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EDITORIAL COMMENT

A Volume-Based Framework Reconciling COAPT, MITRA-FR, and RESHAPE-HF2

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In this issue of *JACC*, the report of the RESHAPE-HF2 (A Randomized Study of the MitraClip Device in Heart Failure Patients With Clinically Significant Functional Mitral Regurgitation) trial by Anker et al has added another significant piece to the puzzle of managing functional mitral regurgitation (FMR) in heart failure (HF) and the role of mitral transcatheter edge-to-edge repair (M-TEER), joining the ranks of the pivotal COAPT (Cardiovascular Outcomes Assessment of the MitraClip) and MITRA-FR (Percutaneous Repair With the MitraClip Device for Severe Functional/Secondary Mitral Regurgitation) trials.[1-4] When placed alongside the landmark COAPT and MITRA-FR trials, RESHAPE-HF2 presents outcomes that are part of a coherent narrative explainable through the lens of left ventricular end-diastolic volume (LVEDV). We propose to reconcile the seemingly disparate results of these trials by using a left ventricular (LV) volume-based framework, which underscores the interplay between mitral regurgitation (MR) severity, LV chamber size, and the effect of M-TEER on patient outcomes.

DIVERGING OUTCOMES OF 3 LANDMARK TRIALS

Although the COAPT and MITRA-FR trials set the stage for M-TEER as a therapeutic option for FMR, they delivered conflicting results.[1,2] COAPT showed a substantial benefit of M-TEER in reducing HF hospitalizations (HFH) (HR: 0.53; 95% CI: 0.40-0.70) and mortality (HR: 0.62; 95% CI: 0.46-0.82) and significant improvement in quality of life at 2 years among patients with severe MR.[2] MITRA-FR, in contrast, failed to show any meaningful benefit of M-TEER in reducing mortality or HFH (OR: 1.16; 95% CI: 0.73-1.84) or quality of life at 12 months, and this remained consistent at 2 years.[1,5]

Enter the RESHAPE-HF2 trial,[3] which enrolled a cohort of 505 patients over 8 years from Europe with FMR receiving optimal guideline-directed medical therapy (GDMT) randomized to the M-TEER group vs control. The trial's results fall somewhere between those of COAPT and MITRA-FR: RESHAPE-HF2 showed significant reductions in HFH over 2 years (HR: 0.57; 95% CI: 0.42-0.77), mirroring COAPT, but did not achieve a statistically significant reduction in mortality.[4]

LV VOLUME AS A FRAMEWORK: EXPLAINING THE OUTCOMES

The framework for interpreting these trial outcomes lies in the relationship between MR severity and LV chamber size (**Figure 1**).

COAPT was characterized by a cohort with mean LVEDV of 192 mL but a mean effective regurgitant orifice area (EROA) of 0.41 cm^2, indicating a relatively less remodeled left ventricle with severe MR. This finding suggested that MR was a major driver of the HF syndrome in this patient population.[6,7] By addressing the MR, M-TEER effectively removed a significant load on the heart, leading to improvement in the primary outcome of total HFH over 24 months and also multiple prespecified secondary outcomes, including mortality.

MITRA-FR, in contrast, with a cohort marked by significantly larger LVEDV (mean 252 mL), failed to show any meaningful benefit of M-TEER in reducing

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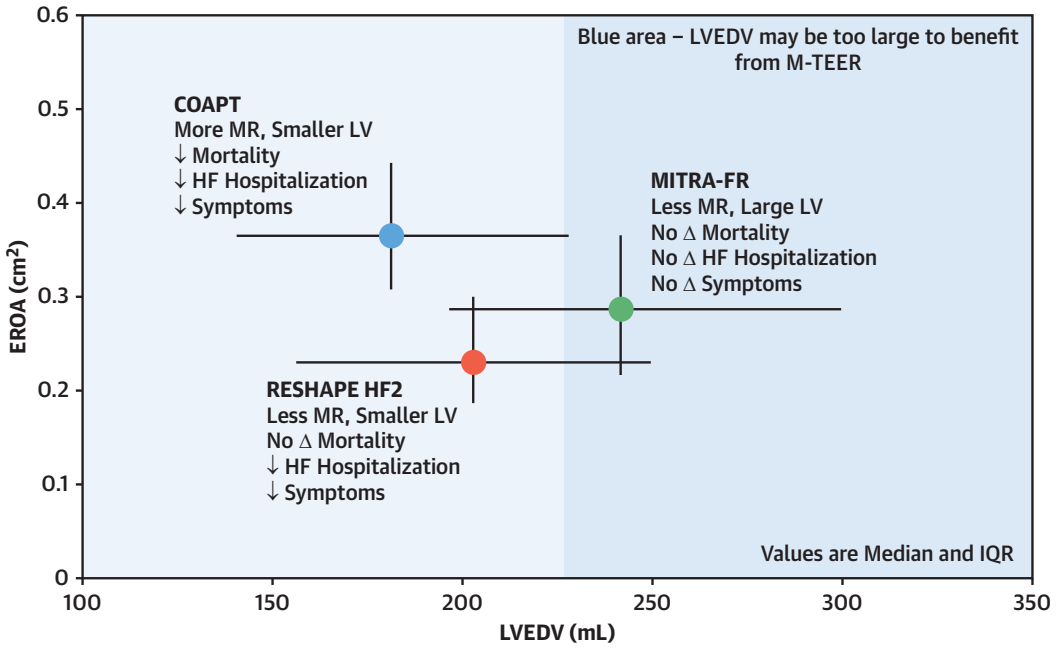
FIGURE 1 Reconciling Findings From COAPT, MITRA-FR, and RESHAPE-HF2 With a Volume-Based Framework



