JSCAI
The official journal of the Society for Cardiovascular Angiography & Interventions

Comprehensive Review

Heart Failure and Secondary Mitral Regurgitation: A Contemporary Review

Anton Camaj, MD, MS [a], Vinod H. Thourani, MD [b], Linda D. Gillam, MD, MPH [c], Gregg W. Stone, MD [a,*]

[a] Zena and Michael A. Wiener Cardiovascular Institute, Icahn School of Medicine at Mount Sinai, New York, New York; [b] Department of Cardiovascular Surgery, Marcus Valve Center, Piedmont Heart Institute, Atlanta, Georgia; [c] Gagnon Cardiovascular Institute, Morristown Medical Center, Morristown, New Jersey

ABSTRACT

Secondary mitral regurgitation (SMR) in patients with heart failure (HF) is associated with significant morbidity and mortality. In recent decades, SMR has received increasing scientific attention. Advances in echocardiography, computed tomography and cardiac magnetic resonance imaging have refined our ability to diagnose, quantify and characterize SMR. Concurrently, the treatment options for this high-risk patient population have continued to evolve. Guideline-directed medical therapies including beta-blockers, angiotensin receptor-neprilysin inhibitors, mineralocorticoid receptor antagonists and sodium-glucose cotransporter-2 inhibitors target the underlying cardiomyopathy, and along with diuretics to treat pulmonary congestion, remain the cornerstone of therapy. Cardiac resynchronization therapy also reduces MR, alleviates symptoms and prolongs life in selected HF patients with SMR. While data supporting surgical mitral valve repair or replacement for SMR are limited, transcatheter edge-to-edge repair (TEER) has been demonstrated to improve survival, reduce the rate of hospitalization for heart failure, and improve functional capacity and quality-of-life in select patients with SMR who remain symptomatic despite medical therapy. Emerging transcatheter mitral valve repair and replacement technologies are undergoing investigation in TEER-eligible and TEER-ineligible patients. The optimal management of HF patients with SMR requires a multidisciplinary team of cardiologists, cardiac surgeons, imaging experts, and other organ specialists to select the best treatment approaches to improve the prognosis of these high-risk patients.

Introduction

Mitral regurgitation (MR) is one of the most common valvular heart disorders and is associated with significant morbidity and mortality, particularly in patients with advanced heart failure (HF).[1,2] In recent decades, MR has attracted significant scientific interest, resulting in new strategies for diagnosing, quantifying, and characterizing the disease process as well as its treatment with a wave of new medical, surgical, and transcatheter-based approaches. To understand MR, it is important to appreciate the anatomical complexity of the mitral valve (MV) apparatus, which consists of the MV leaflets, mitral annulus, and the subvalvular apparatus made up of the chordae tendineae and the papillary muscles that arise from the left ventricle (LV).[3] A lesion or disorder involving any of these structures can lead to MR. Decades ago, the surgeon Alain Carpentier proposed a classification system based on mitral leaflet motion that has become widely adopted and has utility in understanding the various etiologies of MR.[4,5] A contemporary approach defines MR as *primary* (degenerative or organic) or *secondary* (functional). Primary MR is caused by abnormalities of the MV leaflets, annulus, or apparatus, whereas secondary MR (SMR) is usually due to LV dysfunction and remodeling, which geometrically displaces the papillary muscles, tethering the mitral leaflets and preventing their normal coaptation. In ~90% of cases, SMR is due to either regional or global LV dilatation from either ischemic or nonischemic cardiomyopathy. In ~10% of cases, SMR may be due to long-standing atrial fibrillation, an atrial myopathy, or HF with preserved ejection fraction with left atrial (LA) dilatation resulting in mitral annular dilatation and impaired leaflet coaptation. LV dimensions are often normal in such cases of atrial functional MR (AFMR).[6,7] SMR (specifically Carpentier class IIIb MR) is the most prevalent type of MR in the United States[8] and has strongly been associated with increased mortality and hospitalization for HF and poor quality-of-life (QOL) (Figure 1).

In patients with Carpentier class IIIb MR, surgical correction of SMR with MV repair or replacement has not been shown to reduce the rates of hospitalization or death, and both operations confer a substantial risk

Abbreviations: COAPT, Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients With Functional Mitral Regurgitation; GDMT, guideline-directed medical therapy; HF, heart failure; MITRA-FR, Multicenter Study of Percutaneous Mitral Valve Repair MitraClip Device in Patients With Severe Secondary Mitral Regurgitation; MR, mitral regurgitation; SMR, secondary mitral regurgitation; TEER, transcatheter edge-to-edge repair; TMVR, transcatheter mitral valve replacement.

Keywords: heart failure; secondary mitral regurgitation; transcatheter edge-to-edge repair; transcatheter mitral valve replacement.

* Corresponding author: gregg.stone@mountsinai.org (G.W. Stone).

https://doi.org/10.1016/j.jscai.2023.101195
Received 11 August 2023; Received in revised form 15 September 2023; Accepted 26 September 2023
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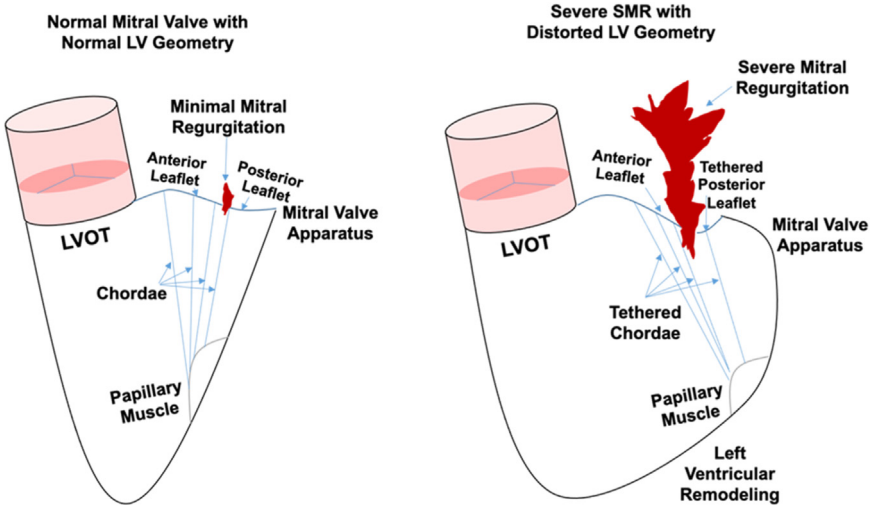


Figure 1.
Mechanism of secondary regurgitation. Relationship between the mitral valve apparatus and normal left ventricular geometry (left) and severe secondary mitral regurgitation due to distorted left ventricular geometry (right). Left ventricular dilatation results in apical and lateral displacement of the papillary muscles with tethering of the mitral leaflets and lack of leaflet coaptation, worsened by reduced closing forces. Annular remodeling occurs late and may further increase the distance between the leaflets. LV, left ventricular; LVOT, left ventricular outflow tract; SMR, secondary mitral regurgitation.

of complications and morbidity.[9,10] However, there are no randomized trials of mitral surgery in patients with severe SMR. Conversely, the randomized COAPT (Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients With Functional Mitral Regurgitation) and MITRA-FR (Multicenter Study of Percutaneous Mitral Valve Repair MitraClip Device in Patients With Severe Secondary Mitral Regurgitation) trials showed that transcatheter edge-to-edge repair (TEER) with the MitraClip device (Abbott) was safe and effective at reducing the severity of MR.[11,12] TEER was associated with a significant reduction in HF hospitalization (HFH) and death compared with guideline-directed medical therapy (GDMT) alone in the COAPT trial but not in the MITRA-FR trial. In this review, we review the role of SMR in HF with an emphasis on the techniques and devices that currently exist and that are being developed to better monitor, stage, risk stratify, and treat this growing patient population.

Prognostic importance of secondary MR

Numerous studies have established a strong, independent association between the presence and severity of SMR and clinical outcomes including all-cause mortality, HFH, and transplantation (Figure 2).[11-15] A meta-analysis including 53 studies with 45,900 patients showed that the presence of SMR in patients with LV dysfunction was associated with a higher risk of all-cause mortality (risk ratio [RR], 1.79; 95% CI, 1.47-2.18; $P < .001$), HFH (RR, 2.26; 95% CI, 1.92-2.67) and the composite of death, HFH, or transplantation (RR, 1.63; 95% CI, 1.33-1.99).[16] SMR has been associated with increased mortality irrespective of the etiology of the underlying cardiomyopathy (ischemic or nonischemic).[17–20] Increasing severity of SMR as assessed by quantitative methods has been correlated with increasing rates of death and HFH.[21] The outcomes may be even worse in patients with poor LV function and SMR. Namazi et al[21] showed in HF patients with SMR that impaired LV global longitudinal strain <7.0% was associated with an increased risk for all-cause mortality (hazard ratio [HR], 1.34; 95% CI, 1.04-1.72; $P = .02$) whereas LV ejection fraction (LVEF) ≤30% was not (HR, 1.06; 95% CI, 0.79-1.40; $P = .71$). However, given the fact that MR reduces LV afterload, characterizing LV function with either LVEF or LV global longitudinal strain may be misleading.

