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STATE-OF-THE-ART REVIEW

Mitral Interventions in Heart Failure

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HIGHLIGHTS

- Significant SMR has major clinical consequences for the already vulnerable HFrEF population.
- GDMT in HFrEF with SMR remains the first step in patient management.
- Persistent SMR despite GDMT requires multidisciplinary evaluation with consideration of transcatheter treatment.
- Current and emerging transcatheter devices will further challenge the conventional approach to SMR in HF patients.

ABSTRACT

Patients with heart failure with reduced ejection fraction who have secondary mitral regurgitation (SMR) have poorer outcomes and quality of life than those without SMR. Guideline-directed medical therapy is the cornerstone of SMR treatment. Careful evaluation of landmark trials using mitral transcatheter edge-to-edge repair in SMR has led to an improved understanding of who will benefit from percutaneous interventions with emphasis on a multidisciplinary approach. The success with mitral transcatheter edge-to-edge repair in SMR has also spurred the evaluation of its role in populations that were not initially studied, such as end-stage heart failure and cardiogenic shock. A spectrum of transcatheter devices in development and clinical trials promise to further provide a growing array of management options for heart failure with reduced ejection fraction patients with symptomatic SMR.
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Mitral regurgitation (MR) is the most common valvular heart disorder, with moderate or greater MR complicating over 50% of all acute heart failure (HF) admissions.[1] MR is classified as primary (degenerative) or secondary (functional) and can have either an acute or chronic presentation. Secondary mitral regurgitation (SMR) is an independent predictor of poor outcomes including mortality and hospitalizations in patients with heart failure with reduced ejection fraction (HFrEF).[2]

Although a fundamentally appreciated mechanism of MR for decades, the SMR phenotype only received separate guideline management considerations within the last decade. Earlier ACC/AHA (American College of Cardiology/American Heart Association)

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ABBREVIATIONS AND ACRONYMS

ARNI = angiotensin receptor-neprilysin inhibitor

CRT = cardiac resynchronization therapy

EROA = effective regurgitant orifice area

GDMT = guideline-directed medical therapy

HFrEF = heart failure with reduced ejection fraction

mTEER = mitral transcatheter edge-to-edge repair

PISA = proximal isovelocity surface area

SMR = secondary mitral regurgitation

SGLT2 = sodium-glucose transporter 2

TMVR = transcatheter mitral valve replacement

valvular heart disease guidelines had MR dichotomized as either acute or chronic with "no generally accepted medical therapy for asymptomatic chronic MR" and a focus on surgical management.[3] In subsequent guidelines, the "degenerative" or "functional" nomenclature was overhauled and replaced with "primary" or "secondary" MR, reflecting the unique pathophysiology, natural history, and response to therapies.[4,5]

Historically, guideline-directed medical therapy (GDMT) and cardiac resynchronization therapy (CRT) were considered the mainstay of the treatment approach in HFrEF, whereas surgical repair/replacement of SMR was recommended in carefully selected patients. The simultaneous publication of the COAPT (Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients with Functional Mitral Regurgitation) and MITRA-FR (Multicenter Randomized Study of Percutaneous Mitral Valve Repair MitraClip Device in Patients With Severe Secondary Mitral Regurgitation) trials resulted in a major paradigm shift for SMR management.[6,7] With the emergence of transcatheter therapies, typified by mitral transcatheter edge-to-edge repair (mTEER), therapeutic options in SMR have evolved significantly.[6] There is a renewed interest in understanding the interplay between left ventricular (LV) dysfunction and the degree of MR in order to identify a phenotype more responsive to specific interventions. However, without the interventions that are aimed at correcting the severe SMR in appropriately selected candidates as well as the underlying HF, the risk of morbidity and mortality remains unacceptably high.[8] This review describes the current landscape of mitral valve (MV) interventions, focusing on SMR, and previews emerging technologies and paradigms.

MV ANATOMY/FUNCTION

ANATOMY. The MV apparatus is a dynamic structure with 4 key components: the mitral annulus (MA), the leaflets, the chordae tendineae, and the papillary muscles; abnormalities involving any of these components can result in MR[9] (**Figure 1**). The mitral leaflets consist of anterior (larger in size and sail-shaped) and posterior (smaller in size and crescent-shaped) leaflets with variable commissural scallops. The ventricular surface of the leaflets is attached to chordae tendineae (primary and secondary) that are classified based on their insertion points on mitral leaflets and 2 main papillary muscles (lateral and medial).

MECHANISMS FOR SMR. The etiologies of SMR can be broadly considered as atrial (ie, related to left atrial [LA] and/or mitral annular dilatation) and ventricular (ie, related to LV dysfunction, focal wall motion abnormalities, and enlargement).[4] Abnormalities involving the left atrium can result in malcoaptation of structurally normal mitral leaflets and loss of LA function, which can eventually lead to the development of SMR. Atrial relaxation after the end-diastolic atrial contraction may also exert a "Venturi effect" on mitral leaflets and aid in their tighter approximation, an effect that is lost in atrial fibrillation. In addition, massive LA enlargement may result in flattening of the anterior mitral leaflet along the mitral annular plane, with bending of the posterior mitral leaflet toward the LV cavity.

