The Choice of Treatment in Ischemic Mitral Regurgitation With Reduced Left Ventricular Function

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Background. **Ischemic mitral regurgitation is a condition characterized by mitral insufficiency secondary to an ischemic left ventricle. Primarily, the pathology is the result of perturbation of normal regional left ventricular geometry combined with adverse remodeling. We present a comprehensive review of contemporary surgical, medical, and percutaneous treatment options for ischemic mitral regurgitation, rigorously examined by current guidelines and literature.**

Methods. **We conducted a literature search of the PubMed database, Embase, and the Cochrane Library (through November 2018) for studies reporting perioperative or late mortality and echocardiographic outcomes after surgical and nonsurgical intervention for ischemic mitral regurgitation.**

Results. **Treatment of this condition is challenging and often requires a multimodality approach. These patients usually have multiple comorbidities that may preclude surgery as a viable option. A multidisciplinary team discussion is crucial in optimizing outcomes. There are several options for treatment and management of ischemic mitral regurgitation with differing benefits and risks. Guideline-directed medical therapy for heart failure is the treatment choice for moderate and severe ischemic mitral regurgitation, with consideration of coronary revascularization, mitral valve surgery, cardiac resynchronization therapy, or a combination of these, in appropriate candidates. The use of transcatheter mitral valve therapy is considered appropriate in high-risk patients with severe ischemic mitral regurgitation, heart failure, and reduced left ventricular ejection fraction, especially in those with hemodynamic instability.**

Conclusions. **The role of mitral valve surgery and transcatheter mitral valve therapy continues to evolve.**

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Optimal medical therapy has proven beneficial in patients with severe ischemic mitral regurgitation (IMR) presenting with heart failure and reduced left ventricular (LV) ejection fraction (LVEF). The mechanism of benefit appears to be by modulation of profibrotic changes of the tethered mitral valve, neurohormonal regulation, and LV mass reduction.[1-3] However, pharmacotherapy has limitations in IMR with reduced LVEF complicated by adverse reverse remodeling, especially in the presence of persistently reduced coronary perfusion.[4-6]

The medical treatment options in IMR with reduced LVEF include diuretics, β-blockade, and inhibition of the renin-angiotensin-aldosterone axis, resulting in symptomatic improvement without the expectation of a substantial mortality benefit.[4,7-9] Surgical mitral valve replacement or repair combined with coronary artery bypass grafting (CABG) is considered the treatment of choice for low- and intermediate-risk patients with severe IMR.[10-12] Outcomes of surgical mitral valve repair plus CABG in patients with reduced LVEF and LV remodeling

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Abbreviations and Acronyms

3D	=	three-dimensional
AATS	=	American Association of Thoracic Surgeon
ACC	=	American College of Cardiology
AHA	=	American Heart Association
BSA	=	body surface area
CABG	=	coronary artery bypass grafting
CAD	=	coronary artery disease
CI	=	confidence interval
CL	=	coaptation length
COAPT	=	Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients With Functional Mitral Regurgitation
CRT	=	cardiac resynchronization therapy
CTSN	=	Cardiothoracic Surgical Trials Network
EROA	=	effective regurgitant orifice area
ESC	=	European Society of Cardiology
GDMT	=	guideline-directed medical therapy
HR	=	hazard ratio
ICD	=	implantable cardiac defibrillator
IMR	=	ischemic mitral regurgitation
IPMD	=	interpapillary muscle distance
LOE	=	level of evidence
LV	=	left ventricle
LVAD	=	left ventricular assist device
LVEF	=	left ventricular ejection fraction
LVESV	=	left ventricular end-systolic volume
LVESVI	=	left ventricular end-systolic volume index
MITRA-FR	=	Percutaneous Repair with the MitraClip Device for Severe Functional/Secondary Mitral Regurgitation
MR	=	mitral regurgitation
MVR	=	mitral valve repair
NYHA	=	New York Heart Association
RA	=	right atrium
RCT	=	randomized controlled trial
RF	=	regurgitant fraction
RHC	=	right heart catheterization
RVol	=	regurgitant volume
SMR	=	secondary mitral regurgitation
STS	=	The Society of Thoracic Surgeons
TA	=	tenting area
TEE	=	transesophageal echocardiogram
TPMA	=	tricuspid, pulmonary, mitral, aortic valve
TTE	=	transthoracic echocardiogram