Until the COAPT trial, whether SMR has a causal relationship with death or HFH or is merely a marker of severe LV dysfunction was unclear. COAPT demonstrated that correcting severe SMR in selected HF

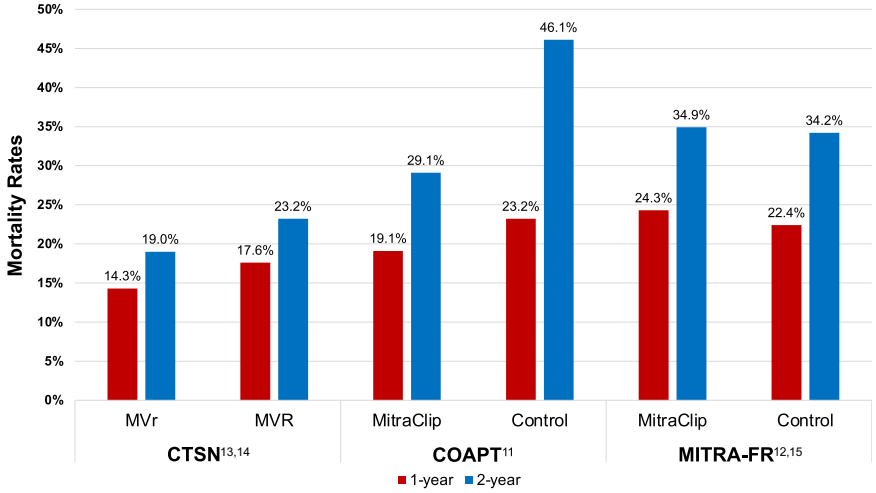


Figure 2.
All-cause mortality rates at 1 and 2 years in patients with severe secondary mitral regurgitation and advanced heart failure treated with surgery, MitraClip, and medical therapy. MVr, surgical mitral valve repair; MVR, surgical mitral valve replacement.

Table 1. Grading the severity of mitral regurgitation by echocardiography.

	Mitral regurgitation severity			
	Mild	Moderate		Severe
Structural				
MV morphology	None or mild leaflet abnormality (e.g., mild thickening, calcifications or prolapse, mild tenting)	Moderate leaflet abnormality or moderate tenting		Severe valve lesions • Primary: flail leaflet, ruptured papillary muscle, severe retraction, large perforation • Secondary: severe tenting, poor leaflet coaptation
LV and LA size[a]	Usually normal	Normal or mild dilated		Dilated[b]
Qualitative Doppler				
Color flow jet area[c]	Small, central, narrow, often brief	Variable		Large central jet (>50% of LA) or eccentric wall-impinging jet of variable size
Flow convergence[d]	Not visible, transient or small	Intermediate in size and duration		Large throughout systole
CWD jet	Faint/partial/parabolic	Dense but partial or parabolic		Holosytolic/dense/triangular
Semiquantitative				
VCW (cm)	<0.3	Intermediate		≥0.7 (>0.8 for biplane)[e]
Pulmonary vein flow[f]	Systolic dominance (may be blunted in LV dysfunction or AF)	Normal or systolic blunting[f]		Minimal to no systolic flow/systolic flow reversal
Mitral inflow[g]	A-wave dominant	Variable		E-wave dominant (>1.2 m/s)
Quantitative[h,i]				
EROA, 2D PISA (cm^2)	<0.20	0.20-0.2.9	0.30-0.39	≥0.40 (may be lower in SMR with ellipitical ROA)
RVol (mL)	<30	30-44	45-59[h]	≥60 (may be lower in low flow conditions)
RF (%)	<30	30-39	40-49	≥50

Reproduced with permission from Zoghbi et al.[7]
AF, atrial fibrillation; CWD, continuous wave Doppler; EROA, effective regurgitant orifice area; LA, left atrium; LV, left ventricle; MV, mitral valve; PISA, proximal isovelocity surface area; RF, regurgitant fraction; RVol, regurgitant volume; SMR, secondary mitral regurgitation; VCW, vena contracta width.
[a] This pertains mostly to patients with primary MR. [b] LV and LA can be within the "normal" range for patients with acute severe MR or with chronic severe MR who have small body size, particularly women, or with small LV size preceding the occurrence of MR. [c] With Nyquist limit 50-70 cm/s. [d] Small flow convergence is usually <0.3 cm, and large is >1 cm at a Nyquist limit of 30-40 cm/s. [e] For average between apical 2- and 4-chamber views. [f] Influenced by many other factors (LV diastolic function, atrial fibrillation, LA pressure). [g] Most valid in patients >50 years old and is influenced by other causes of elevated LA pressure. [h] Discrepancies among EROA, RF, and RVol may arise in the setting of low or high flow states. [i] Quantitative parameters can help subclassify the moderate regurgitation group.

patients can improve prognosis, confirming the prognostic role of SMR in worsening outcomes of these patients. However, in the COAPT trial, the annualized rates of HFH and death remained high at 24 months postrandomization (35.8% and 29.1%, respectively) despite TEER with the MitraClip, exemplifying the poor prognosis driven by the underlying LV cardiomyopathy, which is not directly affected by TEER.[11]

Evaluation of SMR

A comprehensive evaluation of patients with SMR and advanced HF starts with a detailed history and physical examination, medication reconciliation, and laboratory, electrocardiographic, and multimodality imaging assessment to quantify the specific valvular anatomy and degree of MR and to assess ventricular function and geometry. The patient's functional limitations should be characterized according to the New York Heart Association (NYHA) classification, Kansas City Cardiomyopathy Questionnaire, 6-minute walk test, grip strength, and other measures of frailty. Important comorbidities such as chronic obstructive pulmonary disease and renal failure, if present, should also be documented. With this information, the MR can be staged, and the patient can be appropriately risk-stratified.[9,22]

Imaging

Echocardiography. Two-dimensional echocardiography is fundamental to the evaluation of MR. Transthoracic echocardiography (TTE) is the first-line imaging modality used to evaluate MV anatomy, LV and right ventricular (RV) function and geometry, pulmonary artery (PA) pressures, MR severity, and mechanism of MR. Transesophageal echocardiography (TEE) is complementary to TTE and offers a more detailed examination of the MV apparatus and mechanism of MR, and such information is essential for procedural (ie, surgical or transcatheter) planning.[23] Three-dimensional (3D) TEE provides additional data on the feasibility of MV repair by further characterizing papillary muscle displacement, leaflet tethering, and LV volumes and is important in preintervention planning.[1] Nevertheless, TTE is preferred over TEE for quantification of MR severity, as TEE may underestimate MR severity due to the vasodilatory effects of sedation and/or anesthesia or relative hypovolemia in the fasting patient.

Grading the severity of MR by echocardiography requires a multiparametric integration of numerous quantitative and qualitative echocardiographic assessments.[7] Quantitative assessment includes measuring the effective regurgitant orifice area (EROA), regurgitant volume, and regurgitant fraction, with mitral inflow and pulmonary vein flow velocities offering semiquantitative assessments via pulsed wave Doppler. Qualitative assessments are provided by assessing MV morphology as well as color and continuous wave Doppler and color jet features. With this information, a cardiologist can then classify the MR as mild, moderate, or severe (Table 1).[7] However, grading the severity of SMR can be more challenging than in primary MR. In SMR, lack of mitral leaflet coaptation develops *secondary* to LV dysfunction and dilatation (ischemic or nonischemic cardiomyopathy) or annular dilatation due to LA enlargement. Particularly in cases of ischemic cardiomyopathy, the vena contracta area may be elliptical as opposed to circular, and the proximal isovelocity surface area shell is nonhemispherical. This limits the applicability of 2-dimensional flow convergence proximal isovelocity surface area approaches; these jets are best evaluated by 3D TEE via multiplanar reconstruction

Table 2. Stages of secondary mitral regurgitation.

Stage	Valve anatomy	Valve hemodynamics	Associated cardiac findings	Symptoms
A: At risk of MR	• Normal valve leaflets, chords, and annulus in a patient with CAD or cardiomyopathy	• No MR jet or small central jet area <20% LA on Doppler • Small vena contracta <0.30 cm	• Normal or mildly dilated LV size with fixed (infarction) or inducible (ischemia) regional wall motion abnormalities • Primary myocardial disease with LV dilation and systolic dysfunction	• Symptoms attributable to coronary ischemia or HF may be present that respond to revascularization and appropriate medical therapy
B: Progressive MR	• Regional wall motion abnormalities with mild tethering of mitral leaflet • Annular dilation with mild loss of central coaptation of the mitral leaflets	• EROA <0.40 cm^2 • RVol <60 mL • RF <50%	• Regional wall motion abnormalities with reduced LV systolic function • LV dilation and systolic dysfunction attributable to primary myocardial disease	• Symptoms attributable to coronary ischemia or HF may be present that respond to revascularization and appropriate medical therapy
C: Asymptomatic severe MR	• Regional wall motion abnormalities and/or LV dilation with severe tethering of mitral leaflet • Annular dilation with severe loss of central coaptation of the mitral leaflets	• EROA ≥0.40 cm^2 • RVol ≥60 mL • RF ≥50%	• Regional wall motion abnormalities with reduced LV systolic function • LV dilation and systolic dysfunction attributable to primary myocardial disease	• Symptoms attributable to coronary ischemia or HF may be present that respond to revascularization and appropriate medical therapy
D: Symptomatic severe MR	• Regional wall motion abnormalities and/or LV dilation with severe tethering of mitral leaflet • Annular dilation with severe loss of central coaptation of the mitral leaflets	• EROA ≥0.40 cm^2 • RVol ≥60 mL • RF ≥50%	• Regional wall motion abnormalities with reduced LV systolic function • LV dilation and systolic dysfunction attributable to primary myocardial disease	• HF symptoms attributable to MR persist even after revascularization and optimization of medical therapy • Decreased exercise tolerance • Exertional dyspnea

CAD, coronary artery disease; EROA, effective regurgitant orifice area; HF, heart failure; LA, left atrium, LV, left ventricular; MR, mitral regurgitation; RF, regurgitant fraction; RVol, regurgitant volume. Reproduced with permission from Otto et al.[9]

and/or 3D planimetry (notwithstanding the risk of TEE underestimating MR severity, as discussed above).[7,24] Nonholosystolic regurgitant flow poses additional challenges to quantitation in some patients. For preprocedural planning prior to transcatheter repair, additional detailed assessment of mitral anatomy including measurements of mitral cross-sectional area and leaflet length are essential. "Fusion imaging" is an emerging modality that combines 3D TEE with real time fluoroscopy for intraprocedural monitoring of transcatheter MV repair and replacement devices.[25]

Exercise stress echocardiography may be useful in the evaluation of SMR, especially in patients whose symptoms are disproportionate to their resting echo findings, by eliciting severe MR and/or worsening ventricular function with exercise. Alternatively, symptoms and reduced functional capacity can be unmasked in seemingly asymptomatic patients.[9] In addition, stress echocardiography provides prognostic value in patients with secondary MR.[26,27] An increase in EROA ≥13 mm^2 during exercise has been associated with adverse outcomes and symptoms in secondary MR[28]; however, this can be challenging to record due to tachypnea and tachycardia.

