Journal of the American College of Cardiology
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Published by Elsevier Inc.

Vol. 59, No. 17, 2012
ISSN 0735-1097/$36.00
doi:10.1016/j.jacc.2012.01.018

EDITORIAL COMMENT

The Next Frontier of Clinical Trials

Personalized Medicine for Devices*

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Randomized, controlled trials (RCTs) have convincingly proven that in patients with advanced (New York Heart Association functional class III/IV) systolic (left ventricular [LV] ejection fraction ≤35%) heart failure and wide QRS complex (QRS ≥120 ms), cardiac resynchronization therapy (CRT) improves functional status and quality of life (1), decreases heart failure hospitalizations (2), and prolongs survival (3). However, the lack of response to CRT in a substantial portion of patients (one-third) has been a consistent finding (4).

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The lack of a uniform response to an intervention is not unique to trials involving devices. RCTs are interpreted based on the mean response of all participants in the treatment arm to the intervention. A positive trial simply indicates that the mean change observed in the treatment group is in the desired direction but provides no clue to individual responses to the intervention. It is likely that some participants would experience a greater benefit (super responders) than others (responders), yet some may not benefit at all (nonresponders) and few may even experience harmful effects.

The inability to predict individual responses has been the Achilles' heel of heart failure RCTs, including CRT trials. It is remarkable, however, that for CRT, many more efforts have been devoted to identifying and predicting responders (5). Initial small single-center studies reported a favorable outlook for several echocardiographic measures of mechanical dyssynchrony in predicting responders (6–8). A subsequent large multicenter study, however, the PROSPECT (Predictors of Response to CRT) trial, failed to identify a useful measurement using conventional and tissue Doppler–based methods (9). A retrospective subanalysis of that study suggested that assessment of factors such as sex, etiology, and severity of heart failure may enhance the likelihood of identifying responders (10). Likewise, total scar burden has also been proposed to help in predicting responders (11). Recently, a meta-analysis of 5 RCTs evaluating CRT in heart failure found this modality to be effective in reducing mortality and hospitalization only in patients with a QRS complex ≥150 ms (12). This important study not only identified an important parameter for selecting responders, but it also provided indirect support for efforts aimed at identifying predictors of CRT response in individual patients.

Cumulative clinical experiences have indeed identified several parameters that could potentially predict individuals more likely to respond to CRT, including LV dyssynchrony, as assessed by strain imaging (13), optimal LV lead position (14), and absence of myocardial scar (15). A recent analysis of 397 patients with ischemic heart failure who received CRT showed that these 3 parameters were not only independent predictors of 3-year survival, but their addition provided incremental prognostic value (16). Thus, the stage had been set for a prospective, randomized study to assess the impact of a targeted strategy based on these parameters compared with usual care.

In this issue of the *Journal*, Khan et al. (17) report the results of a study integrating information collected by strain imaging that identified the most delayed segment of contraction and absence of scar. The authors conducted an RCT to assess the impact of targeting LV lead placement at the most delayed viable segment defined by speckle-tracking echocardiography compared with usual care. A total of 247 consecutive patients with New York Heart Association functional class III/IV, LV ejection fraction ≤35%, and intraventricular conduction delay (QRS complex ≥120 ms) were evaluated at 2 centers between April 2009 and July 2010.

The primary endpoint was ≥15% reduction in LV end-systolic volume at 6 months. Secondary endpoints included ≥1 improvement in New York Heart Association functional class, all-cause mortality, and combined all-cause mortality and heart failure–related hospitalization.

The image quality was not suitable for 2-dimensional radial strain analysis in 27 patients (11%), who were excluded; thus, a total of 220 patients were randomized.

In the intervention group, an attempt was made to position the LV lead at the optimal site as defined by 2-dimensional speckle-tracking radial strain imaging. A value of <10% was used to define scar. In the control group, patients underwent standard CRT without echocardiographic guidance. Blinding was maintained throughout the study, with all assessors of the primary and secondary endpoints remaining blinded to group assignment. Compared with usual care, the intervention group had a greater proportion of responders at 6 months (70% vs. 50%, p =

*Editorials published in the *Journal of the American College of Cardiology* reflect the views of the authors and do not necessarily represent the views of *JACC* or the American College of Cardiology.

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JACC Vol. 59, No. 17, 2012
April 24, 2012:1519–20

0.031), a higher rate of clinical response (83% vs. 65%, p = 0.003), and a lower rate of heart failure–related hospitalization.

Khan et al. (17) should be commended for the successful completion of this RCT, which provokes several thoughts.

1. The difficulty of designing the "perfect trial." When CRT was initially introduced, its benefits had to be proven first, but if we knew then what we know now, we would have selected a QRS complex ≥150 ms as a selection criterion and would have avoided a scarred area as a lead placement site.

   Thus, this trial could serve as a reminder that although when designing clinical trials we need to be as visionary as possible and include as many mechanistic studies as feasible, the reality nevertheless is that there is no alternative to the process of continuing learning from the accumulated clinical experience gained from applying the new intervention and build on this information to refine the original intervention. Stages cannot be burned. Fine-tuning an intervention requires time to incorporate newly acquired information into hypotheses that require testing.
2. The "second wave" of an RCT should be designed to assess the effect of the intervention on surrogate endpoints. It is unrealistic to look for a decrease in mortality in such trials. The approach that Kahn et al. chose is sound and logical. The mid term effect on LV systolic volume represents a solid surrogate endpoint. It is reassuring that the effect on heart failure hospitalization was in the right direction in this trial; however, it is important to keep in mind that the impact of an intervention on hospitalization and death cannot be assessed by such a small number of events (18 deaths and 18 hospitalizations among patients who received CRT). It is certainly appropriate and desirable to track these events; however, the rapid accumulation of new knowledge is breathtaking, and there will undoubtedly be newer imaging modalities as well as technical innovations in the search for identifying responders. The only practical way to assess their role is by examining surrogate endpoints.
3. An important limitation that the authors identified is the failure to use this approach in one-third of the patients being considered for CRT. Therefore, this trial is likely to not only stimulate further innovations in imaging modalities and technical approaches, but also more clinical trials that incorporate the assessment of the role of surgical approaches in their design.

Although the findings of this trial may not mandate the selection of the most delayed viable segment when CRT is being considered, they do call into question the wisdom of not selecting the most likely responders when an invasive and costly procedure such as CRT is initiated.

Identifying responders to new interventions and strategies is a major challenge that future heart failure trials need to meet.

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Key Words: cardiac resynchronization therapy ■ left ventricular lead placement ■ speckle-tracking echocardiography.