are mixed and deserve careful evaluation.[13,14] Determining the potential risk-to-benefit ratio for IMR therapy is difficult in this high-risk cohort because the evidence is limited to registries and subgroup analyses of randomized clinical trials (RCTs).

An evolving catheter-based option for severe IMR with reduced LVEF is transcatheter mitral valve therapy.[15-18] The use of transcatheter mitral valve therapy is considered appropriate in high-risk patients with severe IMR and reduced LVEF, especially in patients with hemodynamic instability. It provides a less invasive approach that may be better tolerated in high-risk heart failure patients with IMR and LV dysfunction. Recently published clinical trial data have confirmed the benefit of transcatheter mitral valve therapy despite the discordance in the results of the 2 trials.[19,20] Enrolled patients primarily included those with severe secondary MR, reasonable life expectancy, and prohibitive surgical risk due to comorbidities.

Material and Methods

Methodology of the literature search and synthesis is available in the Supplemental Material.

IMR is caused by the geometric disturbance of valve and subvalvular apparatus of the mitral valve. The imbalance between the tethering and closing forces is a consequence of adverse LV remodeling after myocardial injury, with enlargement of the LV and mitral annulus, posterior and lateral displacement of the papillary muscles, leaflet tethering, and reduced closing forces. Leaflet coaptation is compromised, resulting in varying degrees of mitral regurgitation[21] (Figures 1A-1G).

These pathologic perturbations most commonly occur after ischemic events involving the left circumflex coronary artery, but may occur with lesions in the right coronary and left anterior descending coronary arteries, depending on the coronary distribution to the posteromedial papillary muscle. MR resulting from such acute mitral valve distortion often resolves upon myocardial revascularization and restoration of myocardial kinesis.[22,23] Despite revascularization, some myocardial segments may not recover sufficiently to reduce IMR, which persists with the onset of myocardial scarring. IMR, particularly in patients with reduced LVEF, commonly results in LV dilatation, a known independent risk factor for death.[12,22]

Echocardiography-based studies have identified 2 types of restricted systolic leaflet motion according to the tethering shape: the asymmetrical pattern with predominant posterior tethering of both leaflets, which is often observed with an inferior/posterior myocardial infarction, and the symmetrical pattern with predominant apical tethering most commonly seen with anterior myocardial infarctions.[22,24] Three tethering vectors (posterior, apical, and lateral) were observed in IMR, and the displacement of 1 of the papillary muscles exerts a traction and tethering effect on both mitral valve leaflets. In the asymmetric type, the posterior leaflet is moved more posteriorly than apically due to its parallel position with respect to the posterior LV wall, resulting in asymmetric tethering and an eccentric mitral regurgitant jet[24] (Figures 1H-1K). Conversely, in the symmetrical type, there is a combination of apical and posterolateral vectorial tethering, with a more displaced coaptation point. The regurgitant jet is usually located centrally, and its direction reflects the equal involvement of the systolic motion in both leaflets[24] (Figures 1L-1O).

