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EDITORIAL

To clip or not to clip moderate-to-severe functional mitral regurgitation in patients with heart failure?

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Functional mitral regurgitation (FMR) is associated with a poor prognosis, with one-year mortality rates ranging from 15% to 40%. By 2030, an estimated 4 million individuals in the United States will be diagnosed with FMR.[1] FMR commonly occurs in patients with heart failure (HF), affecting approximately 50% of those with ischemic cardiomyopathy and 65% of those with non-ischemic cardiomyopathies.[2] While studies have shown that guideline-directed medical therapy and cardiac resynchronization therapy (CRT) can reduce FMR severity by reversing left ventricular remodeling, many patients do not respond adequately and remain highly symptomatic with persistent FMR and poor survival rates.[3] Surgery is generally not recommended for isolated FMR cases unless combined with other procedures, such as aortic valve replacement or coronary artery bypass surgery. In such scenarios, the transcatheter edge-to-edge repair (TEER) procedure can be considered an attractive option for treating FMR.[3]

Current evidence

Two trials, COAPT (Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients with Functional Mitral Regurgitation) and MITRA-FR (Percutaneous Repair with the MitraClip Device for Severe Functional/Secondary Mitral Regurgitation) have assessed the efficacy and safety of the TEER using the MitraClip device in patients with HF and FMR.[4,5] The results of the MITRA-FR trial reported no significant difference in the primary composite endpoint of all-cause mortality or HF hospitalizations between the intervention and control groups at 1-year follow-up (54.6% *vs* 51.3%, p=0.53).[4] In contrast, the COAPT trial demonstrated that individuals treated with MitraClip devices had lower annual rates of HF-related hospitalization (35.8% *vs* 67.9%, p<0.001) and all-cause mortality at the 2-year follow-up compared to those receiving guideline-directed medical therapy alone (29.1% *vs* 46.1%, p<0.001).[5] In addition, the patients randomized to the MitraClip demonstrated better quality of life and improved MR, left ventricular remodeling, and functional capacity compared to those in the guideline-directed medical therapy alone group.[5] The discrepancies in findings from the two trials may be attributed to differences in the baseline characteristics of the patients, such as variations in HF severity, left ventricular dimensions, and MR severity as measured by effective regurgitant orifice area (EROA) or regurgitant volume. Similarly, differences in the right ventricular dysfunction and the level of standard HF medical treatment optimization prior to MitraClip intervention may have influenced the outcomes.[6,7]

Rationale and research design of the RESHAPE-HF2 trial

Both the MITRA-FR and COAPT recruited mainly patients with severe FMR.[3] The RESHAPE-HF2 study (A Randomized Study of the MitraClip Device in Heart Failure Patients with Clinically Significant Functional Mitral Regurgitation) is investigating the safety and efficacy of the MitraClip device in HF patients with moderate-to-severe FMR. RESHAPE-HF2 is a randomized, multicenter trial which enrolled patients with symptomatic HF with New York Heart Association (NYHA) class II-IV symptoms despite optimal therapy and who had moderate-to-severe or severe FMR, as defined by the European Association of Echocardiography and confirmed by a central echocardiogra-

phy core laboratory. Patients with an ejection fraction between ≥20% and ≤50% were enrolled. Other inclusion criteria included a previous history of hospitalization for HF or elevated natriuretic peptide levels (B-type natriuretic peptide (BNP) ≥300 pg/mL or NT-proBNP ≥1000 pg/mL) within the past 90 days, previous appropriate coronary revascularization and/or CRT, and ineligibility for isolated mitral valve surgery.[8,9] Patients were randomly assigned to the intervention and control groups in a 1:1 ratio, with patients in the intervention group scheduled to receive the MitraClip within 14 days after randomization. RESHAPE-HF2 has three primary endpoints: i) composite of total (first and recurrent) hospitalizations for HF and cardiovascular death over 24 months; ii) total (first and recurrent) hospitalizations for HF within 24 months; and iii) change in the Kansas City Cardiomyopathy Questionnaire (KCCQ) overall summary score from baseline to 12 months. These multiple primary endpoints will be analyzed using Hochberg procedure to control family-wise type 1 error across the three hypotheses.[10]