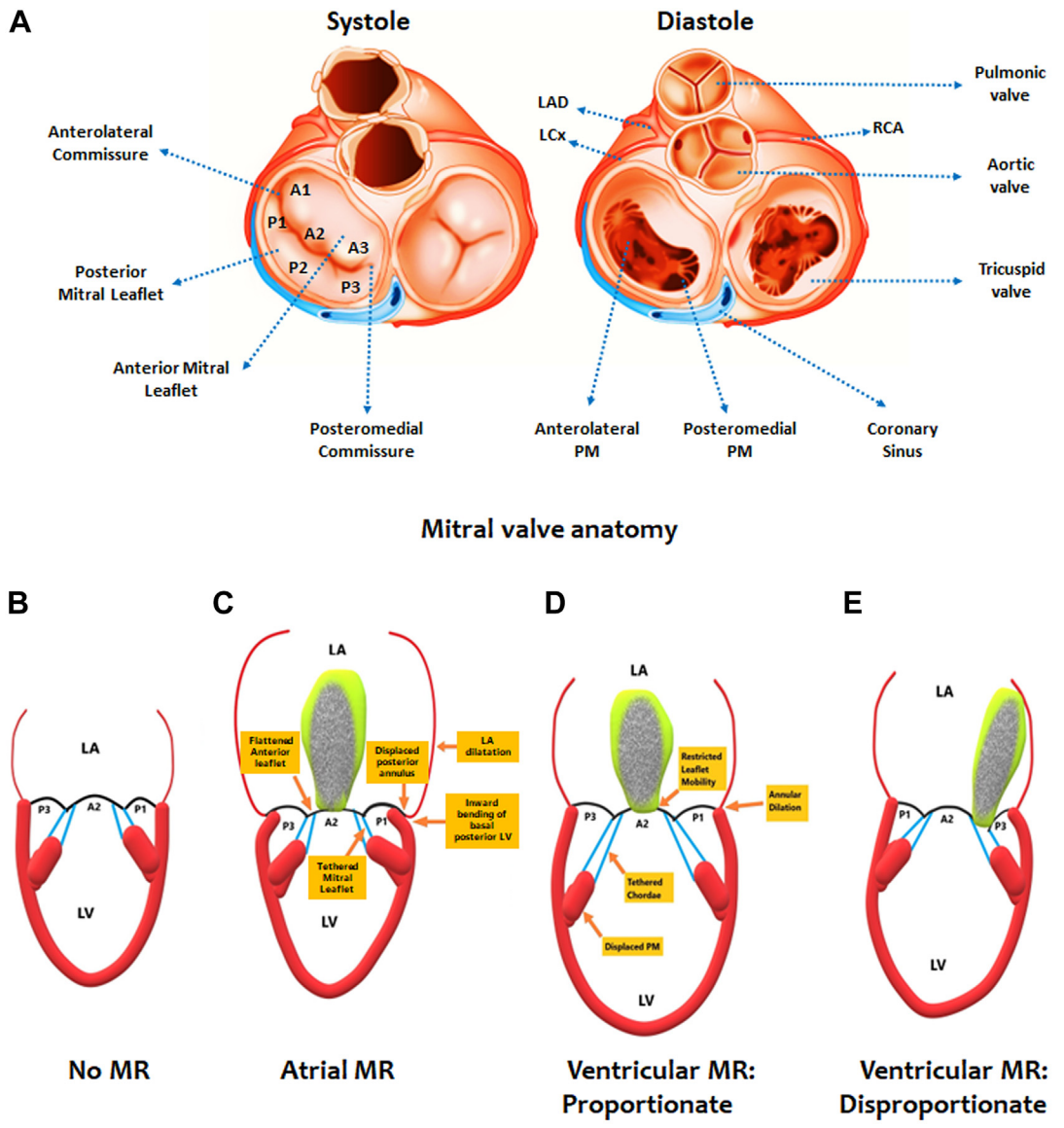
Abnormalities involving the left ventricle, such as dysfunction and enlargement or focal wall motion abnormalities, can also result in the development of SMR. The MA dilatation resulting from global LV enlargement can cause loss of MA folding and saddle-shape accentuation in early systole—a mechanism that can contribute to the development of early systolic SMR. LV dysfunction and enlargement can also result in abnormal tethering geometry because of abnormal interpapillary muscle approximation and paradoxical movement of the posteromedial PM in midsystole—a mechanism that can contribute to the development of mid-to-late systolic SMR.[10]

Regardless of the underlying mechanism, chronic volume overload resulting from progressive SMR induces unfavorable neurohormonal and structural changes and causes worsening of HF symptoms. Progressive SMR leads to higher LV end-diastolic pressure, LA pressure, and pulmonary arterial pressure and results in worsening right ventricular (RV) function and tricuspid regurgitation.

ASSESSMENT OF SMR

Echocardiography remains the screening test of choice for the assessment of MR.[11] Transthoracic echocardiography is often the first-line test of choice for its ease and reproducibility; however, transesophageal echocardiography may be necessary depending on the quality of the acoustic windows, the ability to perform quantitative measurements, and SMR jet eccentricity. The echocardiographic definition of SMR severity has evolved over the last decade. Severe SMR is currently defined by ACC/AHA

FIGURE 1 Mitral Valve Anatomy and Types of Regurgitation



(A) The leaflets of the mitral valve (divided into anterior and posterior segments 1-3) during systole on the left while the right side allows for visualization inferiorly into the left ventricle during diastole, permitting the identification of the papillary muscles. **(B)** A simplified example of normal mitral valve coaptation to contrast to other forms of secondary mitral regurgitation (MR). **(C)** Atrial MR is characterized by severe left atrial dilatation leading to a displaced posterior annulus and inward bending of the basal posterior left ventricle. Tethering of the mitral leaflets causes the MR. Ventricular MR can be proportionate **(D)** or disproportionate **(E)**, a distinction dependent on the degree of ventricular dilatation. LA = left atrium; LAD = left anterior descending coronary artery; LCx = left circumflex coronary artery; LV = left ventricle; PM = papillary muscle; RCA = right coronary artery.

and ESC (European Society of Cardiology) guidelines as an effective regurgitant orifice area (EROA) ≥0.4 cm^2, regurgitant fraction ≥50%, and regurgitant volume ≥60 mL/beat.[12] A proximal isovelocity surface area (PISA) radius ≥1 cm is also considered a criterion.[13]

There are several pitfalls to these methods of SMR characterization. The dynamic nature of SMR means that changes to loading conditions, such as with sedation necessary for transesophageal echocardiography, can cause a significant reduction in MR severity.[13] The calculation of the EROA uses the PISA

method, which requires several assumptions that can be erroneous in SMR. In SMR, the MV often has an elongated or elliptical orifice as opposed to the ideal hemispheric shape in PISA calculation, leading to underestimation of regurgitant severity.[14] Similarly, the PISA shape itself is assumed to be planar when it may be more conical, requiring adjustment in the EROA calculation. Eccentric and multiple jets, which are frequently encountered in SMR, can also lead to the underestimation of severity. The timing of the flow and velocity is also critical, and measurement of a single-frame, midsystolic EROA may overestimate SMR that is biphasic with early and late peaks.[15] Regardless of these limitations, quantitative assessments with EROA as well as regurgitant volume are closely associated with clinical endpoints.[16]

Additive imaging modalities should be considered for the most accurate assessment of SMR severity. Three-dimensional transesophageal echocardiography may allow for more accurate PISA measurement despite eccentric jet or elliptical orifice shape.[17] If mTEER is being considered, 3-dimensional color Doppler allows for spatial recognition of the ideal repair location. Cardiac magnetic resonance can provide highly accurate regurgitant volume measurements despite the presence of eccentric or multiple MR jets.[18]

INITIAL APPROACH TO SMR

The current guidelines give mTEER a Class 2a recommendation for the treatment of patients with moderately severe or severe SMR who meet COAPT criteria.[11,19] Additional recommendations include an emphasis for patients with SMR to be evaluated by a multidisciplinary team (MDT) as well as optimizing GDMT.

