Cardiac Resynchronization Therapy for Heart Failure
Has the Time Come?

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In the current issue of Circulation, Anand and colleagues representing the COMPANION (The Comparison of Medical Therapy, Pacing and Defibrillation in Heart Failure) Investigators have brought forward compelling data that emphasize the substantial morbidity benefit of cardiac resynchronization therapy (CRT) in patients with moderately severe to severe heart failure. Unlike other studies that have reported reductions in heart failure hospitalizations, Anand et al have accounted for the competing risk of death and variations in follow-up time and surmised that CRT resulted in 44% (optimal pharmacological therapy plus CRT [CRT-P]) and 41% (optimal pharmacological therapy plus CRT with defibrillator [CRT-D]) reductions in heart failure–related hospitalizations. Remarkably, the benefit was seen within days to weeks and was a sustained effect throughout the trial. By our calculations using the reported heart failure hospitalization rates (0.73 for optimal pharmacological therapy [OPT], 0.43 for CRT-D, and 0.41 for CRT-P), the number needed to treat with CRT to reduce 1 hospitalization is <4. This is a remarkable benefit for any evidence-based heart failure therapy. These data are sufficiently compelling that when aggregated with the known survival benefits ascribed to CRT, at least some of the residual concerns about efficacy for this device-based intervention should be assuaged. On the basis of these findings, the time may now have come to fundamentally change practice and to more avidly adhere to already extant class I indications for CRT in patients with class III or IV heart failure, with a prolonged QRS, and who are already on appropriate background medical therapy.

Several early data sets established that a prolonged QRS is independently associated with worse outcomes in chronic heart failure. Recent analyses from the EVEREST (Efficacy of Vasopressin in Heart Failure Outcome Study with Tolvaptan) trials have confirmed a similar observation in the setting of acute decompensated heart failure. The pathology represented by a prolonged QRS has not been entirely elucidated, but at least in part it involves inefficient ventricular function with discordant left and right ventricular contractions (ie, ventricular dyssynchrony). This phenomenon can be overcome with biventricular pacing, now described as CRT. The original data describing the benefit of a multisite cardiac pacing strategy emanated from the MIRACLE [Multicenter InSync Randomized Clinical Evaluation] trial. A modest gain in time traversed during a 6-minute walk test and improvement in quality of life were the bases on which this technology became a proof-of-concept idea and gained approval as a therapeutic strategy. The uptake was initially slack because the true benefit was not entirely evident. However, compelling data emerged from both the COMPANION and CARE HF [The Cardiac Resynchronization—Heart Failure] trials and confirmed not only an improvement in functional capacity but also an improvement in survival both for CRT with defibrillation functionality and remarkably for CRT alone. It was on the basis of these findings that CRT was recommended by the 2005 American College of Cardiology and American Heart Association guideline statements for chronic heart failure, with reduced ejection fraction as a class I indication with a level of evidence “A.” The Heart Failure Society of America also positioned the use of CRT strongly in its guidelines though not at the topmost tier. However, recently published data have suggested that among patients with an indication for CRT, the penetration of this therapy is no better than 40%.

Reasons for this apparent hesitancy in the use of an evidence-based therapy for heart failure are several fold: this is an invasive strategy that requires permanent device implantation; initial success with implantation is ~90% to 95% with sustained benefit seen in only ~70% of patients; the cost is not insignificant because the device with defibrillation functionality has a retail price of ~$20 000 to $25 000; despite years of research, the best indication for implantation remains a prolonged QRS because markers of dyssynchrony have not consistently been shown to predict response; patient preference for an invasive approach is a major issue; attainment of appropriate evidence-based background medical therapy is an absolute prerequisite and takes time and resources to achieve; uncertainty about the benefit in the setting of atrial fibrillation, a common comorbidity in heart failure, generates hesitancy in making the referral for CRT; and an ongoing debate about CRT only or CRT with ICD in patients with class IV heart failure creates an inertia point that impedes full utilization. The reasons for pause are not inappropriate.

Hospitalization is an increasingly problematic dimension of heart failure. The economic costs for heart failure hospitalization are staggering, measured in the billions of dollars. Even more staggering, however, are the human costs. After an index hospitalization for decompensated heart failure, for pathological reasons not yet elucidated, the natural history of...
heart failure is profoundly altered. Rehospitalization occurs in 20% of all patients previously hospitalized for HF at 30 days and in 50% at 6 months, and the risk of death at 30 days approximates that of patients admitted with an acute myocardial infarction, \( \approx 15\% \). Avoiding hospitalizations therefore would seemingly be deemed an appropriate goal for intervention. To reduce hospitalization for heart failure by \( \approx 40\% \) or greater would therefore be a remarkable achievement and one that should be seriously considered. We have previously accepted, almost without question, that all evidence-based strategies reduce both mortality [HF-related death] and morbidity [HF exacerbations or hospitalizations], in part because this has often been the composite end point of major HF trials. Yet truly refined analyses that adequately separate the hospitalization benefits from the mortality benefits have not consistently been carried out. This is in part due to the competing risks of hospitalization and death. Patients hospitalized for heart failure die more quickly, and those patients who die are no longer hospitalized, whereas those who survive may survive only to experience more hospitalizations. Therefore, a true determination of the morbidity benefits of a treatment intervention needs to account for both the mortality experience and the time of follow-up effect. To overcome this dilemma, the current investigators resorted to a novel statistical method to account for both death and follow-up time.