Comparison with previous trials

Several patient characteristics in RESHAPE-HF2 are comparable to those in the COAPT and MITRA-FR trials. In all three studies, the mean age was ~70 years, with nearly one-third of patients having prior CRT or cardioverter-defibrillator implantation. The mean LVEF was approximately 31% across all three trials.[3] However, there are important differences in echocardiographic features, laboratory values, and medication use between these trials (Table 1).[3,9] MITRA-FR patients had more severe left ventricular dysfunction than those in the RESHAPE-HF2 and COAPT trials. Notably, the COAPT study had excluded patients with severe left ventricular dilation, while MITRA-FR did not have such exclusion criterion. MITRA-FR included patients with LVEF ranging from 15% to 40%, while both COAPT and RESHAPE-HF2 enrolled patients with LVEF between 20% and 50%. This is an important consideration given that studies have demonstrated that significant left ventricular dilation and dysfunction in patients with HF and FMR are associated with limited reversal of left ventricular remodeling, and an adverse prognosis. Additionally, patients in RESHAPE-HF2 have lower natriuretic peptide levels and higher estimated glomerular filtration rate (56±21 mL/min/1.73 m² compared to ~50 mL/min/1.73 m² in MITRA-FR and COAPT). These differences indicate that the RESHAPE-HF2 cohort is comparatively less sick.

Importantly, individuals enrolled in the RESHAPE-HF2 have lower FMR severity compared to those in the COAPT and MITRA-FR. Patients enrolled in RESHAPE-HF2 have a smaller proximal isovelocity surface area (PISA) radius (0.72 cm), compared to COAPT (0.89 cm). RESHAPE-HF2 has the lowest mean effective regurgitant orifice area (EROA) at 0.25 cm², compared to 0.31 cm² in MITRA-FR and 0.40 cm² in COAPT. RESHAPE-HF2 has a high number of patients (53%) with moderate FMR (EROA: 20-29 mm²) than the previous trials which had higher proportion of patients with moderate-to-severe

Table 1. Important characteristics in the MITRA-FR, COAPT, and RESHAPE-HF2 trials.

	MITRA-FR (n=304)	COAPT (n=614)	RESHAPE-HF2 (n=506)
Age (years)	70	72.2±11.2	70±10
LVESD (cm)	5.8	5.3	5.9±1.0
LVEDD (cm)	6.9	6.2	7.0±1.0
No TR (Grade 0)	NA	1.9%	0.8%
Mild TR (Grade 1+)	81.4%	79.6%	54.3%
Moderate TR (Grade 2+)	NA	15.0%	35.2%
Moderate to severe TR (Grade 3+)	18.6%	0.8%	7.3%
Severe TR (Grade 4+)	NA	0.2%	NA
Vena contracta diameter (cm)	NA	0.58±0.12	0.82±0.43 (n=503)
Moderate EROA (20-29 mm2)	52%	14%	53%
Moderate to severe EROA (30-39 mm²)	32%	46%	17 %
Severe EROA (≥40 mm²)	16%	41%	7%
eGFR (mL/min/1.73 m²)	50±20	49±26	56±21 (n=498)
Medications (%)			
Beta-blockers	89.5	90.3	95.8
ACEI or ARB or ARNI	NA	67.1	82.1
ACEI or ARB	73.7	NA	74.3
ACEI	NA	41.2	56.0
ARB	NA	22.4	19.2
ARNI	10.2	3.6	13.7
MRA	54.6	50.2	82.4

Data are reported as mean ± SD or percentage of patients (%). NA, not available; LVEDD, left ventricular end-diastolic dimension; LVESD, left ventricular end-systolic dimension; TR, tricuspid regurgitation; EROA, effective regurgitant orifice area; eGFR, estimated glomerular filtration rate; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; ARNI, angiotensin receptor-neprilysin inhibitor; MRA, mineralocorticoid receptor antagonist.