Cardiac magnetic resonance imaging and cardiac computed tomography. Evaluation of SMR by cardiac magnetic resonance (CMR) imaging and cardiac computed tomography (CT) offers complementary information to echocardiography.[7] In secondary ischemic MR, the characterization of myocardial infarct size and viability by CMR provides further risk stratification beyond LV volumes and clinical parameters and has implications for treatment such that those with small infarct size stand to benefit most from surgical MV intervention.[29] Assessment of LV volumes with echocardiography can be particularly challenging in HF patients with SMR due to LV foreshortening. CMR, a volumetric technique, has no such limitation. CMR also provides alternative approaches to quantitating MR severity.

Cardiac CT can accurately depict important anatomical relationships, such as those between the mitral annulus, coronary sinus, and circumflex coronary artery, that may be especially important for transcatheter-based interventional planning.[30,31] For example, cardiac CT can help identify the optimal transapical (TA) puncture site for transcatheter procedures.[32] Moreover, during planning for transcatheter MV replacement (TMVR), cardiac CT provides anatomical

Table 3. Key differences between COAPT and MITRA-FR.

	COAPT (N = 614)	MITRA-FR (N = 304)
GDMT		
Baseline	CEC-confirmed patients symptomatic despite maximally-tolerated GDMT	Receiving HF medications
Follow-up	Changes discouraged; few major changes occurred	Changes allowed and could vary between arms
Severe MR entry criteria	US Guidelines: Multiparametric, including PSVFR, EROA >30 mm^2, and RVol >45 mL/beat	European Guidelines: EROA >20 mm^2 or RVol >30 mL/beat
Mean EROA	41 mm^2	31 mm^2
Mean LVEDVi	101 mL/m^2	135 mL/m^2
Procedural complications	8.5%	14.6%
≥3+ MR at 1 y following MitraClip	5%	17%

CEC, clinical events committee; EROA, effective regurgitant orifice area; GDMT, guideline-directed medical therapy; HF, heart failure; LVEDVi, left ventricular end-diastolic volume index; MR, mitral regurgitation; PSVFR, pulmonary systolic venous flow reversal; RVol, regurgitant volume.

information on the shape of the junction between the MV annulus and posterior LA walls as well as provides risk assessment for LV outflow tract (LVOT) obstruction by neo-LVOT prediction.[33]

Staging

The most recent American Heart Association/American College of Cardiology guidelines for the management of patients with valvular heart disease recommend staging SMR and primary MR in similar fashion.[9] Accordingly, stage A defines patients at risk for MR. Stage B defines those with progressive but nonsevere MR. Severe MR is divided into 2 groups based on the absence (stage C) or presence (stage D) of symptoms (Table 2).

The degree of cardiac pathology can broadly impact patient outcomes beyond the severity of SMR and thus should be taken into consideration when staging patients with SMR. Singh et al[34] proposed a staging algorithm for patients with SMR and LVEF $<$ 50%. Stage 1 includes patients with LV involvement alone (LVEF $<$ 50% and LV end-diastolic volume [LVEDV] $\geq$159 mL). Stage 2 includes patients with LA enlargement (indexed LA volume $>$34 mL/m^2) or atrial fibrillation or flutter. Stage 3 includes those with RV pressure/volume overload ($\geq$3+ tricuspid regurgitation or PA systolic pressure $>$65 mm Hg). Stage 4 includes those with biventricular failure such that RV to PA coupling is $<$0.274 mm/mm Hg. In a series of 325 patients with HF and significant SMR, stages 1 and 2 showed similar 3-year survival rates of approximately 85%, whereas 3-year survival was 75% in stage 3 and 60% in stage 4. These findings were recently validated in a cohort of patients undergoing mitral TEER.[35]

Management of SMR

Medical therapy

GDMT (and cardiac resynchronization therapy [CRT] in appropriate patients) is the first-line treatment for HF and SMR and may induce LV reverse remodeling and reduce SMR before or after intervention.[36] Indeed, the differing manner in which GDMT was managed in the COAPT and MITRA-FR trials may have contributed to the discordant results after TEER in these trials (Table 3).[11,12] In COAPT, only patients on maximally tolerated doses of GDMT as confirmed by a pre-enrollment central eligibility committee were randomized, and major changes in GDMT during follow-up were limited in both the TEER and control arms, allowing the benefits of the MitraClip to emerge. Conversely, patients in MITRA-FR may have had suboptimal GDMT titration both before and after TEER, and the trial allowed for differential use of these agents during follow-up in the 2 groups, which may have impacted outcomes.

The most recent HF with reduced ejection fraction (HFrEF) guidelines define 4 pillars of GDMT including: (1) renin-angiotensin system inhibition with angiotensin receptor-neprilysin inhibitor (ARNi, preferred), angiotensin-converting enzyme inhibitor (ACEi), or angiotensin (II) receptor blocker (ARB) alone; (2) beta blockers (BBs); (3) mineralocorticoid receptor antagonists (MRAs); and (4) sodium-glucose cotransporter-2 (SGLT2) inhibitor.[22] The PRIME (Pharmacological Reduction of Functional, Ischemic Mitral Regurgitation) trial studied the efficacy of ARNi on SMR reduction in 117 patients with chronic SMR (EROA $>$0.1 cm^2), LVEF 25% to 50%, NYHA class II to III symptoms, and pre-existing GDMT for HFrEF who were randomized to ARNi or valsartan therapy.[37] At 1 year, the ARNi group experienced a 30% relative reduction in the primary end point of EROA (-0.06 ± 0.10 vs -0.02 ± 0.11 cm^2; $P = .032$) compared with the valsartan group irrespective of the etiology of SMR or baseline rhythm. Regarding BBs, carvedilol has the most robust evidence for its effect on reducing SMR in HFrEF patients.[36] Several observational studies have shown significant reductions in SMR severity by EROA and regurgitant volume as well as improvements in LV reverse remodeling following treatment with carvedilol.[38–41] The direct effects of MRAs on SMR in patients with HFrEF have not been studied; however, there is convincing evidence that MRAs lead to improvements in LVEF and other markers of LV reverse remodeling such as LV end-systolic and end-diastolic volumes and LV mass in patients with ischemic and nonischemic cardiomyopathies.[42–45] SGLT2 inhibitors have also demonstrated significant benefits on LV function, morbidity and mortality in patients with HFrEF irrespective of diabetes status or LVEF.[46] While no data on the effects of SGLT2 inhibitors on SMR are currently available, the ongoing EFFORT (Ertugliflozin for Functional Mitral Regurgitation; NCT04231331) clinical trial is evaluating the role of ertugliflozin in the treatment of patients with LV dysfunction and SMR and is expected to reach study completion in December 2023. Interestingly, approximately 34% and 47% of COAPT patients in the GDMT alone control arm had a reduction in the severity of MR from grade 3+ or 4+ at baseline to grade 2+ or lower at 30 days and 12 months, respectively.[11] This observation likely reflects the dynamic nature of SMR in patients with HF (as well as survival bias). The impact of MR reduction (MR $\leq$2+ vs 3+/4+) at 30 days on the rates of mortality and HFH between 30 days and 2 years as well as QOL during follow-up was comparable whether MR reduction was achieved by the MitraClip or GDMT alone.[47] These observations demonstrate that reduced SMR is the driving mechanism for improved clinical outcomes in patients with HF rather than the mode of SMR reduction.