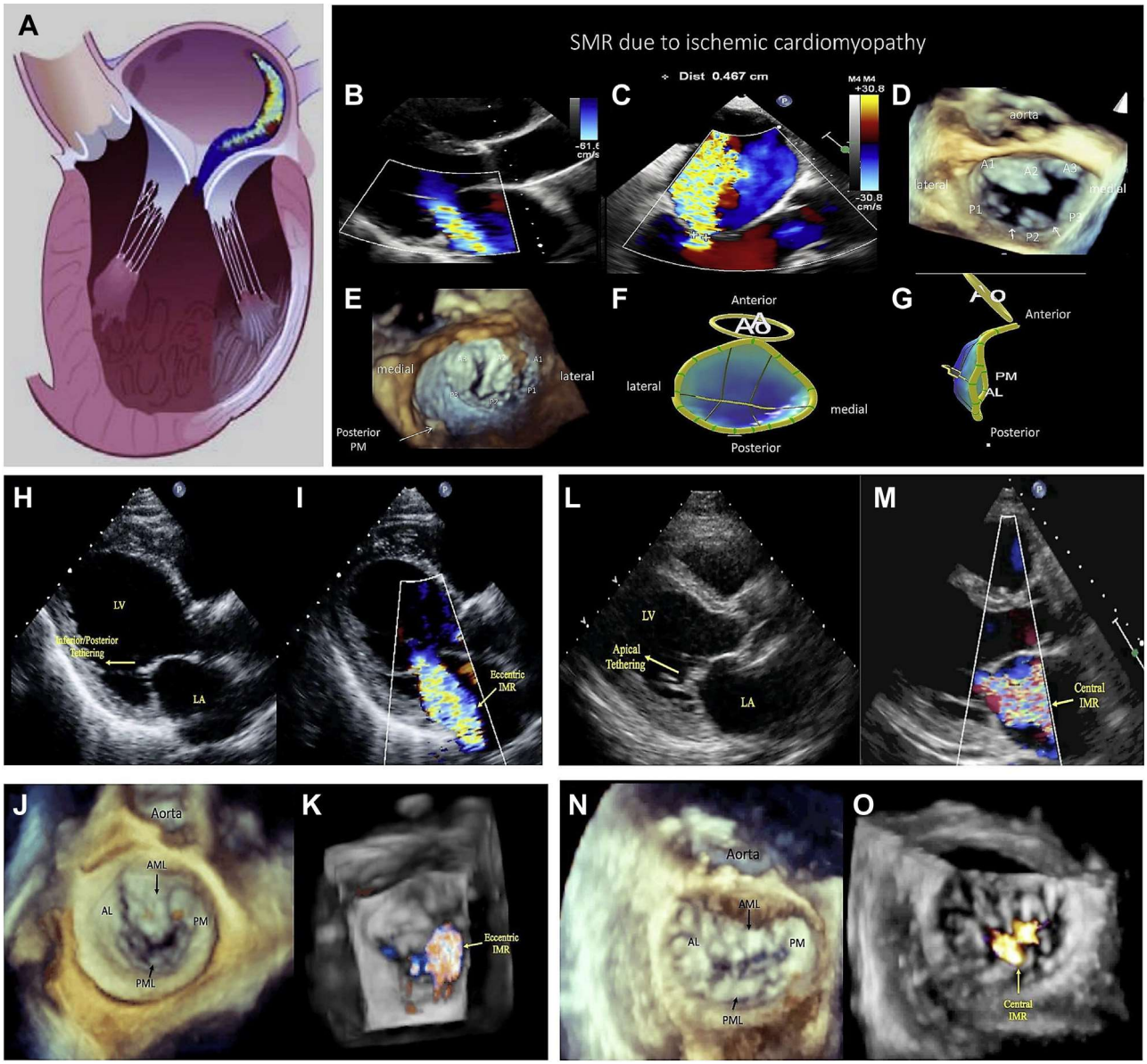

Figure 1. (A) Carpentier type IIIb represents restricted leaflet motion in systole. (B-G) Multimodality echocardiographic imaging for ischemic mitral regurgitation (IMR). (B) Transthoracic echocardiography parasternal long-axis view and (C) transesophageal echocardiography (TEE) left ventricular outflow tract view show eccentric jet of MR due to asymmetrical tethering. (D) Three-dimensional (3D) TEE (en face view from left atrium) shows marked indentations between P2-P3 and P2-P1 (white arrow) due to left ventricular remodeling. (E) 3D TEE (en face view from left ventricle) shows an apical and posterior secondary displacement of posterior papillary muscle (white arrow). (F, G) Reconstruction and model of the mitral valve shows the malcoaptation of mitral leaflets due to a tethering of the posterior valve. (H-K) Asymmetric pattern of mitral valve tethering on 2D and 3D echocardiography in the inferior/posterior direction (yellow arrow) results in posteriorly-directed eccentric ischemic mitral regurgitation (IMR). (L-O) Symmetric pattern of mitral valve tethering on two-and three-dimensional echocardiography. Note central IMR jet. (AL, anterolateral; AML, anterior mitral leaflet; LA, left atrium; LV, left ventricle; PM, posteromedial.)

New experimental contributions are discussed in the Supplemental Material.

Results

Evaluation and Treatment

INTERNATIONAL GUIDELINES. The latest American College of Cardiology/American Heart Association (ACC/AHA) and European Society of Cardiologists Guidelines (2017) for the management of IMR support optimal medical therapy, surgical revascularization, and cardiac resynchronization therapy (CRT) as interventions that result in an improvement of MR severity. These therapeutic interventions improve regional wall motion, promote reverse LV remodeling, and improve LV synchrony.[1,2] Figures 2-5 show the disease stages in patients with IMR,