The analysis of recurrent events in the presence of a terminal event such as death is complex and, surprisingly, very few statistical methods are available to govern such analyses.\(^{10,11}\) Despite extensive research, no conclusive solutions have been found. The method of Ghosh and Lin used by Anand et al merges existing knowledge on recurrent events with that of competing risk.\(^{12,13}\) This method is a nonparametric approach for making inferences about the mean function of a recurrent event rate in the presence of death. It is based on the marginal mean of the cumulative number of recurrent events over time. The mean function accounts for subjects who die who no longer experience other recurrent events. Although this method does not fully account for the effect of possible confounders, it is appropriate for the analysis performed by Anand et al because their analysis was executed on an intention-to-treat basis. Thus, the unaccounted-for confounders should be equally distributed. It is noted, however, that the substantial crossover observed (25% of OPT patients) and the differential withdrawal of consent between study groups (OPT group=26\%, CRT-P=6\%, and CRT-D=6\%) makes even this novel assessment a somewhat compromised test of the true treatment effect of CRT. Had the investigators done an as-treated analysis, the influence of known and, more importantly, unknown confounders would have been too great and would have disqualified the analysis. We believe the statistical computations are valid and support the findings reported by Anand et al.

Even though these limitations must be kept in mind when interpreting the findings of the COMPANION trial, other observations would suggest that the findings as reported are in fact conservative. In particular, the high crossover recorded for the OPT group with subsequent device implantation and reduction in hospitalizations suggests that an even greater than observed reduction heart failure hospitalizations associated with CRT might have occurred. Yet some of the enthusiasm for these findings is tempered by certain other additional limitations to the present data that must be acknowledged. The hospitalization rates in COMPANION were considerable, so the effect size of CRT therapy may have been exaggerated and may not be realized in clinical practice. Though it is opined by the investigators that the burden of hospitalization verifies the disease severity seen in this study, a counterargument can be made that the placebo mortality rate in COMPANION (ie, the 12-month rate of death in the OPT group of 19\%) was not dissimilar from other studies targeting New York Heart Association class III and IV heart failure. Thus, the hospitalization rate seen in this study may indeed represent an outlier or a play of chance. Additionally, certain hospitalizations were not included (that could have been ascribed to the CRT group) and, importantly, hospitalizations for device implantation only were not included. Those hospitalizations matter and come at a cost. How these events would have affected the magnitude of the difference between OPT and device therapy is not readily evident, but more events assigned to the device arms would attenuate the observed effects.

How should we as clinicians interpret these data? The resource expenditure required for broader uptake of CRT therapy is not inconsequential, and in the absence of better strategies to discriminate responders from nonresponders, the ongoing hesitancy of the medical community is understandable even if, in the face of the present data, it is much less tolerable. The optimal threshold penetration for device-based therapy is not clear, but after considering patients who refuse or have insurance limitations or other overt contraindications, no reason exists why there should be dissimilar thresholds for device-based heart failure therapy compared with medical therapy (eg, angiotensin-converting enzyme inhibitors or \( \beta \) blockers). Thus, it appears evident that greater use of device-based therapy for heart failure is warranted. In addition to the overall lesser use of CRT, a greater concern is the inequitable use of device-based therapy. Women and minorities are much less likely to receive CRT with or without ICD (or even ICD alone) despite having similar indications. The use of device-based therapies in these important patient cohorts may be as much as 50\% less than in others even when they have similar indications for therapy.\(^{14,15}\) This is an especially egregious example of disparate health care, and if the rationale for withholding therapy is in part a question of efficacy, that question, on the basis of the current data, should no longer exist.

Thus, the time has come to reconsider the use of device-based therapy for heart failure. As stated in the 2005 American College of Cardiology/American Heart Association chronic heart failure guidelines and now reiterated in the 2008 device-based therapy guidelines: “For patients who have left ventricular ejection fraction (LVEF) less than or equal to 35\%, a QRS duration greater than or equal to 0.12 seconds, and sinus rhythm, CRT with or without an ICD is indicated for the treatment of NYHA functional class III or ambulatory class IV heart failure symptoms on optimal recommended medical therapy.” This is a class I, level of evidence ‘A’ recommendation.\(^{16}\) Even in the absence of a
more refined patient selection algorithm, further hesitancy in the uptake of this therapy appears unwarranted. Evidence-based, guideline-indicated therapies for heart failure that offer the potential to positively impact the natural history of this disease should be used, used avidly, and used equitably. The time has come.

Disclosures
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