While the benefits of GDMT in patients with HFrEF and SMR are unquestionable, long-term mortality rates in HF patients with severe SMR remain $>$50% with GDMT alone.[48,49] Additionally, in a study of 163 patients with HFrEF and SMR, nearly 1 in 5 patients with nonsevere SMR progressed to severe SMR during a median follow-up of 56 months despite optimal medical therapy.[50] The poor prognosis in HF patients with severe SMR on GDMT alone was corroborated in the COAPT and MITRA-FR trials. In COAPT, the 2-year rate of HFH in the control arm (GDMT alone) was 56.7%, and the 2-year rate of death was 46.1%.[11] Similarly, in MITRA-FR, the composite end point of death or HFH at 1 year occurred in 51.3% of patients in the control arm.[12] In COAPT, most enrolled patients were unable to tolerate target goal doses of GDMT, and only 2.2% of patients tolerated target doses of all 3 GDMT classes (excluding SGLT2 inhibitors, which were not used for HF during COAPT).[51]

CRT has a class I indication for treatment of HFrEF (LVEF $\leq$35%) patients in sinus rhythm with cardiac dyssynchrony (QRS $\geq$150 ms with left bundle branch block configuration) and should be performed prior to surgical or transcatheter intervention with at least a 3-month waiting period to assess its effects on symptoms and MR severity.[22] In a study by Sitges et al,[52] CRT resulted in significant, immediate, and sustained reductions in SMR in nearly 50% of patients with both ischemic and nonischemic cardiomyopathy; however, patients with larger MV tenting areas reflecting more severe apical tethering appeared to derive less benefit. Other studies have similarly demonstrated immediate and sustained improvements in the severity of SMR following CRT implantation with improvements in SMR associated with better survival.[53–55] Mechanistically, these CRT-derived reductions in MR can be explained by reductions in LV dimensions, restoration of papillary muscle geometry, and by increasing the systolic transmitral pressure gradient, thereby improving the balance between MV closing and tethering forces.[55] Furthermore, in some studies, patients with more severe SMR at baseline appeared to benefit most from CRT implantation and experienced relatively greater LV reverse remodeling than those with lesser degrees of SMR.[56] Nonetheless, severe MR remains an independent predictor of nonresponse to resynchronization therapy such that those with severe MR are at a nearly 3-fold higher risk of nonresponse than those with lesser degrees of MR.[57] Moreover, those with absent or only mild SMR after CRT derive the greatest survival benefit,

whereas those with residual severe MR remain at high risk for all-cause and cardiovascular mortality.[56,58,59]

In patients with AFMR in which the principal derangement is annular dilatation, there is no consensus on medical management (beyond diuretics to address pulmonary congestion), although standard HF GDMT may be beneficial if LV dysfunction is also present. Some studies show an effect of rhythm management on MR reduction among patients with atrial fibrillation (AF) and AFMR by promoting atrial/annular reverse remodeling,[60] but outcomes data are lacking.[61]

Surgical therapy

Surgical approaches for patients with advanced HF and SMR include MV repair or replacement, LV assist device (LVAD) implantation and orthotopic heart transplantation. Although both MV repair and replacement can reduce or eliminate SMR, neither approach addresses the underlying LV cardiomyopathy or has been shown to improve survival.[1,6]

MV surgery. The most commonly performed MV surgery for SMR is MV annuloplasty with a downsized annuloplasty ring to decrease the mitral annular anterior-posterior diameter, which enhances mitral leaflet coaptation. Prior reports demonstrated modest symptomatic and LV functional benefits following MV annuloplasty in this patient population.[62–64] Nonetheless, these results have yet been demonstrated to improve survival or reduce HFH. In a single-center propensity adjust analysis of 419 patients with severe SMR (LVEF $\leq$30%) undergoing isolated MV annuloplasty or treated medically, mortality at a mean follow-up of 5.5 years was 48% after annuloplasty vs 38% with medical treatment.[65] Moreover, progression of the underlying cardiomyopathic process with increasing LV dilation and mitral leaflet tethering over time leads to high rates of recurrent MR after annuloplasty, up to 70% at 5 years in one report, with associated increases in morbidity and mortality.[13,66,67]

Valve-sparing surgical MV replacement preserves LV function and is preferred over earlier techniques that included excision of the mitral leaflets and subvalvular apparatus.[6] In a prospective randomized trial from the Cardiothoracic Surgical Network (CTSN) in 251 patients with severe ischemic SMR, there were no significant differences in mortality at 1 or 2 years between surgical MV repair and replacement (2-year mortality: 19.0% vs 23.2%, respectively; $P = .39$)[13,14] nor were there significant differences in LV volumes or function. However, patients who underwent MV repair rather than replacement had higher rates of recurrent MR of at least moderate severity at 2 years (58.8% vs 3.8%, $P < .001$).[14] Notably, the 2-year rates of mortality in both arms of the CTSN trial were lower than in patients treated with MitraClip in the MITRA-FR trial (34.9%) and similar to patients treated with the MitraClip in the COAPT trial (29.1%), although the COAPT patients were significantly sicker, and most were not considered surgical candidates (Figure 2).[11,15] The 2020 American Heart Association/American College of Cardiology guidelines provide a class IIa recommendation for MV surgery in patients undergoing coronary artery bypass grafting (CABG).[9] Conversely, the 2021 European Society of Cardiology/European Association for Cardio-Thoracic Surgery Guidelines for the Management of Valvular Heart Disease provide a class I recommendation for MV surgery in patients with severe SMR who remain symptomatic despite GDMT and are undergoing CABG or other cardiac surgery.[10] Both guidelines provide a class IIb recommendation for MV surgery in patients with isolated severe SMR.[9,10] In the United States, MV surgery for isolated SMR is rarely performed.[68]

In a second randomized prospective trial from the CTSN in patients (N = 301) with moderate ischemic MR undergoing CABG, the addition of MV repair with annuloplasty to CABG was not associated with improved LV reverse remodeling, the primary end point of the trial.

Figure 3.
Transcatheter edge-to-edge repair devices. Close-up views of the fabric-covered clip of the Abbott MitraClip device (top left), the MitraClip G4 Clip Delivery System and Steerable Guide Catheter (top right), the Edwards Lifesciences PASCAL Implant (bottom left), and PASCAL Precision System (bottom right).

Although the incidence of moderate or severe MR was reduced after MV repair, bypass time, hospital length of stay, and neurologic events were increased compared with CABG alone, and there was no difference in survival at 1 and 2 years between the groups. Thus, MV surgery (as well as transcatheter intervention) is only indicated for severe SMR.

LVAD. The incidence of significant (moderate or severe) SMR is approximately 44% in patients with advanced HF undergoing LVAD implantation.[69] Despite this, concomitant mitral surgery during LVAD implantation in patients with significant MR is performed in only about 5% of patients.[70] SMR present at the time of LVAD implantation may be reduced as a result of the ventricular unloading afforded by the LVAD.[69,71] Morgan et al[72] reported significant and sustained MR reduction following continuous flow LVAD implantation in patients with significant MR, from a prevalence of 76% pre-LVAD to 8% and 11% at 1 month and 6 months post-LVAD, respectively. Moreover, several studies have reported that LVAD outcomes including survival are not adversely affected by the presence of MR at the time of LVAD implantation.[70,73,74] As a result, international guidelines do not support routine concomitant MV surgery during LVAD implantation.[75]

However, some reports have challenged the dogma that MR typically resolves following LVAD implantation. Kitada et al[76] showed that in patients with significant MR at baseline, up to 34% had significant residual MR post-LVAD. Patients with significant residual MR had higher PA pressures, worse RV function, and shorter times from LVAD implantation to rehospitalization and death.[77,78] A more recent analysis showed that the rate of residual MR following LVAD implantation was less frequent in those receiving the newer HeartMate 3 device compared with the older HeartMate II (6.2% vs 14.3%; RR, 0.43; 95% CI, 0.22-0.84; $P = .01$).[69] The strongest multivariable predictor of significant residual MR following LVAD implantation was severe MR at baseline even after adjusting for LVAD type. Nonetheless, residual MR at 1-month post-LVAD with either device was unrelated to mortality in this study. Further research is needed to better characterize the frequency, predictors, and impact of residual MR on post-LVAD outcomes.[71,79]

Transcatheter therapies

Prior to the development of the MitraClip device, a majority of HF patients with SMR were not offered MV surgery due to the uncertain risk-benefit ratio and therefore had limited therapeutic options if symptoms persisted on GDMT.[6] Over the last decade, transcatheter technologies have been developed to address this unmet clinical need. Devices approved to date as well as those still under clinical investigation include those that perform TEER, direct or indirect annuloplasty, TMVR, and others.[80]

TEER. Transcatheter edge-to-edge repair with the MitraClip device is the most common transcatheter treatment currently offered to patients with HF and SMR (Figure 3).[81] The MitraClip is the only device with both CE Mark and Food and Drug Administration (FDA) approval for the treatment of HF patients with SMR. The MitraClip is a polyester-covered cobalt-chromium clip inserted via the femoral vein and advanced into the LA via transseptal (TS) puncture under fluoroscopic and TEE guidance. The MitraClip is then opened above the regurgitant jet and advanced into the LV. Emulating the surgical Alfieri stitch, the device is then retracted to grasp the free edges of the anterior and posterior mitral leaflets responsible for the MR after which it is released. Multiple clips may be required to effectively reduce MR, depending on the mitral anatomy, severity and pattern of MR, and other factors.