MEDICAL THERAPY FOR SMR. Optimizing GDMT is the first-line therapy for all patients with HFrEF, including those with SMR.[11] The long-term administration of GDMT reverses LV remodeling, which may in turn lead to improved MV leaflet coaptation.[20] Nearly 60% of patients with HFrEF and SMR may have a significant improvement in the degree of MR after treatment with GDMT.[21] Of note, none of these studies had a substantial number of patients on sodium-glucose cotransporter 2 inhibitors—a drug class that also improves adverse LV remodeling.[22] Moreover, continuing GDMT with reassessment of up-titration plays a key role in achieving optimal outcomes after mTEER.[6,23]

Beta-blockers, angiotensin-converting enzyme inhibitors, and sacubitril/valsartan have established benefits with improving LV remodeling and SMR in patients with HFrEF. In small, nonrandomized studies, carvedilol in patients with HFrEF and SMR led to a significant improvement in left ventricular ejection fraction (LVEF), a reduction in EROA and regurgitant volume, and an improvement in the grade of SMR.[24,25] Additionally, metoprolol resulted in a significant improvement in MR in 1 double-blind, placebo-controlled trial of patients with LV systolic dysfunction.[26] Captopril has also demonstrated a dose-dependent improvement in SMR.[27] Sacubitril/valsartan, an angiotensin receptor–neprilysin inhibitor (ARNI), has demonstrated superiority over angiotensin-converting enzyme inhibitors or angiotensin receptor blocker treatment with respect to clinical outcomes and LV reverse remodeling in patients with HFrEF.[28,29] In the PRIME (Pharmacological Reduction of Functional, Ischemic Mitral Regurgitation) trial, the ARNI group had a significantly larger reduction in EROA and lower regurgitant volume compared with the valsartan group in patients with SMR and LV systolic dysfunction.[30] In the open-label PROVE-HF (Effects of Sacubitril/Valsartan Therapy on Biomarkers, Myocardial Remodeling and Outcomes) trial, just under 15% had 3 to 4+ MR at baseline, and ARNI led to an improvement to ≤2+ MR in 45% of that subgroup, a majority of whom were previously treated with angiotensin-converting enzyme inhibitors or angiotensin receptor blockers.[31] Outside of their long-known acute hemodynamic benefits in afterload reduction and MR improvement, hydralazine and nitrates have unclear long-term benefits, specifically in the SMR population, although they certainly are appropriate to initiate in the context of their Class 1 recommendation in African Americans with symptomatic HFrEF.[19,32]

The COAPT trial is 1 of the first trials to require HF medication optimization systematically by HF experts. A recent analysis of the trial's GDMT use by Cox et al[33] provides much needed insight. Given the timing of COAPT enrollment, sodium-glucose cotransporter 2 inhibitors were not an approved "pillar" of GDMT for HFrEF, and the use of ARNI was also low (3.2%). Only 2.2% of all patients with HFrEF tolerated target doses of all 3 GDMT medications. These rates of target-dose GDMT use are lower than desired for "optimal titration" and are not far from what has been found in other real-world HF registries, such as CHAMP-HF (Change the Management of Patients with Heart Failure).[34] COAPT patients, being a higher-risk group of patients (by virtue of their SMR), may be expected to have more GDMT intolerance. Medication changes during the follow-up period are also low, likely because of both the intense prerandomization screening for optimal

up-titration and the suggestion to investigators to limit routine medication changes in the first 2 years postrandomization. As proposed by the editorial[35] to the paper by Cox et al,[33] future trials may benefit from objective criteria for drug intolerance, prioritization of ARNI over angiotensin-converting enzyme inhibitors and angiotensin receptor blockers, and protocolized "tolerance" of asymptomatic blood pressure or minor changes in renal function.

OTHER THERAPIES. COAPT trial inclusion also mandated the use of implantable cardiac defibrillators and CRT in patients who met Class 1 guideline recommendations. CRT results in a quantifiable improvement in the LV end-systolic volume index and MR area.[36,37] Inversely, the withdrawal of CRT can lead to worsening of SMR.[38] Treatment of SMR also includes addressing concurrent conditions such as atherosclerotic coronary artery disease in the presence of LV dysfunction via percutaneous or surgical revascularization.[13]

MV INTERVENTIONS IN HF PATIENTS

TRANSCATHETER EDGE-TO-EDGE REPAIR (MitraClip). Based on the results of the COAPT trial, mTEER with MitraClip (Abbott Vascular) was the first percutaneous therapy to be approved for the treatment of SMR in the United States.[6] In COAPT, there was a significant reduction in the primary endpoint of HF hospitalizations (35.8% vs 67.9%; HR: 0.53 [95% CI: 0.40-0.70]; $P < 0.001$) at 2 years of follow-up in the intervention group compared with GDMT alone. Furthermore, all 10 secondary endpoints were improved with mTEER, including all-cause mortality at 2 years (29.1% vs 46.1%; HR: 0.62 [95% CI: 0.46-0.82]; $P < 0.001$), NYHA functional class I or II at 1 year (72.2% vs 49.6%; $P < 0.001$), a change in the Kansas City Cardiomyopathy Questionnaire (KCCQ) score (12.5 vs −3.6; $P < 0.001$), and so on. The 5-year follow-up of the COAPT trial reported that in the intention-to-treat analysis, the annualized HF hospitalization rate (33.1%/y vs 57.2%/y; HR: 0.53 [95% CI: 0.41-0.68]) and all-cause mortality (57.3% vs 67.2%; HR: 0.72 [95% CI: 0.58-0.89]) were significantly lower in the mTEER arm compared with GDMT alone.[39] Patients treated with mTEER were more likely to show improvements in health status and exercise capacity than were those treated with GDMT alone.[40]

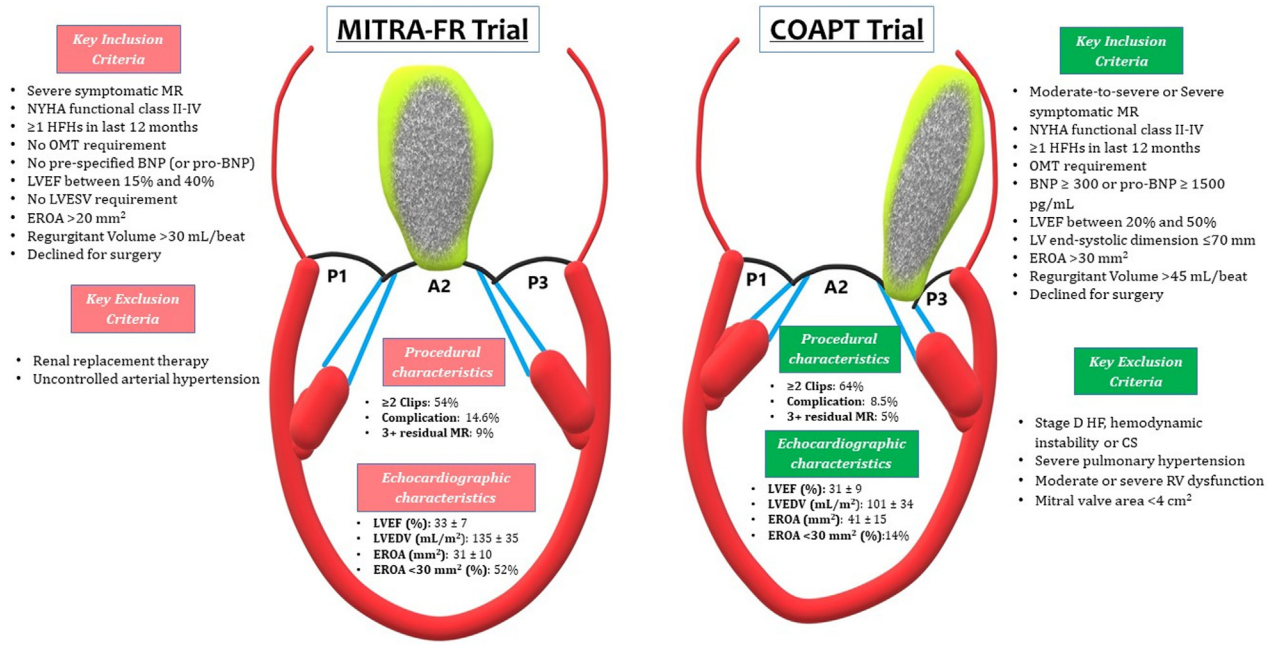
On the contrary, the MITRA-FR trial reported no difference in the primary outcome of all-cause mortality or HF hospitalization at 1 year between the MitraClip and GDMT arms (54.6% vs 51.3%; HR: 1.16 [95% CI: 0.73-1.84]; $P = 0.53$)[7] (**Figure 2**). In addition to the combined endpoint, there was no difference in the individual endpoints of all-cause mortality (24.3% vs 22.4%; HR: 1.11 [95% CI: 0.69-1.77]) or HF hospitalizations (48.7% vs 47.4%; HR: 1.13 [95% CI: 0.81-1.56]) at 1 year. The 2-year follow-up of the MITRA-FR trial showed comparable results with no difference between the intervention and control arms.[41]