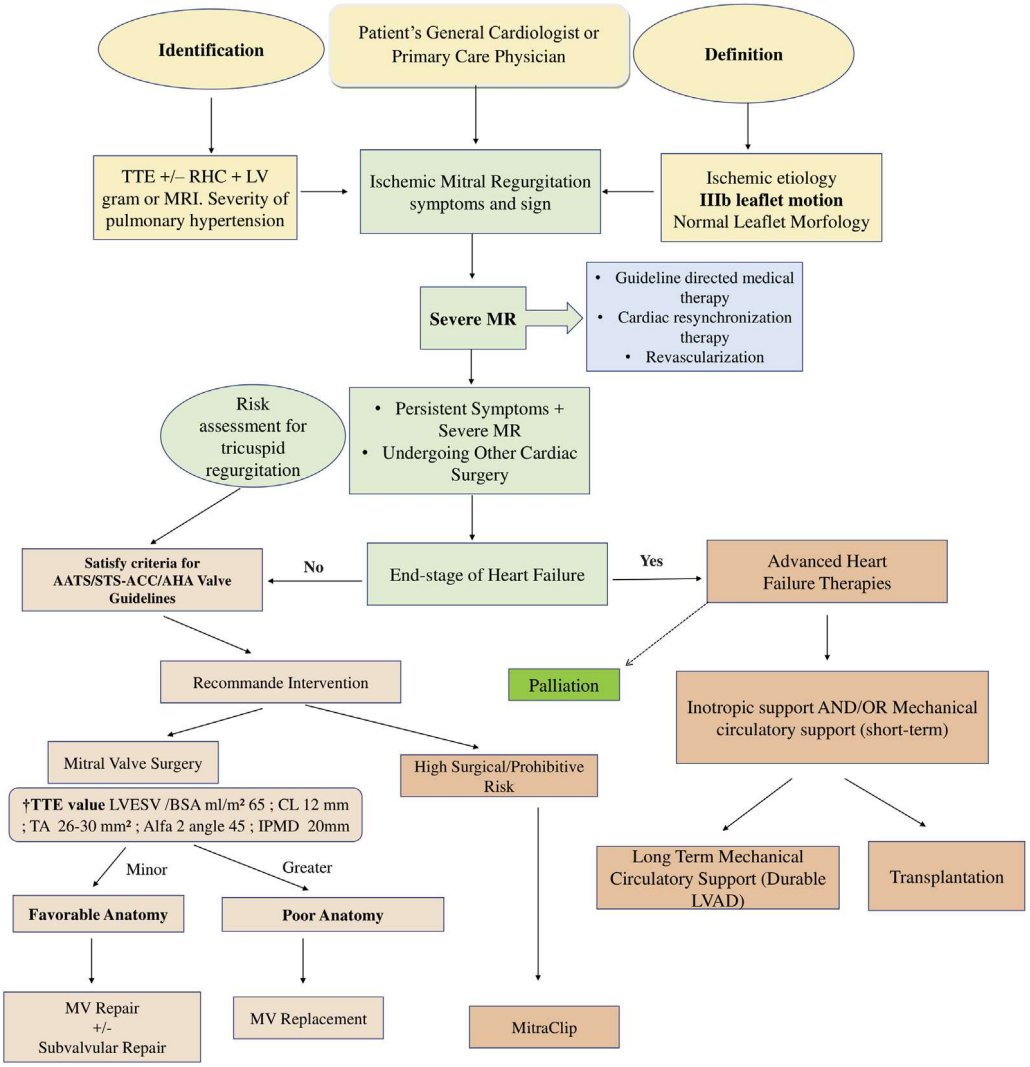

Figure 2. Overview of decision making for patients presenting with mitral regurgitation secondary to ischemic cardiomyopathy. Data were derived from Nappi and colleagues.[22,25] (AATS/STS, American Association of Thoracic Surgeon/The Society of Thoracic Surgeons; ACC/AHA, American College of Cardiology/American Heart Association; BSA, body surface area; CL, coaptation length; IPMD, interpapillary muscle distance; LV gram, left ventriculogram; LVAD, left ventricular assist device; LVESV, left ventricular end-systolic volume; MitraClip, Abbott Vascular, Menlo Park, CA; MR, mitral regurgitation; MRI, cardiovascular magnetic resonance imaging; MV, mitral valve; RHC, right heart catheterization; TA, tenting area; TTE, transthoracic echocardiography.) †Favorable echocardiographic values for mitral valve surgery.

and a proposed algorithm for management. Medical therapy of IMR with reduced LVEF is discussed in the Supplemental Material.

CARDIAC RESYNCHRONIZATION THERAPY. CRT is a firmly established treatment choice in selected patients with severe IMR and reduced LVEF who have LV dyssynchrony. The use of CRT is recommended by current guidelines and position papers of professional societies (Class I) in patients presenting in sinus rhythm with New York Heart Association (NYHA) Functional Classification II to IV symptoms to guide direct medical therapy with an LVEF of 0.35 or less, left bundle branch block, and a QRS duration of 150 