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EDITORIAL COMMENT

Super-Responders and Nonresponders in the COAPT Trial

Not as Simple as Clip or No Clip*

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Whereas prior studies of surgical intervention have failed to show survival benefit for secondary mitral regurgitation (SMR) (1), guideline-directed medical therapy (GDMT) and cardiac resynchronization therapy (CRT) are associated with improved outcomes (2). The COAPT (Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients With Functional Mitral Regurgitation) trial (3) has changed the clinical approach to this disease (4) by showing safety, efficacy, and improved survival with the addition of edge-to-edge transcatheter mitral valve repair (TMVr) to GDMT. Examining subgroups of clinical responsiveness may help clinicians define appropriate patients for treatment.

The concept of clinical super-responders is not new to heart failure (HF) therapy. António et al. (5) defined super-responders to CRT as a reduction of ≥1 New York Heart Association functional classes, a ≥2-fold increase or absolute left ventricular (LV) ejection fraction of >45%, and a decrease in LV end-systolic volume (LVESV) of >15% (5). Ypenburg et al. (6) defined CRT super-responders by the decrease in LVESV: ≥30% in super-responders, 15% to 29% in responders, and 0% to 14% in nonresponders. More extensive LV reverse remodeling was associated with greater SMR reduction, fewer HF hospitalizations (HFHs), and lower mortality during long-term follow-up (log-rank $p < 0.001$).

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In this issue of the *Journal*, Grayburn et al. (7) look at super-responders in the COAPT trial (8). They defined responder groups by clinical outcomes at 12 months: super-responders were those alive, without HFH, and with a ≥20-point improvement in the Kansas City Cardiomyopathy Questionnaire overall summary (KCCQ-OS); responders were those alive without HFH and with a 5- to <20-point KCCQ-OS improvement; and nonresponders were those who either died, were hospitalized for HF, or had a <5-point improvement in the KCCQ-OS. The TMVr + GDMT and GDMT alone cohorts had the following responder breakdown: 79 (27.2%) versus 29 (10.2%) super-responders; 55 (19.0%) versus 46 (16.3%) responders; and 156 (53.8%) versus 208 (73.5%) nonresponders (overall $p < 0.0001$). Independent baseline predictors of clinical responder status were lower serum creatinine level, lower KCCQ-OS score, and MitraClip (Abbott, Santa Clara, California) treatment. When the treatment groups were analyzed separately for predictors of super-response, lower serum creatinine level remained a multivariable predictor only in the control arm, whereas baseline KCCQ-OS score predicted super-response in both treatment arms.

The authors are to be commended for attempting to further characterize patients who may benefit from edge-to-edge SMR therapy. Given the findings of the

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randomized trial, the results of this post hoc analysis seem a forgone conclusion. The data, however, raise some interesting questions about the responder groups. First, does the Grayburn et al. (7) definition of super-responder translate to meaningful outcomes other than mitral regurgitation (MR) and right ventricular (RV) systolic pressure improvement? A treatment group comparison of changes in LV or RV size or function in the super-responder group (alive at 12 months by definition; thus, no survivorship bias), which could eventually translate to improved long-term outcomes, would be of interest. Second, the ratio of effective regurgitant orifice area to LV end-diastolic volume (LVEDV) for each responder group is the same (approximately 0.21), suggesting that the proportionality of SMR severity (7) does not play a role in functional response and, thus, may not help refine patient selection. Finally, the high nonresponder rate in both treatment groups (53.8% vs. 73.5% for TMVr + GDMT and GDMT, respectively) is surprising and deserves our attention.

Nonresponders had higher RV systolic pressure ($p = 0.02$) and mean transmitral gradients ($p = 0.03$). There was a trend to larger LVEDV and LVESV ($p = 0.08$ and $p = 0.09$, respectively) and a higher incidence of inferior basal aneurysm (16.7%, 12.6%, and 22.5% in super-responders, responders, and nonresponders, respectively; $p = 0.08$). Posterior leaflet tethering (and higher posterolateral angle) is associated with recurrent MR after repair surgery (8), and the combination of myocardial infarct with leaflet tethering may stimulate leaflet fibrosis (9), reducing the efficacy of medical and surgical therapy. This raises the possibility that the pathoanatomy of SMR may play a role in both medical and interventional treatment response.

Although the severity of MR seems to play a major role in the response to therapy, failure to achieve optimal GDMT may also influence response rates. A subanalysis of the GUIDE-IT (Guiding Evidence-Based Therapy Using Biomarker Intensified Treatment in Heart Failure) randomized trial by Fiuzat et al. (10) shed light on the reasons for the dismal 15.5% of patients achieving optimal GDMT. Compared to the group of patients who achieved GDMT, patients who did not had higher mean serum creatinine levels, which was a parameter responsible for failing to uptitrate medications. In the current study, there was a strong trend toward differences in serum creatinine in the GDMT nonresponder group (1.3 ± 0.7 in super-responders, 1.6 ± 0.7 in responders, and 1.9 ± 1.6 in nonresponders; $p = 0.06$). High creatinine was similarly seen in the TMVr + GDMT nonresponder group (1.9 ± 1.3). It is possible that nonresponders in both treatment arms did not receive optimal GDMT in the setting of baseline renal dysfunction, opening the possibility for improving outcomes with more aggressive medical therapy.

GDMT can significantly reduce SMR in 30% to 40% of patients with HF (11,12); however, the definition of GDMT continues to evolve. The PRIME (Pharmacological Reduction of Functional, Ischemic Mitral Regurgitation) study was a double-blind trial of 118 patients with HF and chronic SMR randomized to receive either sacubitril/valsartan or valsartan, in addition to standard HF therapy (13). After 12 months, the SMR effective regurgitant orifice area was significantly more reduced in patients treated with maximal tolerable doses of sacubitril/valsartan compared to valsartan: -5.8 ± 9.5 mm^2 (30% reduction) versus -1.8 ± 10.5 mm^2 (9% reduction) ($p = 0.032$). Greater MR reduction with sacubitril/valsartan was associated with a greater reduction in LV end diastolic volume index ($p = 0.044$). The COAPT trial completed enrollment before the updated Societal guidelines that give a Class I indication to an angiotensin receptor-neprilysin inhibitor (valsartan/sacubitril) and a Class IIa recommendation for a sinoatrial node modulator (ivabradine) in the treatment of HF with reduced ejection fraction (14). The addition of these medications could significantly improve MR response in both cohorts.

A deeper look into the determinants of clinical responsiveness in both the GDMT and MitraClip cohorts of the COAPT trial is certainly warranted. Determining whether the SMR pathoanatomy, optimization of GDMT, or other factors are the key to responsiveness may help clinicians make informed decisions regarding appropriate treatment options, understanding that both transcatheter devices and GDMT continue to improve.

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