Despite having similar LVEF, patients enrolled in the MITRA-FR trial had lower EROA (0.31 cm^2 vs 0.41 cm^2) and higher left ventricular end-diastolic volume (LVEDV) (135 mL/m^2 vs 101 mL/m^2) compared with those in the COAPT trial. Of note, outcomes in the GDMT arms of both trials were similar at 2 years with a composite endpoint of all-cause mortality or HF hospitalization of 67.1% in MITRA-FR and 67.9% in COAPT. Therefore, the differences in outcomes between the trials are secondary to the outcomes in their mTEER arms. These differences could be explained by the proportionality hypothesis, using EROA as a quantitative estimation of MR severity and LVEDV as a quantitative measurement of LV dilatation.[42] For a given LVEF and regurgitant fraction, EROA normalized to LVEDV allows for the creation of a proportionate SMR "trend line" (**Figure 3**). Visualized relative to this trend line, COAPT patients fall in the "disproportionate severe MR" category, whereas the MITRA-FR patients land on the other side (MR proportionate to the degree of LV dilation) of the trend line. The MR in patients with proportionate MR would respond to drugs and devices that reduce LVEDV, whereas those with disproportionate MR would preferentially benefit from interventions directed at the MV. However, significant interobserver variability exists in the measurement of EROA and LVEDV by echocardiography that may limit the general applicability of the proportionality hypothesis.[43]

In a subanalysis of the COAPT trial, there was no benefit of mTEER in terms of HF hospitalizations and/or all-cause mortality at 2 years in patients with proportionate MR (smaller EROA ≤0.30 cm^2 and larger LV end-diastolic volume index >96 mL/m^2, similar to patients in MITRA-FR). However, mTEER plus GDMT resulted in significant improvements in quality of life (KCCQ score) and 6-minute walk distance at 12 months compared to GDMT alone. The results suggest that the benefits of mTEER may be greatest in those with disproportionate SMR but that some benefits on hospitalization may be present in "proportionate" SMR when the analysis was extended to 24 months.[44]

The risk for major complications, including death and major stroke, is low after MitraClip placement, with rates much lower compared to open surgical repair[45] (Videos 1 to 4). Complications may include

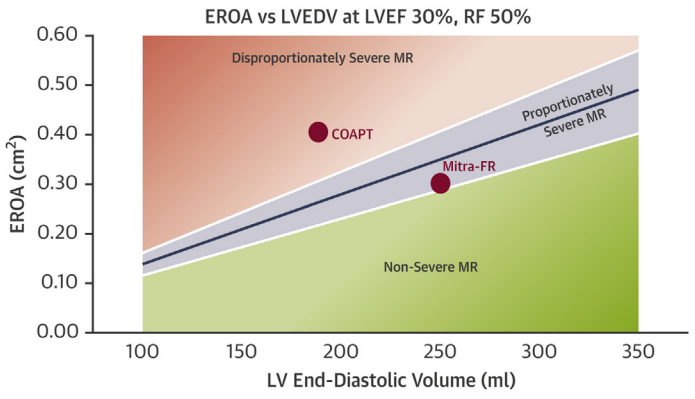
FIGURE 2 Comparison of MITRA-FR and COAPT Trials Including Key Inclusion and Exclusion Criteria and Important Procedural and Echocardiographic Differences



BNP = brain natriuretic peptide; COAPT = Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients with Functional Mitral Regurgitation; CS = cardiogenic shock; EROA = effective regurgitant orifice area; HF = heart failure; HFH = heart failure hospitalization; OMT = optimal medical therapy; LVEF = left ventricular ejection fraction; LVEDV = left ventricular end-diastolic volume; LVESV = left ventricular end-systolic volume; MITRA-FR = Multicenter Randomized Study of Percutaneous Mitral Valve Repair Mitra Clip Device in Patients with Severe Secondary Mitral Regurgitation; RV = right ventricle; LV = left ventricular; other abbreviation as in Figure 1.

access site bleeding, transseptal complications, pericardial effusion, clip detachment from a single leaflet, or very rarely device embolization. It is also important to note that the current generation of the MitraClip system (G4) allows for independent grasping and multiple sizing options. The procedural results with G3 and G4 have been incrementally better than the older-generation devices (G1 and G2) that were used in the COAPT trial, with 97% patients having ≤2+ residual MR at 1 year[46] (Table 1).

FIGURE 3 Proportionate and Disproportionate Mitral Regurgitation



Relationship between EROA and LVEDV at LVEF 30%, RF 50% and corresponding visualization of average population for the COAPT and MITRA-FR trials. Figure used with permission from Grayburn et al.[42] RF = regurgitant fraction; other abbreviations as in Figures 1 and 2.