milliseconds or more. Moreover, clinical benefit after CRT implantation was noted in patients with sinus rhythm and nonleft bundle branch block pattern with a QRS duration of 150 milliseconds or more, and in those with left bundle branch block and a QRS duration 120 to 149 milliseconds (Class IIa recommendation).[26]

RCTs have shown improvement in rehospitalization rates for heart failure and survival for CRT recipients (with and without defibrillator function),[27] together with reduction in LV end-diastolic and end-systolic dimensions and improved LVEF. Although most reports show reduced overall MR severity with restoration of synchronous ventricular contraction and LV remodeling, the effect of CRT implantation in secondary MR is inconsistent. One sham-controlled trial (Multicenter InSync Randomized Clinical Evaluation [MIRACLE])[28] included 450 patients in NYHA functional class III/IV and heart failure with LVEF of 0.35 or less and a QRS duration of 130 milliseconds or more and reported a significant improvement in LV end-diastolic, LV end-systolic volumes (LVESVs) and LVEF with preserved reduction in MR. Another study reported a significant reduction of secondary MR by restoring papillary muscle geometry and altering the balance between the closing and tethering forces on the mitral valve.[29] The clinical benefit associated with the use of CRT was evident in no more than half of the patients, although this improvement identifies CRT recipients who have an improved