In the EVEREST II (Endovascular Valve Edge-to-Edge Repair Study) study, performed during the initial operator learning curve with the MitraClip device, 278 relatively low-risk patients with ≥3+ MR were randomized to TEER or surgical MV repair in a 2:1 fashion.[82] Although MV surgery was superior in terms of the composite primary effectiveness end point of freedom from death, surgery for MV dysfunction, or grade 3+ or 4+ MR at 12 months, the MitraClip was safer than surgery, effectively reduced the severity of MR, promoted LV remodeling, and resulted in similar long-term survival and NYHA functional class improvement compared with surgery.[83] Only 27% of patients in this study had SMR; however, a significant interaction was present between treatment and the primary composite effectiveness end point of death, MV surgery, or 3+/4+ MR at both 1 and 5 years according to MR etiology such that patients with primary MR had significantly improved results with surgical MV repair, whereas outcomes were similar with the MitraClip in patients with SMR.[82,83]

The role of MitraClip therapy in selected patients with SMR due to HF was subsequently established by the COAPT[11] and MITRA-FR[12] trials (Table 3). The COAPT trial randomly assigned 614 patients with chronic HF, LVEF 25% to 50%, LV end-systolic dimension ≤7 cm, NYHA class II, III, or IV symptoms, and severe SMR despite stable maximally tolerated doses of GDMT and CRT when appropriate to TEER with the MitraClip plus GDMT vs GDMT alone. At 2 years postrandomization, patients in the MitraClip group had a lower risk of the annualized rate of HFH (HR, 0.53; 95% CI, 0.40-0.70; $P < .001$), the primary end point of the study, as well as all-cause death (HR, 0.62; 95% CI, 0.46-0.82; $P < .001$).[11] MitraClip treatment also led to improvements in QOL according to the Kansas City Cardiomyopathy Questionnaire,[84] improved severity of symptoms according to the NYHA functional classification, enhanced LV reverse remodeling, more effectively reduced MR than medical therapy alone, and was cost effective.[85] The outcomes from COAPT were sustained through 5-year follow-up, corroborating long-term registry data.[86,87]

The MITRA-FR trial randomly assigned 304 patients with chronic HF with NYHA class II, III, or IV symptoms, LVEF 15% to 40%, and severe SMR to TEER with the MitraClip or to a control group. At 12 months, the rate of the primary composite end point of death from any cause or unplanned hospitalization for HF was similar in both groups (54.6% vs 51.3%; OR, 1.16; 95% CI, 0.73-1.84; $P = .53$).[12] Additionally, MitraClip therapy did not reduce LV volumes at 1 year, and there were no differences in NYHA functional class between groups. The 2-year results were similar.[15]

Several hypotheses have been advanced to explain these conflicting results. One possibility relates to the differences in baseline and follow-up GDMT use between the trials. Patients in COAPT were required to be titrated to maximally tolerated doses of all available GDMT and to be treated with CRT if appropriate prior to randomization, ensuring minimal changes during follow-up, whereas these were not required in MITRA-FR. GDMT during follow-up was not reported from MITRA-FR but may have varied between the groups, and the NYHA class of the control arm improved more during follow-up in MITRA-FR than in COAPT.

Perhaps a more important contributor to the varying outcomes in the 2 trials relates to differences in the severity of MR and LV dysfunction of the patients enrolled. To describe these differences, Grayburn, Sannino, and Packer[88] proposed the concept of proportionate vs disproportionate MR based on the proportional severity of baseline LV remodeling (LVEDV and EROA). Compared with the patients enrolled in COAPT, those enrolled in MITRA-FR had substantially larger LVEDVs (mean 252 vs 192 mL) and smaller EROAs (mean 31 mm^2 vs 41 mm^2). These differences in LV volumes and EROA arose due to the specific enrollment criteria of the trials. To avoid enrolling patients with end-stage heart disease in whom the prognosis would be dominated by LV dysfunction, COAPT excluded patients with LV end-systolic diameter >70 mm. In contrast, 70% of the patients in MITRA-FR had LV end-systolic diameter >65 mm. Differences in the definitions of what constituted severe SMR according to US vs EU guidelines led to the higher EROAs of patients enrolled in COAPT compared with MITRA-FR. The net effect was that the COAPT trial enrolled patients with substantially worse SMR and less LV dilatation in whom correcting MR was likely to have greater hemodynamic benefits.

Finally, compared with MITRA-FR, COAPT investigators used a greater number of clips per patient, had higher procedural success rates, fewer procedural complications, and had a lower recurrence rate of severe MR (Table 3). These differences likely contributed to the improved early and late outcomes following MitraClip treatment of patients in the COAPT trial compared with MITRA-FR.

This concept was further investigated in 1022 patients treated with the MitraClip in the EuroSMR (European Registry of Transcatheter Repair for Secondary Mitral Regurgitation) registry.[89] Approximately 35% of patients met all COAPT criteria ("COAPT-eligible"), and 65% had at least one criterion not fulfilling COAPT criteria ("COAPT-ineligible"). Approximately 48% of patients met all MITRA-FR criteria ("MITRA-FR-eligible"), whereas 52% did not meet at least one MITRA-FR criterion ("MITRA-FR-ineligible"). The rates of 2-year all-cause mortality were similar between MITRA-FR-eligible and MITRA-FR-ineligible patients (31.8% vs 36.8%; $P = .19$), whereas 2-year mortality was significantly lower in COAPT-eligible patients compared with COAPT-ineligible patients (25.2% vs 38.2%; $P < .001$), consistent with the findings from the COAPT trial (2-year all-cause mortality: 29.1% after MitraClip vs 46.1% with GDMT alone; $P < .001$).

The COAPT trial utilized the first generation MitraClip device. Several generations of device improvements have since been introduced that have expanded the length, width, and independence of the graspers. The recent EXPAND registry of 1041 patients treated for MR (50.5% primary MR and 49.5% SMR) with newer generation MitraClip devices (NTR and XTR systems) demonstrated a reduction in MR to ≤1+ in 93.0% of SMR patients at 1 year.[90] In comparison, this degree of MR reduction at 1 year was achieved in only 68.6% of patients in the COAPT trial,[11] highlighting that the newer MitraClip devices may be more successful in markedly reducing SMR. Notably, in EXPAND, the combined end point of all-cause mortality or first HFH occurred significantly less frequently in the group of patients that achieved MR ≤1+ vs ≤2+ (29.7% vs 69.6%; $P < .0001$).[90]

Emerging evidence further supports utility of the MitraClip in patients with more advanced HF than in those included in the COAPT trial. In the MitraBridge Registry, 119 patients with chronic advanced HF (NYHA III or IV and/or LVEF ≤30%) and concomitant moderate-to-severe or severe SMR who were considered potential candidates for heart transplantation at 17 centers in Europe and Canada were treated with MitraClip.[91] At 1 year, freedom from the composite primary end point (death, urgent heart transplantation or LVAD implantation, or HFH) was 64%.[91] At 2 years, the annualized HFH rate per patient-year was 44%, elective heart transplant was performed in 21%, 13.5% maintained or obtained their eligibility for transplantation, and 22.5% no longer had an indication for transplantation because of significant clinical improvement.[92] Randomized trials are warranted to examine the role of TEER in patients with end-stage heart disease and cardiogenic shock.

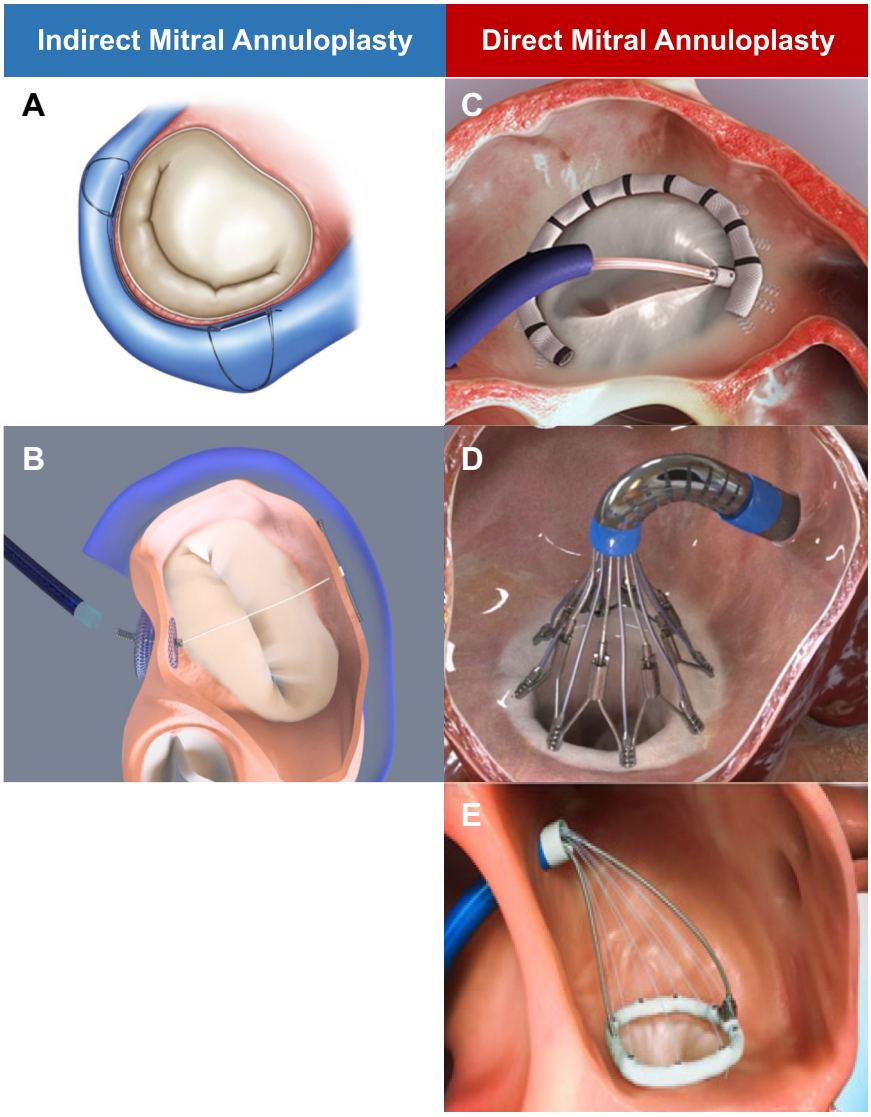


Figure 4.
Indirect and direct transcatheter mitral annuloplasty devices. (**A**) The Cardiac Dimensions Carillon Mitral Contour System; (**B**) the MVRx ARTO system; (**C**) the Edwards Lifesciences Cardioband Mitral; (**D**) the Boston Scientific Millipede Mitral Annuloplasty System; (**E**) the Valfix Transcatheter Direct Mitral Annuloplasty System.