Plot of effective regurgitant orifice area (EROA) (y-axis) and left ventricular end-diastolic volume (LVEDV) (x-axis) for the 3 randomized clinical trials of mitral transcatheter edge-to-edge repair + medical therapy vs medical therapy alone. COAPT, which had greater mitral regurgitation (MR) severity and small LVEDV, had improvements in mortality, heart failure (HF) hospitalization, and patient-reported symptoms. RESHAPE-HF2 had less MR and similar LVEDV, with no mortality improvement but improved HF hospitalization and symptoms. MITRA-FR had values of MR severity that were intermediate between COAPT and RESHAPE-HF2, with no measurable benefits in any of the outcome measures. The blue shaded area represents a potential degree of left ventricular enlargement that is not associated with improved outcomes with mitral transcatheter edge-to-edge repair relative to medical therapy. COAPT = Cardiovascular Outcomes Assessment of the MitraClip; LV = left ventricle; MITRA-FR = Percutaneous Repair With the MitraClip Device for Severe Functional/Secondary Mitral Regurgitation; RESHAPE-HF2 = A Randomized Study of the MitraClip Device in Heart Failure Patients With Clinically Significant Functional Mitral Regurgitation.

the primary outcome of mortality and HFH.[1,5] The failure to show benefit for any of the outcomes in this trial underscores the limitations of M-TEER in the context of advanced LV remodeling. The large LVEDV with a smaller EROA (mean 0.31 cm^2) in this trial for patients receiving GDMT reflects a population in which the extent of LV enlargement and marked displacement of the mitral valve-supporting apparatus prevent the efficacy of interventions that are focused on the valve leaflets.

With that background, the results of RESHAPE-HF2 are consistent with those of the COAPT trial. RESHAPE-HF2 enrolled patients with symptomatic HF with a mean LVEDV of 205 mL and less severe MR (mean EROA of 0.25 cm^2; only 14% had EROA >0.40 cm^2, and 23% had an EROA <0.20 cm^2).[8] Although Ponikowski et al[3] characterize their cohort as having moderate to severe MR, the EROA values suggest that many, perhaps most, had only moderate MR. HFH within 1 year before enrollment was present in 66% of the patients. The trial's outcomes indicate that although M-TEER can still improve quality of life and reduce HFH, it does not improve mortality in patients with a mild to moderately remodeled left ventricle and lesser degrees of MR. Combining the 3 trials (Figure 1), the resulting framework suggests that the ability to influence clinical outcomes is limited when LV size increases beyond a certain threshold, although the exact threshold cannot be precisely defined.

THE ROLE OF GDMTs

It is critical to emphasize the importance of robust medical therapy to cause LV reverse remodeling and

thus reduce the displacement of the mitral valve-supporting structures that leads to FMR. GDMT leads to reduction in severity and improved outcomes for FMR: studies report 28% to 50% reduction in grade of FMR from baseline in patients receiving optimal or maximally tolerated doses of GDMT.[9,10] The benefit of GDMT to reduce FMR is likely to be most apparent in patients with meaningful LV enlargement (ie, >220 mL). A greater proportion of patients in the RESHAPE-HF2 trial received GDMT compared with those in the COAPT and MITRA-FR trials.[8] Specifically, 4 of 5 patients in RESHAPE-HF2 were taking mineralocorticoid receptor antagonists, whereas only about one-half of the patients in the COAPT and MITRA-FR trials were similarly treated. The use of angiotensin receptor-neprilysin inhibitors and beta-blockers was also more prevalent in RESHAPE-HF2, albeit <15%. A randomized trial comparing sacubitril/valsartan vs valsartan alone showed greater FMR reduction with neprilysin inhibition in 118 patients whose LVEDV and EROA were similar to those in RESHAPE-HF2.[11] The robust utilization of GDMT likely eliminated the enrollment of patients in whom marked LV enlargement would be a contributory factor to significant FMR, likely selecting for patients amenable to achieving the benefits of MR reduction and reverse remodeling after M-TEER.

The current landscape of HF management has shifted toward the rapid sequencing or even simultaneous initiation of all four pillars of GDMT—angiotensin receptor-neprilysin inhibitors, beta-blockers, mineralocorticoid receptor antagonists, and sodium-glucose cotransporter 2 inhibitors—reflecting a more aggressive and multi-pronged approach.[12] Future studies should focus on the impact of these intensive GDMT regimens on FMR, both as standalone therapies and in conjunction with interventions such as M-TEER.

CONCLUSIONS

We should consider the results of RESHAPE-HF2 in a volume-based framework that reconciles its results with those of COAPT and MITRA-FR. The success of M-TEER hinges on careful patient selection that takes into account the extent of LV enlargement and MR severity with the background of robust multipronged GDMT. MITRA-FR's lack of benefit illustrates the limits of M-TEER in patients with marked LV enlargement. The success of RESHAPE-HF2 and COAPT highlights the potential of M-TEER in patients with smaller LVEDV in whom marked mitral supporting apparatus displacement cannot explain the severity of FMR. The current evidence suggests that the benefits of M-TEER may be limited in patients with severely dilated LVEDV (>220 mL).

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