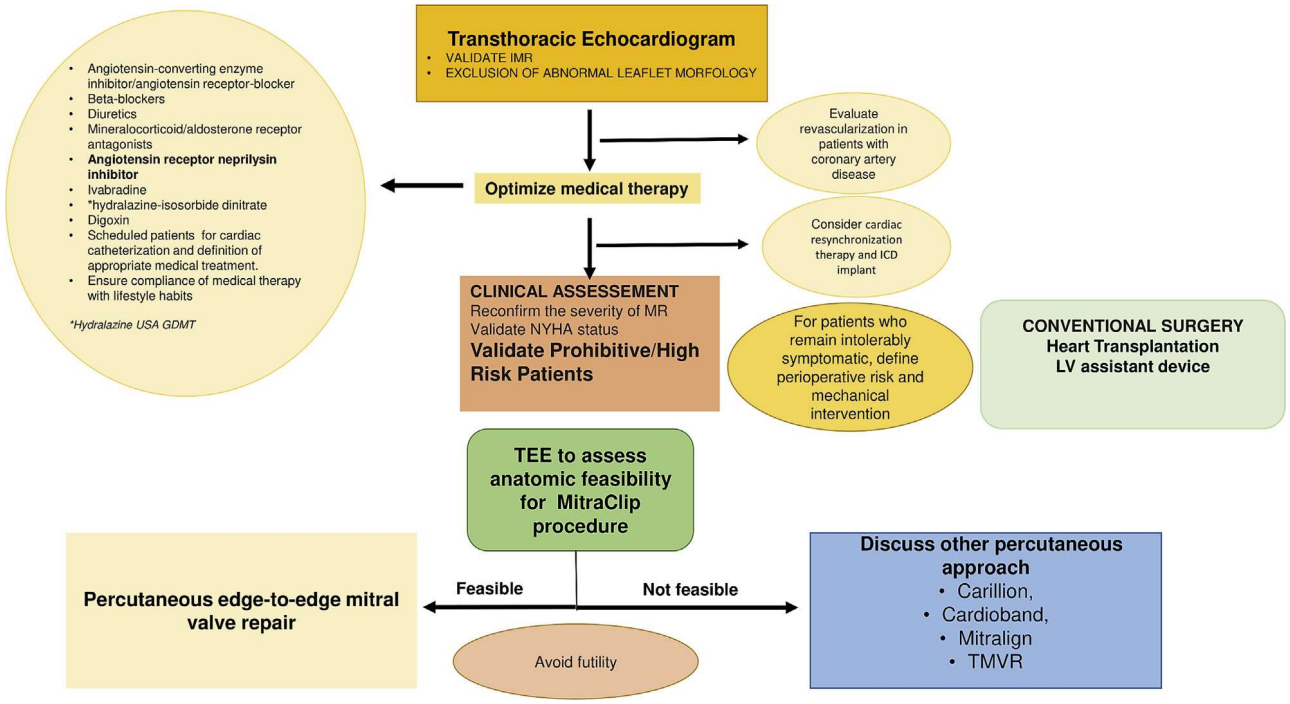

Figure 3. Decision making of feasibility for high-risk patients suitable of percutaneous repair with edge-to-edge transcatheter mitral valve repair (TMVR). (ICD, implantable cardiac defibrillator; IMR, ischemic mitral regurgitation; LV, left ventricular; MitraClip, Abbott Vascular, Menlo Park, CA; MR, mitral regurgitation; NYHA, New York Heart Association; TEE, transesophageal echocardiography; USA GDMT, United States of America guideline-directed medical therapy.)