The PASCAL (Edwards Lifesciences) MV repair system is a second TEER device under active investigation (Figure 3). PASCAL is composed of 2 broad and curved paddles that distribute the stress on the native valve leaflets and is capable of independent leaflet capture, with a nitinol woven spacer that enables optimized leaflet capture to reduce MR.[93] The initial CLASP trial, a multicenter, single-arm, prospective study, evaluated the short-term safety and efficacy of the PASCAL repair system in 62 patients with 3+ or 4+ MR of primary, secondary or mixed etiology. MR grades ≤2+ and ≤1+ were achieved in 98% and 86% of patients, respectively, and all-cause mortality at 30 days was 1.6%. The subsequent CLASP IID randomized trial evaluated the safety and effectiveness of the PASCAL device compared with the MitraClip device in 180 patients with 3+ or 4+ degenerative MR with prohibitive surgical risk.[94] PASCAL was noninferior to the MitraClip for the primary safety end point of major adverse events (cardiovascular mortality, stroke, myocardial infarction, need for new renal replacement therapy, severe bleeding or nonelective MV reintervention at 30 days −3.4% vs 4.8%, *P* for noninferiority < .05) and for the primary effectiveness end point, the proportion of patients with MR grade ≤2 at 6 months (96.5% vs 96.8%). Based on these data, the FDA cleared PASCAL for use in patients with severe symptomatic degenerative MR at high or prohibitive surgical risk. The prospective randomized CLASP IIF trial comparing PASCAL to MitraClip in patients with SMR (NCT03706833) is underway.

The efficacy of TEER in patients with AFMR has been examined in a few, small retrospective studies.[95–98] The largest existing cohort of symptomatic AFMR patients treated with TEER consisted of 126 patients from the European Registry of Transcatheter Repair for Secondary Mitral Regurgitation. Procedural success, defined as MR of ≤2+, was achieved in 87% of patients, and the 2-year survival rate was 70%. Following TEER, 40% of patients had NYHA class III/IV symptoms compared with 90% pre-TEER.[98] An analysis from the COAPT trial comparing echocardiographic features of patients with and without AF showed that patients with AF had more LA and mitral annular enlargement and less LV dysfunction and enlargement, the former representing features of both AFMR and ventricular SMR. Treatment with the MitraClip compared with GDMT alone reduced death or HFH both in those with (HR, 0.61; 95% CI, 0.46-0.82) and without (HR, 0.46; 95% CI, 0.33-0.66) a history of AF (P_{int} = .18) and, of interest, was associated with a lower risk of stroke in patients with a history of AF (HR, 0.18; 95% CI, 0.04-0.86) but not in those without a history of AF (HR, 1.64; 95% CI, 0.58-4.62; P_{int} = .02).[99] Of note, however, all patients in COAPT had LV dysfunction, including those with an atrial phenotype,

although these data suggest that patients with pure AFMR and normal LV function would also likely benefit from TEER.

Direct and indirect transcatheter mitral annuloplasty systems. Several transcatheter mitral annuloplasty systems have been developed (Figure 4); however, their safety and effectiveness have not yet been established in a pivotal randomized trial, and none have been FDA approved.[100] Transcatheter mitral annuloplasty devices aim to reduce the mitral annular circumference to promote better mitral leaflet coaptation. These devices can be categorized as either indirect-acting or direct-acting according to their placement and mechanism of action. Indirect annuloplasty systems are introduced through the coronary sinus (CS) that runs posterior and roughly parallel to the mitral annulus and provide indirect compression of the annulus to narrow its anterior-posterior diameter. Direct annuloplasty systems, in contrast, are partial or full ring-based systems that reach and are implanted directly on or adjacent to the mitral annulus either through retrograde access to the LV or TS puncture from the right atrium to LA that when cinched reduce the mitral annular anterior-posterior diameter.

Indirect transcatheter mitral annuloplasty systems include the Carillon Mitral Contour System (Cardiac Dimensions), which received CE mark approval for use in Europe in 2011, and the ARTO system (MVRx). Direct mitral annuloplasty devices address some of the limitations of the CS approach (inconsistent MR reduction and left circumflex artery compression in some cases) but are technically more challenging to implant. Examples of direct annuloplasty systems include the Cardioband Mitral System (Edwards Lifesciences) and the Millipede Mitral Annuloplasty System (Boston Scientific), both of which reach the mitral annulus via a TS approach with a steerable guide catheter.

The Carillon System consists of 3 components: the sizing catheter, the delivery system, and the Carillon implant. The sizing catheter is used to estimate the dimensions of the CS and great cardiac vein to facilitate appropriate implant size selection. The delivery system enables percutaneous delivery of the implant via the jugular vein, engagement of the locking mechanism, and repositioning or recapture of the implant, if necessary. The Carillon XE2 implant is composed of a distal anchor (positioned in the great cardiac vein), proximal anchor (positioned in the CS), ribbon connector (joining the anchors), and proximal and distal crimp tubes. The implant is designed to be deployed, tensioned, and secured in the coronary vein. The MR reduction is immediate and can be modulated during the procedure. The Carillon System has a few key limitations: the distance between the CS and the mitral annulus can be variable and are not always parallel, which may limit its therapeutic effectiveness; and a risk of compression of the left circumflex coronary artery by the tensioned system. Moreover, the Carillon System is not recommended in patients with a device lead in the CS.[100]

Following a series of observational studies,[101–103] the randomized, sham-controlled REDUCE FMR trial was performed in 120 HF patients with SMR on GDMT. Treatment with the Carillon reduced MR volumes compared with the sham-controlled arm (−7.1 mL/beat vs +3.3 mL/beat; $P = .049$).[104] Additionally, the Carillon significantly reduced LVEDVs and end-systolic volumes compared with sham-control. These findings appear to be durable with favorable survival through 5 years.[105] The actively enrolling CARILLON sham-controlled randomized trial (NCT03142152) is comparing the Carillon device to GDMT alone in 352 HF patients with SMR at 75 sites.

The ARTO indirect transcatheter mitral annuloplasty system uses an adjustable bridge suture technique to connect 2 magnetic catheters or "anchors": one placed in the CS over the lateral wall of the LA, also called a "T-bar," via right internal jugular vein access and the other in the atrial septum via TS puncture to improve mitral leaflet coaptation and thereby decrease SMR. The adjustable bridging suture then reduces the mitral annular anteroposterior diameter until an acceptable reduction in MR is achieved.[106]

The prospective, nonrandomized MAVERIC trial consisting of 45 patients with NYHA class greater than or equal to II systolic HF and SMR grade ≥2+ who underwent ARTO implantation demonstrated that the ARTO system was safe and effective in decreasing SMR up to 2 years postprocedure.[107,108] The rates of the primary safety composite end point (death, stroke, myocardial infarction, device-related surgery, cardiac tamponade, or renal failure) at 30 days, 1 year, and 2 years were 4%, 18%, and 24%, respectively. The mitral annular anteroposterior diameter decreased from 41.4 mm at baseline to 36.0, 35.3, and 35.5 mm at 30 days, 1 year, and 2 years, respectively. Serial results in 31 patients showed that 67% had MR grade 3+/4+ at baseline vs only 16%, 10%, and 10% of patients at 30 days, 1 year, and 2 years postprocedure, respectively. These findings translated into symptomatic relief such that 69% of patients had NYHA class III to IV symptoms at baseline, improving significantly to 25%, 22%, and 20% of patients at 30 days, 1 year, and 2 years postprocedure, respectively.

The Cardioband is a transcatheter, TS adjustable direct mitral annuloplasty system developed to reproduce surgical annuloplasty by fixing a flexible, incomplete Dacron band to the annulus on the LA side using multiple helical anchors placed 8 mm apart. The Cardioband implant consists of a polyester sleeve that covers the delivery system and is available in different sizes. Multiplanar TEE and 3D-TEE views are necessary to verify correct placement. The first anchor is fixed at the anterolateral commissural annulus. The anchors are repeatedly placed along the posterior side at the mitral annulus until the implant catheter tip reaches the last anchoring site at the medial side. During this process, coronary angiography is performed to rule out any damage to the left circumflex coronary artery. A contraction wire following the same path as the sleeve is connected to an adjusting spool, which once activated, cinches the Cardioband device to reduce the mitral annular anteroposterior diameter.[100] The degree of MR reduction is then assessed by TEE.

In a single-arm study of 60 HF patients with moderate or severe SMR, survival, survival free of readmission for HF, and survival free of reintervention were 87%, 66%, and 78%, respectively at 1 year.[109] MR grade at 12 months was less than or equal to moderate in 95% of the 39 patients who underwent a TTE at 1 year. Functional status (NYHA class I/II: 79% vs 14%), QOL (−19 points on the Minnesota Living with Heart Failure Questionnaire score), and exercise capacity (+58 m by 6-minute walk test) improved significantly at 1 year following Cardioband implantation ($P < .01$ for all). The device also demonstrated a good safety profile. There were 2 in-hospital deaths (none device-related), 1 stroke, 2 coronary artery complications, and 1 tamponade. However, anchor disengagement was observed in 10 patients and resulted in device inefficacy in 5 patients. Technical, device, and procedural successes per the Mitral Valve Academic Research Consortium criteria were 97% (58/60), 72% (43/60), and 68% (41/60), respectively. The anchor system has been redesigned to reduce long-term effectiveness. To our knowledge, further development of this device for SMR is currently paused.

