Editorial

Cardiac Resynchronization Therapy in New York Heart Association Class IV Heart Failure
It Is All About Selection

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In recent years, cardiac resynchronization therapy (CRT) has emerged as an important therapeutic strategy in patients with advanced heart failure. It has become common practice to use CRT in combination with implantable cardioverter-defibrillator (so-called CRT-D) in patients with impaired left ventricular systolic function and New York Heart Association (NYHA) class III symptoms.1 Evidence is also mounting regarding the potential benefit of CRT in delaying disease progression in patients with symptomatic heart failure.2-3 However, the role of CRT and CRT-D is less clear in patients with very advanced heart failure, especially in those with NYHA class IV symptoms (those with symptoms at rest and worsening with exertion). In fact, <5% of all heart failure subjects enrolled in large multicenter mortality device trials fulfilled this category.4 Although there has been increasing debate over this issue,5-7 patients in the intensive care unit requiring inotropic and mechanical support are still not considered suitable candidates for CRT or CRT-D “salvage” therapy.8 Some patients with very advanced, refractory heart failure are ambulatory, however; in these patients, neither cardiac transplantation nor permanent mechanical support devices are appropriate or imminent. Many of these patients are still considered as approaching “stage D heart failure,” in which they can be best characterized by experiencing end-stage disease refractory to optimal medical therapy. Even now, we have few data in such patients because they have been systematically excluded or avoided in most CRT trials, perhaps because of a presumed shortened lifespan.

With this in mind, the Comparison of Medical, Pacing, and Defibrillation Therapies in Heart Failure (COMPANION) trial investigators retrospectively reviewed their experience with this severely symptomatic but ambulatory cohort to assess the benefits of both CRT and CRT-D.9 As described, COMPANION is the single largest clinical experience of CRT/CRT-D devices implanted in patients with NYHA class IV heart failure (without spontaneous or inducible sustained ventricular tachyarrhythmias). In fact, the 217 NYHA class IV subjects in the COMPANION trial encompassed almost half (48%) of all NYHA class IV subjects enrolled in multicenter CRT trials published to date. The COMPANION investigators observed that CRT and CRT-D significantly improved time to the combined end point of all-cause death or heart failure hospitalization compared with optimal medical therapy.9 Some interesting insights become obvious, however, after careful scrutiny of the data presented by Lindenfeld and colleagues.9

First, the line between the NYHA classes is not distinct; it is always more or less in the eyes of the beholder and can be highly variable.8 In general, NYHA classification is judged clinically by the patient’s symptom burden either by self-report or by physician assessment. It does not necessarily reflect the underlying chronicity or stability of the clinical presentation. In fact, determining disease severity in heart failure still requires a wide range of clinical, biochemical, and functional parameters. A “staging” process has been used in transplantation evaluation, but universally accepted and definable measures are still lacking. Therefore, drawing comparisons between patients, let alone between trials, can be a great challenge. For now, the true testimony of heart failure severity in any trial lies in the direct comparison of annualized mortality with other trials, which can be vastly different even when patients were selected within the same NYHA III-IV class range. As described in the Lindenfeld et al article, the 1-year mortality rate for the NYHA class IV optimal medical therapy cohort in COMPANION (44%), even in the best-case scenario with CRT-D (30%), was higher than most contemporary neurohormonal antagonist and oral inotropic drug trials in severe heart failure (12% to 26%) and only slightly lower than that observed in the intravenous inotropic drug trials and destination therapy trials (51% to 76%). This is perhaps because of the requirement of a wide QRS duration and a heart failure hospitalization in the preceding 12 months at the time of enrollment, both markers of advanced diseases and powerful predictors of mortality. Hence, the NYHA class IV experience in COMPANION is perhaps the closest to what we would consider a stage D heart failure cohort.

Previous studies also have suggested that patients in NYHA class IV may derive significant benefit from a reduction of sudden cardiac death, presumably by receiving more frequent but appropriate delivery of defibrillator therapy.11 This is confirmed in this COMPANION analysis, in which adjusted rates for sudden cardiac death were found to be significantly lower in the CRT-D group compared with the CRT or optimal medical therapy groups in the NYHA class

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IV cohort. Furthermore, there was improvement in self-reported quality-of-life scores and changes in NYHA class in both NYHA class III and IV cohorts, although this was practically an unblinded comparison between optimal medical therapy (no device implantation) and CRT/CRT-D device implantation. However, it is more difficult to explain the fact that the incidence of heart failure death (heart failure caused by "pump failure") or time to heart failure death was not significantly affected by CRT/CRT-D therapies in this COMPANION analysis. It is important to emphasize that while a mortality benefit was observed with the use of CRT-only devices in the Cardiac Resynchronization Heart Failure (CARE-HF) trial, most patients enrolled had predominantly NYHA class III symptoms, and the annualized mortality rate was only 12%. Although the sample size was too small to draw any conclusions, it is conceivable that the apparent diminishing returns of CRT in reducing heart failure deaths can be explained by the difference in the COMPANION population rather than the degree of symptom burden (NYHA class IV), whereby reverse remodeling in this stage D cohort may not be realistically possible. That being said, there is currently no evidence to demonstrate that defibrillators alone can be as effective as CRT-D in this population.

What is reassuring from this COMPANION post hoc analysis is that appropriately selected ambulatory patients with severe but stable heart failure and no need for inotropic support can have acceptable risks for procedure-related complications. These observations have clearly raised some important challenges, however, particularly in light of limited published NYHA class IV and/or stage D heart failure experience. Clearly, the role of CRT in the management of advanced heart failure with NYHA class IV symptoms depends largely on appropriate patient selection, much the same way as determining the risk-to-benefit ratio of various other stage D treatment options. The goals and potential benefits of CRT/CRT-D therapy can be very different as symptom burden increases, and Lindenfeld and colleagues have presented insightful findings that call for more research in this area. But how can we better distinguish a stage C from a stage D heart failure patient in the presence of overt NYHA class IV symptoms? Is there enough evidence to justify the morbidity and mortality benefits of CRT for all NYHA class IV patients beyond an implantable defibrillator? What is the best way to determine a clinical benefit in this population with advanced disease: deterring death or improving symptoms? The precise algorithm for this selection process to achieve long-term clinical benefits still needs to be defined.

Disclosures

Dr Tang is a consultant for Medtronic, Inc, and Boston Scientific, Inc. Dr Francis reports no conflicts.

References


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