The COAPT and MITRA-FR trials and the ongoing trials of SMR have primarily focused on ventricular SMR. Recent studies suggest that 5% to 10% of all MR patients and 25% of SMR cases may have atrial SMR.[47] mTEER has been evaluated in retrospective studies of atrial SMR and is effective in reducing the grade of MR similar to that seen in ventricular SMR. The hemodynamic impact and symptom relief have varied among studies, which may be related to different definitions used to define atrial SMR.[48,49]

Other devices. The PASCAL system (Edward Lifesciences) also uses the concept of edge-to-edge repair and received Food and Drug Administration approval for primary MR in 2022. There is limited retrospective experience comparing PASCAL with MitraClip showing similar results in terms of MR reduction and

TABLE 1 Effectiveness of MitraClip in Reducing MR in Clinical Trials

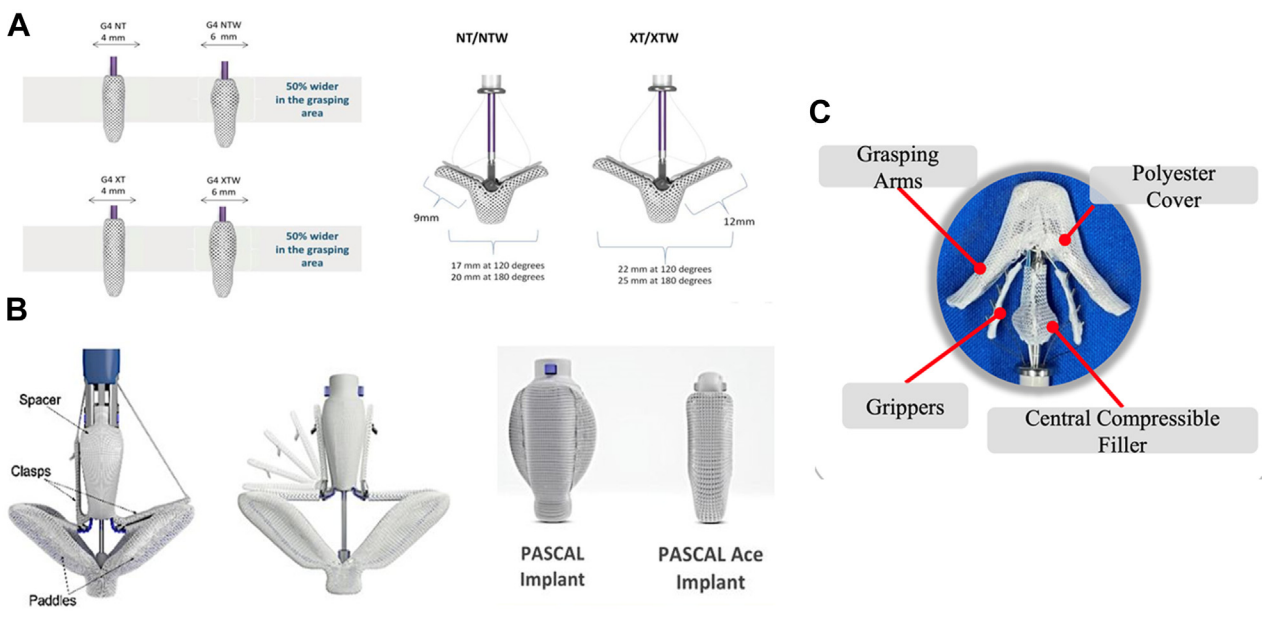
	Years Enrolled	Type of MR	N	MitraClip Generation System	≤2+ Residual MR at 1 Year (%)	≤1+ Residual MR at 1 Year (%)
EVEREST II RCT (PMID: 21463154)	2005-2008	Primary (73%) and secondary MR	184	NT (G1)	82	43
Everest II Realism registry (PMID: 30586701)	2005-2013	Secondary MR	616	NT (G1)	84.5	42.9
MITRA-FR	2013-2017	Secondary MR	152	NT (G2)	83.0	49.5
COAPT trial	2013-2017	Secondary MR	302	NT (G2)	94.8	69.1
EXPAND prospective registry	2018-2019	Primary and secondary MR (~50/50)	509	G3	96.0	83.5
EXPAND Secondary MR	2018-2019	Secondary MR	213	G3	99.1	89.5

COAPT = Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients with Functional Mitral Regurgitation; EVEREST = Endovascular Valve Edge-to-Edge Repair Study; EXPAND = A Contemporary, Prospective, Multi-Center Study Evaluating Real-World Experience of Performance and Safety for the Next Generation of MitraClip Devices; MR = mitral regurgitation; PMID = PubMed identifier; RCT = randomized controlled trial.

safety.[50,51] The CLASP IIF (Edwards PASCAL CLASP IID/IIF Pivotal Clinical Trial; NCT03706833) randomized trial is currently enrolling and is evaluating the safety and effectiveness of PASCAL compared to MitraClip in SMR patients. Another transcatheter repair system, the DragonFly Transcatheter Repair device (Hangzhou Valgen Medtech Co, Ltd), also uses the concept of edge-to-edge degenerative MV repair with a compressible spacer in the center[52] (Dragonfly-M Early Feasibility Study; NCT04528576) (Figure 4).

TRANSCATHETER MITRAL VALVE REPLACEMENT. Demand exists for alternative device-based therapies such as transcatheter mitral valve replacement (TMVR) considering that up to one-third of individuals with significant (all-cause) MR have anatomy that is not ideal for mTEER.[53] The initial experience with TMVR began with transapically implanted prostheses, namely the Tendyne (Abbott Vascular) and Intrepid (Medtronic) valves. Two-year data from the multicenter, international single-arm early feasibility study enrolling 100 participants

FIGURE 4 mTEER Devices



Specifications of mitral transcatheter edge-to-edge repair devices for the generations of MitraClip **(A)**, PASCAL **(B)**, and Dragonfly **(C)**.

with 3+ or 4+ MR demonstrated very high rates of successful implantation (97%), no residual MR, and a reduction in HF hospitalization.[54] The ongoing SUMMIT (Clinical Trial to Evaluate the Safety and Effectiveness of Using the Tendyne Transcatheter Mitral Valve System for the Treatment of Symptomatic Mitral Regurgitation; NCT03433274) trial is currently enrolling a target of 958 people with symptomatic 3 to 4+ MR and randomizing them to mTEER with the MitraClip device vs Tendyne with a primary endpoint of all-cause mortality at 1 year. The Intrepid valve, a bovine pericardial trileaflet valve, is now deployed transeptally and is being evaluated in the APOLLO (Transcatheter Mitral Valve Replacement with the Medtronic Intrepid[TM] TMVR System in Patients with Severe Symptomatic Mitral Regurgitation) trial.[55] The number of transfemoral TMVR devices is rapidly expanding and includes devices like the Sapien M3 (Edwards Lifesciences), EVOQUE (Edwards Lifesciences), Altavalve (4C Medical), Clarity (HighLife), Cephea (Abbott Vascular), Cardiovalve (Cardiovalve), Innovalve (Innovalve), and Saturn (InnovHeart) valves[56-61] (**Table 2**). Alternative mechanisms for replicating the effects of annuloplasty have also been explored with devices that externally remodel the annulus via the coronary sinus.[62,63]

Of note, most of these potential interventions are still in initial trials, with little to no evidence for SMR application. TMVR has unique challenges that hinder its widespread application such as left ventricular outflow tract obstruction, annular sizing, leaflet morphology, and valve shape. A recently published study reported the outcomes of patients undergoing TMVR for SMR and compared them to patients in the GDMT arm of the COAPT trial.[64] The propensity-matched comparison reported that the rate of HF hospitalizations was significantly lower (32.8% vs 54.4%) in the TMVR group compared to GDMT alone, whereas all-cause mortality at 2 years was similar. Future clinical trials need to compare TMVR to mTEER-based strategies in SMR patients.

