Letter by Shanmugam et al Regarding Article, “Primary Results From the SmartDelay Determined AV Optimization: A Comparison to Other AV Delay Methods Used in Cardiac Resynchronization Therapy (SMART-AV) Trial: A Randomized Trial Comparing Empirical, Echocardiography-Guided, and Algorithmic Atrioventricular Delay Programming in Cardiac Resynchronization Therapy”

To the Editor:

We read with great interest the recent article by Ellenbogen et al,1 who compare atrioventricular optimization (AVOpt) in cardiac resynchronization therapy (CRT) with a fixed atrioventricular (AV) delay. Using improvement in left ventricular end-systolic volume (LVESV) at 6 months as the primary end point, the authors conclude that the routine use of AV optimization is no longer warranted.

We believe that the study was underpowered to detect the additional response to AVOpt. In the sample size calculation the authors assumed a standard deviation of 60 mL and an expected response to CRT of a 30-mL reduction in LVESV. They then assumed a further 50% reduction in LVESV (15 mL) over that seen with the CRT effect following AVOpt, and they stated that this 15 mL was the smallest “clinically meaningful difference.” However, because cardiac output improves by 20% at most in selected patients following AVOpt,2 and as in clinical practice using iterative AVOpt, <50% of patients actually require a significant change in AV delay, this mean change of a 15-mL reduction in LVESV across the whole cohort randomized to optimization was unrealistic.

In fact, the overall benefit seen after CRT alone in this study was almost half of the expected outcome (based on the outcomes of major CRT trials that did use AVOpt). Because the actual response to CRT alone was 15 mL (50%) less than predicted, the study had already deviated significantly from the original plan and, by the authors’ own standards, this 15-mL underresponse was likely to be “clinically relevant.” Indeed, because the confidence intervals of medians of improvements in each of the 3 treatment groups included −15, it could even be concluded that the benefit of CRT was not significantly above the “clinical relevance threshold.”

We have recalculated power and sample size using the same t test formula the authors used, but using 50% of the actual median improvement in LVESV in the fixed group (15 mL×50% = 7.5 mL) as the minimal required difference between the fixed and optimized groups. The recalculation showed that the study had only a 36% power to show a difference of 7.5 mL. To show a 7.5-mL difference with 80% power, 1001 patients/group would be needed, 3 times more than currently randomized. (A more accurate calculation would be possible using the raw data of the SMART-AV study.)

In summary, we believe that 15 mL was too strict a threshold when looking for a difference between the fixed and optimized groups, and as a statistical consequence, a too permissive threshold has been used for the noninferiority test. More importantly, as a result of a lower than anticipated response to CRT, the study was underpowered to detect a further 50% change in LVESV. It would therefore be unwise to categorically exclude all patients who have responded to CRT therapy on the basis of this study.

Disclosures

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References


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