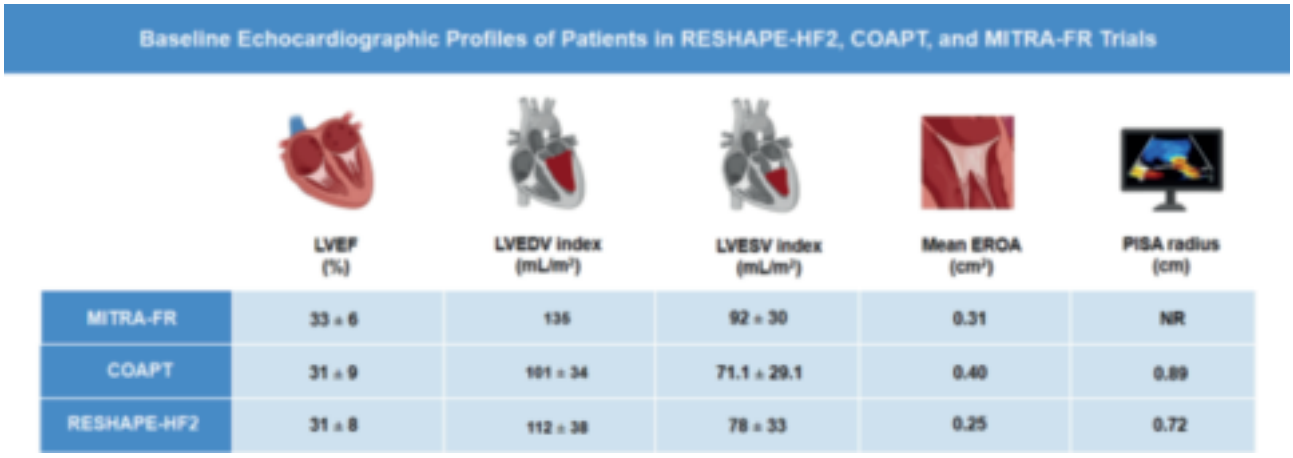

Figure 1. Summary of the baseline echocardiographic features of patients enrolled in the RESHAPE-HF2, COAPT, and MITRA-FR trials. NR, not reported; LVEDV, left ventricular end diastolic volume; LVESV, left ventricular end systolic volume; EROA, effective regurgitant orifice area; LVEF, left ventricular ejection fraction.

MR (EROA: 30-39 mm²) and severe MR (EROA ≥40 mm²). It should be noted that numerical head-to-head comparison of FMR grade severity across trials is restricted due to differences in FMR severity classifications employed by each study, as well as some missing EROA data in each trial.

Additionally, the RESHAPE-HF2 trial included a higher proportion of patients with tricuspid regurgitation (TR) severity grades 2+ (35.2% *vs* 15.0%) and 3+ (7.3% *vs* 0.8%) compared to the COAPT trial. Given that right ventricular function has a significant effect on mortality and morbidity in patients with HF and FMR, this distinction will facilitate understanding how TEER may affect patients with varying right ventricular function (Figure 1). The RESHAPE-HF2 trial also has a higher proportion of patients receiving guideline-directed medical treatment. Four out of five patients in RESHAPE-HF2 were on aldosterone receptor antagonists (MRA), compared to around half in COAPT and MITRA-FR. Similarly, RESHAPE-HF2 has higher use of angiotensin receptor-neprilysin inhibitors (ARNI) and beta-blockers. This is important as studies have shown that these drugs are associated with reduced morbidity and mortality in patients with FMR and HF and may reduce FMR severity. This also suggests that patients in the RESHAPE-HF2 trial were less sick and hence more tolerant of HF medications.

RESHAPE-HF2 trial will meaningfully inform the future treatment of HF and FMR, as it evaluates the effect of MitraClip device on background of contemporary therapies and in patients with predominately moderate FMR. The RESHAPE-HF2 trial is also anticipated to provide additional information into the concepts presented previously regarding which patients are likely to benefit from the TEER procedure. It had been proposed that individuals similar to those enrolled in MITRA-FR, where MR is «proportionate» to left ventricular enlargement, may not benefit from MitraClip. In contrast, patients resembling those in COAPT with MR that is «disproportionate» to left ventricle dilatation may derive more benefits from the MitraClip. The question of whether to clip or not to clip moderate FMR in symptomatic patients with HF is critical as a recent real-world registry showed that mean EROA of patients receiving MitraClip in FMR is 0.30 cm², and almost half of the patients had FMR severity of only Grade 2 + or lower.

Conclusions

The findings of RESHAPE-HF2 will be crucial in providing key insights into how the impact of TEER on patients with HF and moderate-to-severe FMR, providing both new evidence to better contextualize prior trials as well as give insights into patients with less severe FMR.

This patient population is common in practice with little evidence regarding the utility of MitraClip. The trial results will aid clinicians in contemporary practice to manage symptomatic patients with HF who have moderate-to-severe FMR.

Contributions

The authors contributed equally.

Conflict of interest

Dr Butler: Consultant to Abbott, Adaptyx, American Regent, Amgen, Applied Therapeutic, AskBio, Astellas, AstraZeneca, Bayer, Boehringer Ingelheim, Boston Scientific, Bristol Myers Squibb, Cardiac Dimension, Cardiocell, Cardior, CSL Bearing, CVRx, Cytokinetics, Daxor, Edwards, Element Science, Faraday, Foundry, G3P, Innolife, Impulse Dynamics, Imbria, Inventiva,

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