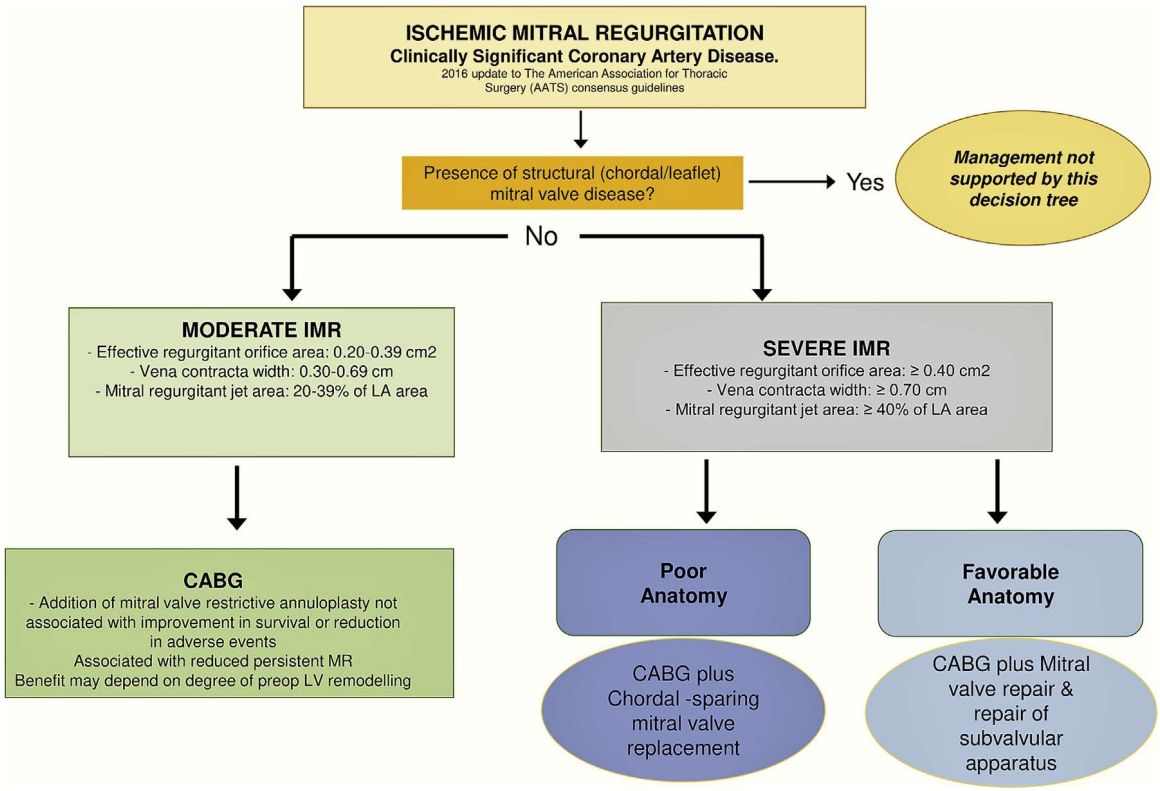

Figure 4. Transthoracic echocardiography evaluation for decision tree in assessing severity of chronic ischemic mitral regurgitation (IMR). (CABG, coronary artery bypass grafting; LA, left atrium; LV, left ventricular; MR, mitral regurgitation.)