SURGICAL MV INTERVENTIONS. Although surgical interventions to re-establish mitral competence in SMR have been performed since the 1990s, there are no convincing data for survival benefit in SMR associated with HFrEF.[65] The RIME (Randomized Ischemic Mitral Evaluation) randomized trial reported that MV repair combined with surgical revascularization improved function capacity and promoted reverse LV remodeling.[66] A notable MR recurrence rate of 58% at the 2-year follow-up after mitral annuloplasty alone in the Cardiothoracic Surgical Trials Network has led the surgical community to favor MV replacement instead in this setting.[67] The 2021 European Society of Cardiology/European Association for Cardio-Thoracic Surgery and American Association for Thoracic Surgery consensus guidelines currently recommend (Class 1) concomitant mitral surgery for severe MR when cardiac surgery is performed for other indications.[68,69] Isolated MV surgery may be considered in symptomatic patients with HFrEF and severe MR secondary to nonischemic cardiomyopathy if judged appropriate by the MDT (Class 2b).[68,69] Although there are no data on the superiority of surgical mitral repair vs replacement in the nonischemic setting, mitral replacement may be preferred in advanced LV remodeling in which valve repair is not feasible.[70] In fact, a chordal-sparing mitral replacement is favored over a downsizing annuloplasty approach (Class 2b) given the high rate of SMR recurrence with the latter.[11] Features associated with subsequent surgical failure include LV end-diastolic diameter >65 mm, MV tenting height >10 mm, posterior leaflet-annulus angle >45°, anterior leaflet-annulus angle >25°, end-systolic interpapillary distance >20 mm, systolic sphericity index >0.7, and a spherical LV shape.[65,71,72]

CONSIDERATIONS FOR THERAPEUTIC OPTIONS. Various clinical, echocardiographic, and anatomical criteria have been described to screen symptomatic HFrEF patients with SMR (**Figure 5**). Patients referred with symptomatic SMR benefit from HF clinic-led rapid GDMT and volume optimization. After a period of 1 to 6 months (a duration that requires further data to support), repeat clinical and imaging assessments may reaffirm or defer the need for mTEER. Similarly, reassessment may reveal prior barriers to mTEER such as pulmonary hypertension or RV dysfunction have improved with optimization and no longer are an additive risk.

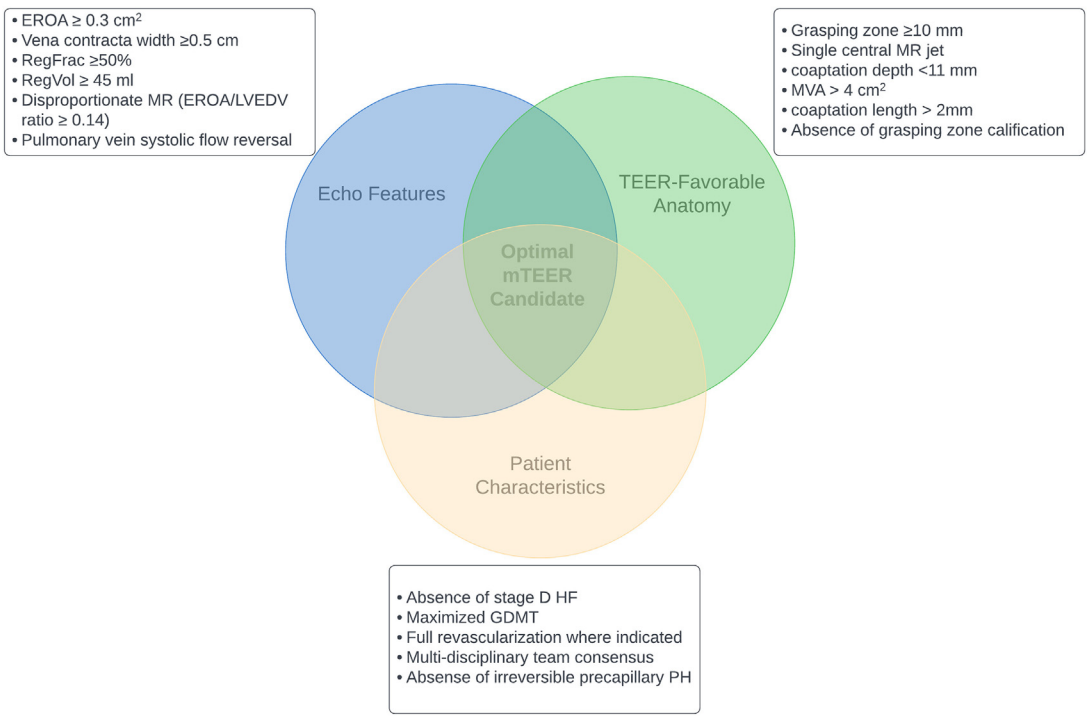
The COAPT trial criteria have been widely adopted as a guide for SMR assessment and intervention candidacy for mTEER. Key inclusion criteria in the trial include NYHA functional class II, III, or ambulatory IV; LVEF of 20% to 50%; LV end-systolic diameter ≤70 mm; estimated pulmonary artery systolic pressure ≤70 mm Hg; and absence of end-stage HF.[6] When combined with the trial's novel hierarchical approach to screen for severe SMR, incrementally lower EROA cutoffs can be used with the other parameters such as pulmonary vein systolic flow reversal (should the EROA not be consistent with severe SMR).[73] Over time, transcatheter experience has