The Millipede IRIS System is a transcatheter, TS direct mitral annuloplasty device currently under investigation. The Millipede IRIS device has a complete (closed), semirigid ring design. It has a nitinol stent frame that is circumferentially fixed to the annulus by 8 helical stainless-steel anchors that are preattached to the base of the ring. The device has been designed to allow repositioning and retrieval until the ring has been fully released from the delivery system; each anchor can be retracted or "unscrewed," moved, and redeployed. The upper part of the frame has 8 slider components that can be individually manipulated to achieve a customized cinching of the mitral annulus. The IRIS procedure consists of 3 basic steps: placement, anchoring, and actuation. The delivery catheter is designed for the transvenous TS delivery route and has a 27F catheter profile.[110]

In an initial report of 7 patients who had 3/4+ MR with annular dilation, NYHA class II to IV symptoms, and LV end-systolic dimensions ≤65 mm, there were no procedural deaths or myocardial infarctions

Transapical Delivery

Name (Manufacturer)	Intrepid (Medtronic)	Tendyne (Abbott Vascular)	Tiara (NeoVasc)
Frame	Dual-stent self-expanding Nitinol	Dual-stent self-expanding Nitinol	Self-expanding Nitinol
Components	1	1	1
Delivery system size	35F	34F	32F & 36F
Anchoring Mechanism	Radial force/perimeter oversizing	Apical tether & epicardial pad	D-shaped ventricular

Transseptal Delivery

Name (Manufacturer)	Intrepid (Medtronic)	EVOQUE (Edwards Lifesciences)	AltaValve (4C Medical)	Cephea (Abbott Vascular)	Cardiovalve (Cardiovalve)	HighLife (HighLife Medical)	SAPIEN M3 (Edwards Lifesciences)
Frame	Dual-stent self-expanding Nitinol	Self-expanding Nitinol	Spherical self-expanding Nitinol	Dual-stent self-expanding Nitinol	Dual-frame self-expanding Nitinol	Self-expanding Nitinol	Balloon-expandable cobalt-chromium
Components	1	1	1	1	1	2	2
Delivery system size	35F	28F	32F	NA	28F	NA	20F
Anchoring Mechanism	Radial force/perimeter oversizing	Mitral valve leaflets, cords & annulus	Supra-annular	Axial compression	Mitral valve leaflets/annulus	Subannular ring	Subannular Nitinol dock

Figure 5.
Summary of selected transcatheter mitral valve replacement device characteristics. Top row: transapical devices. Bottom row: transseptal devices. Note: Intrepid is also a transseptal device.

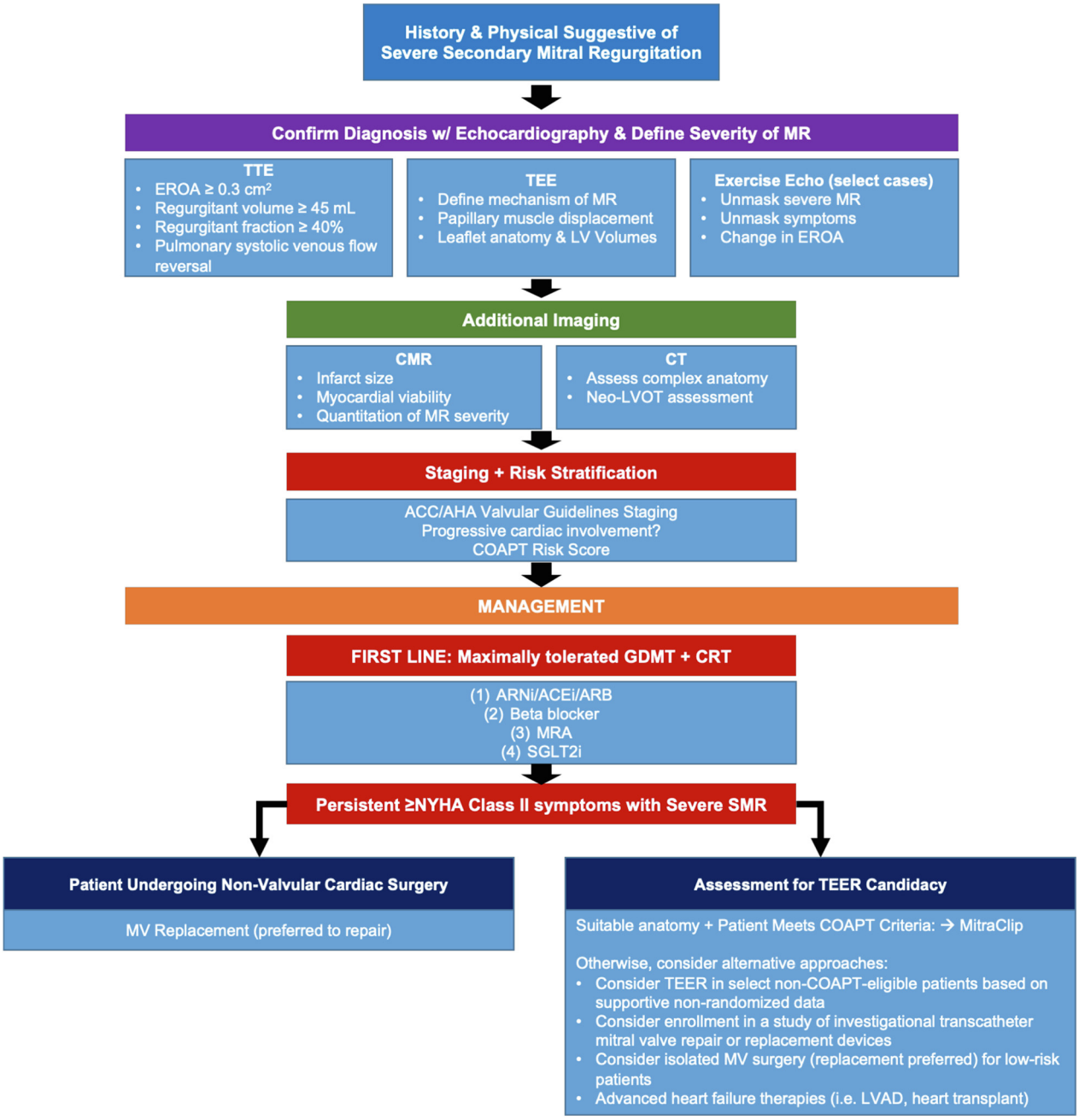
following Millipede IRIS implantation.[110] The mitral septal–lateral diameter was reduced from 38.0 to 25.9 mm at 30 days. MR was reduced from baseline 3+ to 4+ to <2+ in all patients at 30 days. There were improvements in NYHA class such that all patients had NYHA class I to II symptoms at 30 days, and there was a decrease in diastolic LV volumes from 182.4 to 115.3 mL at 30 days. To our knowledge, further development of this device is currently paused.

Technical issues including loss of fixation have impeded progress with annuloplasty systems. The Valfix Transcatheter Direct Mitral Annuloplasty system (Valfix Medical) has been developed to address this issue. The device consists of a complete D-shaped annuloplasty ring covered in Dacron that is available in multiple sizes ranging from 26 to 32 mm, is delivered to the LA via a TS approach and is sutured to the annulus via 8 self-expanding flower-shaped nitinol anchors designed for enhanced fixation security. Animal studies have demonstrated feasibility, and first-in-human studies are expected in 2024.

TMVR. In COAPT, TEER with the MitraClip was safe and highly effective for patients enrolled in this trial. However, the discrepant findings between COAPT and MITRA-FR indicate that not all patients with HF and severe SMR are appropriate for TEER. Still other patients were excluded from both trials because of suboptimal anatomy for TEER, such as small annulus, multiple jets, lack of leaflet coaptation, or mitral annular calcification. TMVR may be useful to treat most of these patients, and even for COAPT-eligible patients may more reliably achieve ≤1+ MR. Early TMVR systems involved a TA approach given its direct path to the MV; however, newer TS devices have emerged that promise to mitigate the morbidity and mortality associated with the TA approach, especially in high-risk HF patients with SMR.[111] TMVR devices implanted via the TA approach have included the Intrepid (Medtronic), Tendyne (Abbott Vascular), and Tiara (NeoVasc). TMVR devices using the TS technique have included Intrepid, the AltaValve (4C Medical), Cardiovalve (Cardiovalve), Cephea (Abbott Vascular), EVOQUE (Edwards Lifesciences), HighLife (HighLife Medical), and SAPIEN M3 (Edwards Lifesciences).[112–114] This listing is far from exhaustive; other devices have been used and have been discontinued, whereas many others are under development. A summary of individual device characteristics is provided in Figure 5.

The early experience in 50 consecutively enrolled patients receiving the Intrepid device was reported in the Intrepid Global Pilot Study. The TA implantation success rate was 96%, with a 14% 30-day mortality, 76.5% 1-year survival, and mild or less MR in 100% of patients on echocardiographic follow-up at median 173 days.[115] There were no disabling strokes or reinterventions. In the subsequent Intrepid TMVR Early Feasibility Study consisting of 15 prohibitive surgical risk patients with significant MR, 14 TS implants of a 35F catheter Intrepid system were successful. At 30 days, there were no deaths, strokes, or reinterventions, 6 access site bleeds, and all patients who underwent successful device implantation had trace or no valvular or paravalvular MR.[116] The ongoing APOLLO (Transcatheter Intrepid TMVR System in Patients With Severe Symptomatic Mitral Regurgitation) study (NCT03242642) is investigating TMVR with the TS Intrepid system in a multiarm nonrandomized registry in 550 to 800 patients with primary or secondary MR ineligible for surgery or TEER.

