in trials to CRT, one might question whether this contributed to overperformance of CRT in this cohort.

The prevalence of AF was substantially higher in the upgrade cohort (58% vs 27%), and 40% of the upgrade cohort presented in AF at the time of their procedure. Unlike other CRT upgrade studies, the Brandão report utilized

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contemporaneous AV nodal ablation in 10 of 56 upgrade patients to maximize CRT delivery. However, the authors did not provide specific methodology regarding specific criteria used to pursue AV nodal ablation either at the time of upgrade or during follow-up. Given the strong correlation between reduced effective biventricular pacing and clinical outcomes, one wonders whether nodal ablation could have been utilized more broadly in the trial.[3]

The Brandão study also lacks an active control cohort (ie, patients not undergoing upgrade), and thus any potential harm associated with the upgrade intervention can only be inferred from reported complication rates. Enthusiasm for CRT upgrade is tempered by data from several observational studies that have demonstrated a high rate of procedural complications with CRT upgrade. The REPLACE registry reported complications in 18.7% of 420 patients receiving upgrade to or revision of CRT systems.[4] There was also a 1.1% incidence of late procedure-related death in patients receiving a new transvenous lead from this registry. Although the Brandão study did not specifically enumerate procedure-related complications in their methodology, the authors report an 8.9% rate of lead-related complications. Rates of long-term device infection and need for lead extraction are included; however, the timing of these events was not reported. It is worth noting that more than half of all deaths in the upgrade cohort occurred very early on the survival analysis in Figure 2.[1] Moreover, the early MACE and mortality curves are nearly superimposable, suggesting that nearly all early MACE events were deaths.

Overall, the Brandão study suggests a substantial subjective and objective benefit to CRT upgrade in a high-risk cohort of patients with (largely) pacing-associated systolic heart failure. This benefit is of similar magnitude to that seen in a propensity-matched cohort of patients receiving de novo CRT implants for standard indications. The use of contemporaneous AV nodal ablation to facilitate CRT delivery is an important clinical consideration and distinguishes the Brandão report from other contemporary trials. Further prospective studies are needed to determine the relative benefit of CRT upgrade in patients with less severe heart failure, and to define the threshold for employing upstream AV nodal ablation in patients with AF undergoing upgrade.

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