TABLE 2 Transcatheter Mitral Valve Devices

Mechanism	Device	Manufacturer	Implant Method	Sheath Size	Device Details	Study Details	EFS	Pivotal	CE Mark	FDA
mTEER	MitraClip	Abbott Structural	TFV, TS	24-F	Recapitulates the surgical Alfieri stitch, creating a biorifice MV that reduces MR. 4 clip sizes.	COAPT (NCT01626079)		X	X	X
	Pascal	Edwards Lifesciences	TFV, TS	22-F	1 clip size. Central spacer reduces central MR.	CLASP IIF (NCT03706833)		X	X	X
	Dragonfly	Hangzhou Valgen	TFV, TS	24-F	4 clip sizes: 4- to 6-mm width, 9- to 12-mm length	NCT04528576	X			
TMVR	Tendyne	Abbott Structural	TA	34-F	Valve seated in an inner frame, which rests within a conformable outer frame. Device is secured by an apical tether.	SUMMIT (NCT03433274)		X	X	
	Intrepid	Medtronic	TA, TFV, TS	35-F	Dual construction with a conformable outer stent with flexible brim and a circular inner stent housing the valve	APOLLO (NCT03242642)		X		
	Sapien M3	Edwards Lifesciences	TFV, TS	20-F	2-component device: valve implanted within a subannular dock	ENCIRCLE (NCT04153292)		X		
	Evoque Eos	Edwards Lifesciences	TFV, TS	28-F	Bovine pericardial valve secured by subannular anchors	MISCEND (NCT02718001)	X			
	AltaValve	4C Medical	TA	32-F	Valve secured within a supra-annular spherical cage	NCT03997305	X			
	Clarity	Highlife Medical	TFV, TS	39-F	2-component device; valve implanted within a subannular ring	HighFLO (NCT04888247)	X			
	Cephea	Abbott Structural	TFV, TS	38-F	Valve anchored by axial compression created by ventricular and atrial disks	NCT05061004	X			
	Cardiovalve	Cardiovalve	TFV, TS	28-F	Low-profile design featuring 3 scalloped bovine pericardial leaflets	AHEAD (NCT03339115)	X			
	Saturn	Innovheart	TA		Central valve component anchored in an annular ring	NCT04464876	X			
	Innostay	Innovalve	TFV, TS	32-F	Circumferential arm design seals annulus using a rotational maneuver during deployment	TWIST-EFS (NCT04919980)	X			
Annuloplasty	Carillon	Cardiac Dimensions	CS	9-F	Device with proximal and distal helical anchors that plicate mitral periannular tissue	EMPOWER (NCT03142152)		X	X	
	ARTO	MVRx	CS	12-F	Anchors implanted in the lateral wall via the CS and the septum are bridged to reduce the MV minor axis dimensions.	MAVERICK (NCT03311295)	X			
Other	NeoChord	NeoChord	TA (DS1000) TFV, TS (NeXuS)	28-F	Neochordae created using a device that features a helical papillary muscle anchor and a suture that grasps the MV leaflet.	ReChord (NCT02803957) (TA)		X	X (TA)	
	Half Moon	Half Moon	TFV, TS	29-F	Improved native leaflet coaptation by filling the posterior aspect of the regurgitant orifice with an ePTFE-coated device implanted in a circular frame	NCT04343313	X			

CE = Conformite Europeenne; CS = coronary sinus; EFS = early feasibility study; ePTFE = expanded polytetrafluoroethylene; FDA = Food and Drug Administration; mTEER = mitral transcatheter edge-to-edge repair; MV = mitral valve; TA = transapical; TFV = transfemoral vein; TMVR = transcatheter mitral valve replacement; TS = transseptal; other abbreviation as in Table 1.

FIGURE 5 Imaging and Patient-Specific Characteristics Pertinent to mTEER Candidate Consideration



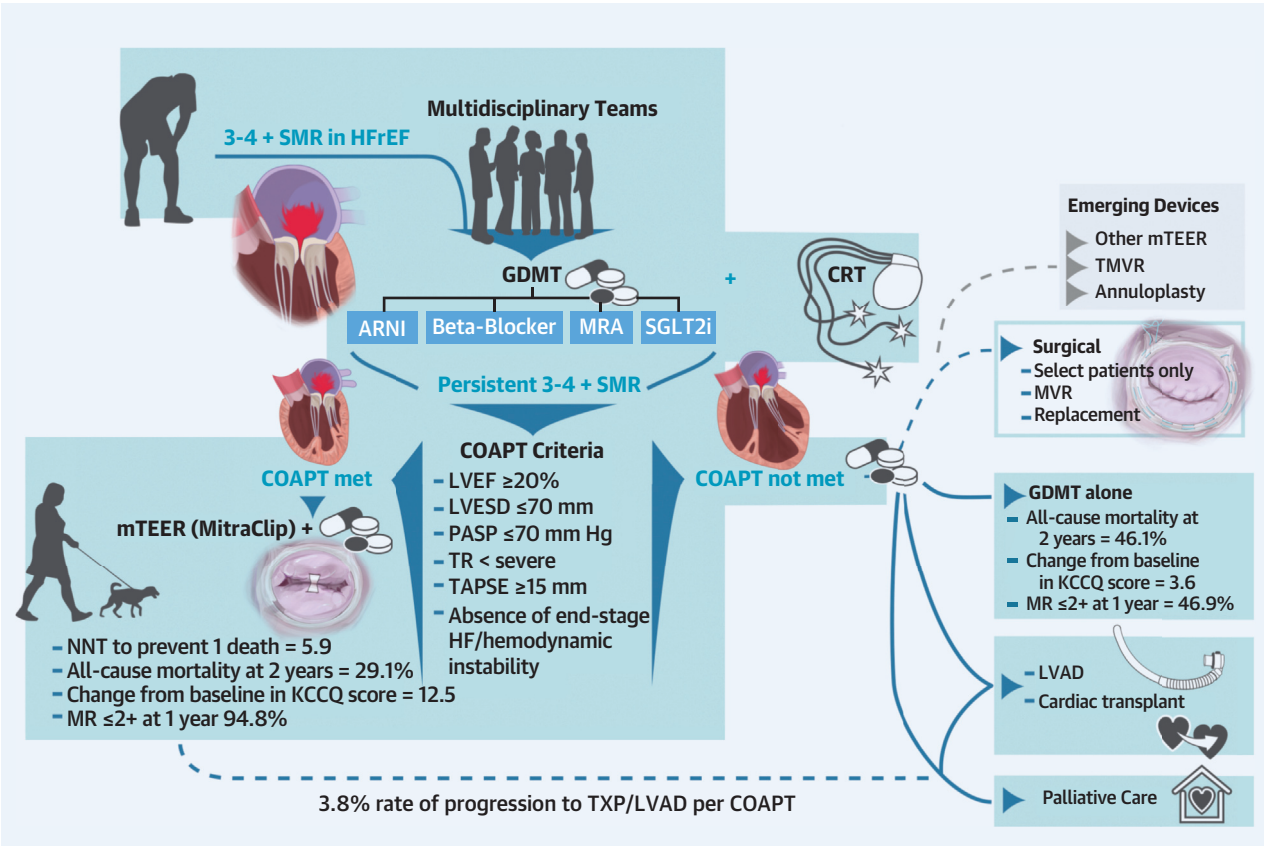
GDMT = guideline-directed medical therapy; mTEER = mitral transcatheter edge-to-edge repair; MVA = mitral valve area; PH = pulmonary hypertension; RegFrac = regurgitant fraction; RegVol = regurgitant volume; TEER = transcatheter edge-to-edge repair; other abbreviations as in Figures 1 and 2.

allowed for further identification of characteristics that are less favorable for TEER, including MV area <4 cm², severe mitral annular calcification (MAC), rheumatic MV disease, MV clefts, commissural MR, flail gap >10 mm, flail width >15 mm, and coaptation length <2 mm and depth >11 mm.[13]