The largest experience with TMVR worldwide has been with the Tendyne TA platform, which received CE mark approval in Europe in 2020. Data from the first 9 patients receiving the device showed a 100% device implantation success rate and no procedural mortality. At 12 months, there were 2 deaths (1 cardiac, 1 noncardiac) and 2 rehospitalizations for HF, and 100% of patients had grade 0 MR.[117] An expanded open-label, nonrandomized, prospective study of the TA Tendyne device in 100 patients reported an implant success rate of 97% with 39% all-cause mortality at 2 years.[118] Among survivors, 93% had no MR. The HFH rate was reduced from 1.30 events per year preprocedure to 0.51 per year post-TMVR. The SUMMIT (Clinical Trial to Evaluate the Safety and Effectiveness of Using the Tendyne Transcatheter Mitral Valve System for the Treatment of Symptomatic Mitral Regurgitation) trial (NCT03433274) is a prospective study investigating the use of



Central Illustration.

Diagnostic and management pathways for patients with heart failure and secondary mitral regurgitation. ACC, American College of Cardiology; ACEi, angiotensin-converting-enzyme inhibitor; AHA, American Heart Association; ARB, angiotensin receptor blocker; ARNi, angiotensin receptor-neprilysin inhibitor; CMR, cardiac magnetic resonance imaging; CRT, cardiac resynchronization therapy; CT, computed tomography; Echo, echocardiography; EROA, effective regurgitant orifice area; GDMT, guideline-directed medical therapy; HF, heart failure; LA, left atrium, LV, left ventricular; LVAD, left ventricular assist device; LVOT, left ventricular outflow tract; MR, mitral regurgitation; MRA, mineralocorticoid receptor antagonist; MV, mitral valve; NYHA, New York Heart Association; SGLT2i, sodium-glucose cotransporter-2 inhibitor; SMR, secondary mitral regurgitation; TEE, transesophageal echocardiography; TEER, transcatheter edge-to-edge repair; TMVR, transcatheter mitral valve replacement; TTE, transthoracic echocardiography.

Tendyne in 3 cohorts: (1) 382 TEER-eligible patients randomized 1:1 to the MitraClip; (2) 313 non–TEER-eligible patients without mitral annular calcification (MAC), and (3) 102 patients with severe MAC. The MAC arm has completed enrollment with results anticipated in 2024. Enrollment is ongoing in the other 2 cohorts.

The SAPIEN M3 system is based on the 29-mm diameter SAPIEN 3 transcatheter aortic valve with the addition of an external knitted polyethylene terephthalate seal that covers the outer surface of the valve frame and is implanted via a TS approach into a nitinol dock that encircles the chordae tendineae and native MV leaflets.[119] In the first-in-human study, 10 patients with severe MR (4 degenerative, 4 functional, and 2 mixed) were treated with the SAPIEN M3. The primary end point of technical success as defined by Mitral Valve Academic Research Consortium criteria was achieved in 90% of patients. By TEE, MR was reduced to less than or equal to trivial in all implanted patients, and the mean transmitral gradient was 2.3 ± 1.4 mm Hg. At 30 days, there were no deaths, stroke, myocardial infarction, rehospitalization, LVOT obstruction, device migration, embolization, or conversion to

mitral surgery.[119] In the single-arm nonrandomized ENCIRCLE registry (NCT04153292), the SAPIEN M3 TS TMVR system is being studied in 400 patients with primary or secondary MR not suitable for surgery or TEER.

The lack of randomized trial data notwithstanding, registry data has shown favorable outcomes of TMVR in patients with SMR and advanced HF. Ludwig et al[120] performed a propensity score-matched comparison of HF patients with SMR who underwent TMVR from the CHOICE-MI registry (Choice of Optimal Transcatheter Treatment for Mitral Insufficiency) and control group patients from the COAPT trial treated with GDMT alone. Among 97 propensity-matched patient pairs, the 2-year rate of HFH was significantly lower in the TMVR group (32.8% vs 54.5%; HR, 0.59; 95% CI, 0.35-0.99; $P = .04$) as was the rate of none to minimal residual MR (100% vs 7.7%; $P < .001$). Mortality at 2 years was similar between groups (36.8% vs 40.8%; $P = .98$). In a second propensity score-matched analysis, patients from the CHOICE-MI registry treated with TMVR were compared with patients from the EuroSMR registry treated with TEER. After propensity score matching, 235 TMVR patients (94% treated with a TA device) and 411 TEER patients were included. There were no differences in 30-day or 1-year mortality between groups; however, TMVR was associated with higher rates of no or minimal residual MR at discharge (95.8% vs. 68.8%; $P < .001$). At 1 year, 77.8% of patients in the TMVR group vs 64.3% in the TEER group had NYHA class I or II symptoms ($P = .015$).[121]

Most TMVR studies have imposed restrictive enrollment criteria, excluding patients with severe LV dysfunction, previous mitral or aortic valve surgery, severe pulmonary hypertension, severe tricuspid regurgitation, severe RV dysfunction, mitral annulus dimensions too large or small for available devices, and anatomy predisposing to an increased risk of LVOT obstruction.[122,123] To date, approximately 30% of screened patients have been eligible for TMVR implant.[123] Lower profile devices and a greater range of available sizes will likely increase the proportion of patients that may undergo TMVR. In addition to LVOT obstruction, other potential complications include hemolysis, issues with valve fixation, vascular complications and bleeding, residual atrial septal defects, and bleeding from the need for systemic anticoagulation for 3 to 6 months or longer postprocedure.[112] Ultimately, adequately powered randomized trials of TMVR vs TEER in TEER-eligible patients and either randomized trials (preferably) or registries of TMVR in TEER-ineligible patients will be required to establish the safety and effectiveness of TMVR in HF patients with severe SMR.

Risk stratification

Risk stratification of patients with SMR may provide more accurate prognostication and appropriate identification of high-risk patients who stand to benefit from new therapies. While standard surgical risk assessment tools such as the Logistic EuroSCORE and the Society of Thoracic Surgery risk score have demonstrated good prediction for early outcomes, they have poor discriminatory power and calibration in predicting 1-year or longer surgical and transcatheter outcomes.[124] The EuroSCORE II, an updated version of the logistic EuroSCORE, was developed to address these shortcomings and demonstrated improved predictive performance compared to both older risk scores.[125,126] Even so, EuroSCORE II may suboptimally predict perioperative mortality.[126] More recently, the COAPT risk score was developed to predict the risk of 2-year death or HFH in patients with symptomatic HF with SMR after both GDMT and TEER with MitraClip.[127] Ranging from −3 to 15, the COAPT risk score was derived from 4 clinical, 4 echocardiographic, and 1 treatment-related variable and demonstrated moderate predictive power for the primary end point (C statistic = 0.74) with excellent model calibration. Additionally, the COAPT risk score significantly outperformed 4 other risk scores including the Logistic EuroSCORE and Society of Thoracic Surgery risk scores. While encouraging, external validation studies are needed to examine the reproducibility of the COAPT risk score and the extent to which it is generalizable to cohorts not meeting COAPT inclusion criteria (eg, the MITRA-FR study population). Currently, there are no good predictive tools for outcomes after TMVR.

Conclusions

SMR in patients with HF has attracted immense scientific and clinical interest in recent decades leading to refined approaches to its diagnosis, evaluation, and treatment. The ways that patients with SMR are classified, staged, and risk-stratified have evolved with advances in echocardiography, CT, and CMR imaging. Concurrently, the treatment armamentarium for this high-risk patient population has expanded and continues to evolve. Novel medical therapies targeting the underlying cardiomyopathy remain the cornerstone of therapy. Electrical therapies improve both symptoms (CRT) and survival (CRT and implantable defibrillators) in eligible patients. Surgical MV repair and replacement have shown mixed results and are principally reserved for patients with severe SMR undergoing cardiac surgery for other reasons, such as CABG. TEER has been demonstrated to improve survival, reduce HFH, and enhance functional capacity and QOL in HF patients with SMR meeting eligibility criteria from the COAPT trial. Additional randomized trials are essential to determine which COAPT noneligible patients with SMR may benefit from TEER (e.g., asymptomatic patients, those with less than severe MR without LV dilatation, atrial SMR, patients with end-stage HF or cardiogenic shock, etc.). Emerging MV repair and replacement technologies may prove synergistic with TEER in the same patients (eg, annuloplasty plus TEER) or allow TEER-ineligible patients to be treated. Continued investigation is essential to better define the treatment strategies for individual patients (Central Illustration). Management of these high-risk patients in whom multiple comorbidities are often present requires a multidisciplinary team of cardiologists, cardiac surgeons, imaging experts, and other organ specialists to select the best treatment approaches to optimize outcomes.

Declaration of competing interest

Vinod H. Thourani has been an advisor for Abbott Vascular, ARtivion, Atricure, Boston Scientific, Edwards Lifesciences, Medtronic, and Shockwave. Linda D. Gillam is a consultant for Edwards Lifesciences, and Philips and directs an echocardiography core laboratory for Abbott, Edwards Lifesciences, and Medtronic, for which she receives no direct compensation. Gregg W. Stone has received speaker honoraria from Abiomed, Infraredx, Medtronic, and Pulnovo; has served as a consultant for Ablative Solutions, Adona Medical, Amgen, Ancora, Apollo Therapeutics, Cardiomech, CorFlow, Elucid Bio, Gore, HeartFlow, Impulse Dynamics, Millennia Biopharma, Miracor, Neovasc, Occlutech, Robocath, TherOx, Valfix, and Vectorious; owns equity/options from Ancora, Applied Therapeutics, Aria, Biostar family of funds, Cagent, Cardiac Success, Orchestra Biomed, SpectraWave, Valfix, and Xenter; his daughter is an employee at IQVIA; and is employed by Mount Sinai Hospital, which receives research support from Abbott, Abiomed, Biosense Webster, Bioventrix, Cardiovascular Systems Inc, Phillips, Pulnovo, Shockwave, Vascular Dynamics, and V-Wave. Anton Camaj reported no financial interests.

Funding sources

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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