For symptomatic HFrEF patients with SMR who do not meet the COAPT trial criteria by echocardiography, options include conservative management with GDMT or, for a subset, heart replacement therapies (**Central Illustration**). The impact of mTEER in patient populations excluded in COAPT because of other comorbidities such as concomitant chronic obstructive pulmonary disease, severe tricuspid regurgitation, severe pulmonary hypertension, and RV dysfunction is being evaluated in multiple registry-based studies. Recent real-world data from the TVT and EuroSMR (European Registry of Transcatheter Repair for Secondary Mitral Regurgitation) registry shows that mTEER with MitraClip was associated with a significant improvement in quality of life and NYHA functional class, a durable reduction in MR, and a low adverse event rate.[74]

SMR IN UNIQUE PATIENT POPULATIONS. Although there is enthusiasm for the expansion of mTEER candidacy outside of COAPT criteria, there remains a lack of data to support widespread adoption of this strategy.[12] Future studies should evaluate the role of mTEER in patients with atrial functional MR, those with borderline elevated mitral gradients, and those on inotropic support, among other populations. The RESHAPE-HF2 (A Clinical Evaluation of the Safety and Effectiveness of the MitraClip System in the Treatment of Clinically Significant Functional Mitral Regurgitation; NCT02444338) trial is ongoing and evaluating the impact of MitraClip in patients with SMR and LVEF ≥15% to ≤35% (if in NYHA functional class II) or ≥15% to ≤45% (if in NYHA functional class III or IV).

CENTRAL ILLUSTRATION **Considerations in Patient Selection for Secondary Mitral Regurgitation Intervention in HFrEF Patients**



Lander MM, et al. J Am Coll Cardiol HF. 2023;11(8):1055–1069.

ARNI = angiotensin receptor–neprilysin inhibitor; COAPT = Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients with Functional Mitral Regurgitation; CRT = cardiac resynchronization therapy; GDMT = guideline-directed medical therapy; HF = heart failure; HFrEF = heart failure with reduced ejection fraction; KCCQ = Kansas City Cardiomyopathy Questionnaire; LVAD = left ventricular assist device; LVEF = left ventricular ejection fraction; LVESD = left ventricular end-systolic dimension; MR = mitral regurgitation; MRA = mineralocorticoid receptor antagonist; mTEER = mitral transcatheter edge-to-edge repair; MVR = mitral valve replacement; NNT = number needed to treat; PASP = pulmonary artery systolic pressure; SGLT2i = sodium-glucose cotransporter 2 inhibitor; SMR = secondary mitral regurgitation; TAPSE = tricuspid annular plane systolic excursion; TMVR = transcatheter mitral valve replacement; TR = tricuspid regurgitation; TXP = transplant.

Cardiogenic shock. About 5% to 10% of patients with acute myocardial infarction–associated coronary sinus present with severe MR, which portends additional poor prognosis.[75] Recent reports have suggested that mTEER may improve in-hospital and 30-day survival in patients with cardiogenic shock and MR (both functional and degenerative).[76-78] Carefully designed clinical trials and predefined subgroup analysis are required to identify patient and procedural characteristics, hemodynamic parameters, and the optimal time for intervention to ultimately address this benefit.[79]

End-stage HF. End-stage HF patients were excluded from the mTEER trials, leaving a gap in the literature on best practices for this group. The MitraBridge (Transcatheter Mitral Valve Repair as Bridge Therapy to Heart Transplantation) registry included patients with end-stage HF with transplant eligibility with a long wait time or potentially reversible transplant contraindications.[80] This nonrandomized trial totaled 119 patients across 17 centers on maximal GDMT who underwent mTEER, of whom nearly one-fourth were later removed from transplant consideration because of clinical improvement. This suggests that mTEER

may provide a safe bridge to improvement or eventual transplant candidacy in the right patients, although further data are necessary for any firm recommendations.

There are emerging tools to assist the clinician faced with concerns of "missing the window" for a patient in between heart replacement candidacy and mTEER. Several risk stratification scores have been developed (MITRALITY, MitraScore, and COAPT risk score) that all consider various preprocedural variables to predict postprocedural outcomes with mTEER.[81-83] However, these scores have their own deficiencies, such as a lack of external validation, modest discrimination, and for the end user a lack of real cutoffs or guidance as to what score should impact decision making. Clinicians who want to follow high-risk patients post-mTEER, and perhaps identify "nonresponders," may be best served by tools already widely used such as the KCCQ, as demonstrated in a COAPT substudy by Arnold et al.[84] For example, a 10-point or greater improvement from baseline to month 1 in the KCCQ overall summary score was associated with a significant difference in death or HF hospitalization incidence at 2 years from those with no change (40.2% vs 58.2%; $P < 0.001$).

Mitral annular calcification. MAC is increasingly prevalent with an aging population with associated risk of MV dysfunction and mortality. Contemporary transcatheter trials have often excluded patients with severe MAC, limiting uniform understanding of these interventions for this population. Coincident severe MAC and SMR (although uncommon) are typically found in elderly patients with comorbidities and prohibitive surgical risk and are best addressed using a multidisciplinary heart team approach with careful attention to anatomical compatibility, which may elicit candidacy for TMVR.[85] Although there is a paucity of data on TEER in MAC and SMR, a recent real-world cohort with ~60% SMR suggested high technical success and a low rate of complications with similar improvements in HF readmissions and mortality.[86]

Left ventricular assist device therapy. Left ventricular assist device (LVAD) placement frequently leads to a reduction in the severity of functional MR. Although a notable number of LVAD-supported patients have residual MR, its impact on outcomes and hence the role of MV interventions/concomitant MV repair at the time of LVAD implant is controversial. Patients with moderate or severe RV dysfunction are particularly susceptible to the afterload exerted by significant residual MR and have a much higher incidence of postoperative RV and renal failure.[87,88] In contrast, a MOMENTUM 3 (Multicenter Study of MagLev Technology in Patients Undergoing Mechanical Circulatory Support Therapy with HeartMate) analysis showed that although nearly half (43.5%) of the patients undergoing LVAD had clinically significant MR at baseline, residual MR was present in only 6.2% of patients with HeartMate 3 (Abbott Vascular) implant at 1 month.[89] Moreover, residual MR at 1 month postimplant did not impact 2-year mortality (HR: 1.41 [95% CI: 0.52-3.89]; $P = 0.50$). The risk of performing concomitant MV repair must be weighed for individual patients. It is important to note that mitral stenosis, especially with TEER, may affect LVAD outcomes significantly.

CONCLUSIONS

Technical and technological advances in the field of valvular heart disease, especially SMR, have amplified the role of an MDT approach and GDMT. A variety of percutaneous or transcatheter valve repair/replacement systems are now available for the management of SMR. Avoiding the need for cardiopulmonary bypass, these MV interventions offer a remarkable safety profile and broadening clinical applications. The growing experience and evidence regarding the safety and efficacy of MitraClip has made mTEER the first-line therapy in patients with HF and significant SMR despite maximal GDMT. Moreover, results from COAPT have set the benchmark for future trials in the field of percutaneous mitral repair. We continue to witness expansion in minimally invasive transcatheter techniques with better safety and efficacy profiles over time.

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APPENDIX For supplemental videos, please see the online version of this paper.