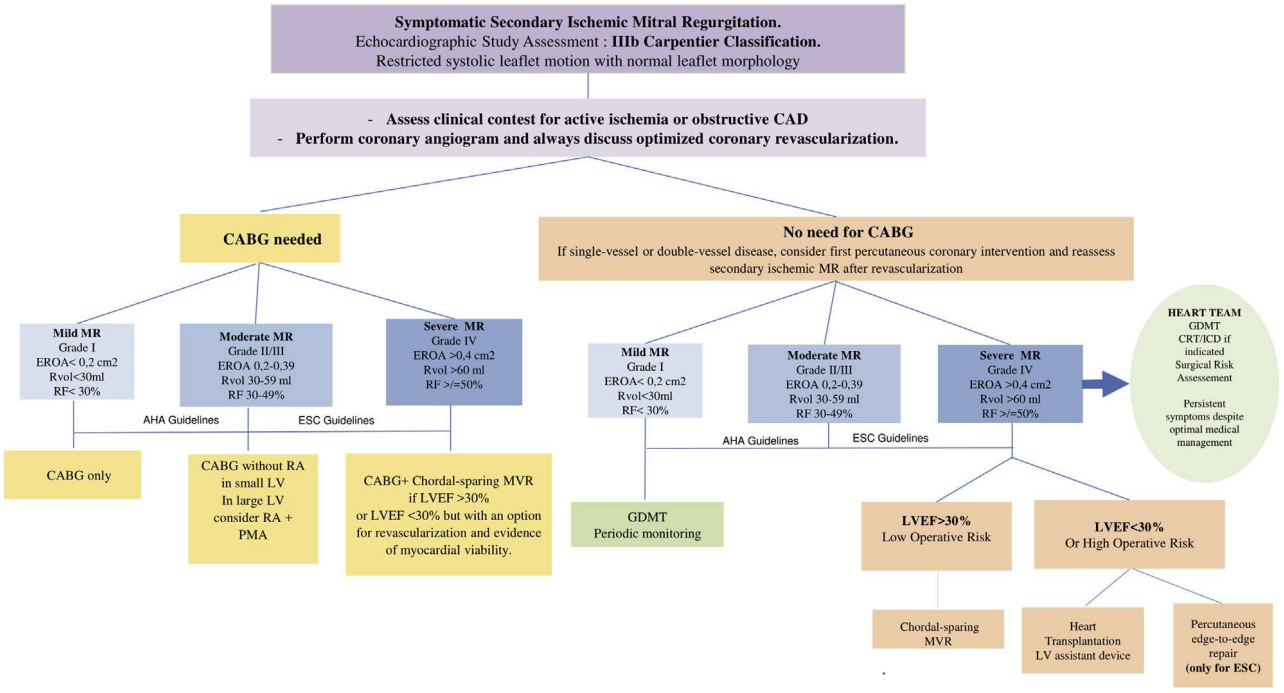

Figure 5. Decisional algorithm for surgery of moderate to severe ischemic mitral regurgitation (IMR). (AHA, American Heart Association; CABG, coronary artery bypass grafting; CAD, coronary artery disease; CRT, cardiac resynchronization therapy; EROA, effective regurgitant orifice area; ESC, European Society of Cardiology; GDMT, guideline-directed medical therapy; ICD, implantable cardiac defibrillator; LV, left ventricle; LVEF, left ventricular ejection fraction; MVR, mitral valve repair; RA, right atrium; RF, regurgitant fraction; RVol, regurgitant volume; TPMA, tricuspid, pulmonary, mitral, aortic valve.)

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prognosis.[30] Nonetheless, patients with severe IMR and heart failure with an effective regurgitant orifice area (EROA) of 0.20 cm^2 or more have a poor response to CRT alongside increased mortality and heart failure rehospitalization rates.

SURGERY FOR ISCHEMIC SECONDARY MITRAL REGURGITATION: WHEN AND HOW TO TREAT? Combined revascularization and mitral surgery should be offered to patients with moderate-to-severe IMR with high-grade proximal coronary lesions. The indications for mitral valve surgery are limited due to the lack of a survival benefit. Therefore, surgical treatment for IMR is only recommended in patients who remain symptomatic despite optimal medical and device therapies.[1,2,13] The American Association of Thoracic Surgeon/The Society of Thoracic Surgeons[31] and ACC/AHA 2017 guidelines recommend that mitral valve surgery is reasonable for patients with chronic severe IMR (stages C and D) undergoing CABG or aortic valve replacement (Class IIa; level of evidence [LOE], C).[1,10] The usefulness of surgical mitral repair is uncertain in patients with chronic moderate IMR (stage B) undergoing CABG (Class IIb; LOE, B-R).[1,11]

Mitral valve repair for IMR using an undersized restrictive mitral annuloplasty ring may be performed at the time of myocardial revascularization in patients with moderate IMR, although the overall benefit is certain.[32-35] This is of particular concern for patients who are undergoing CABG with an LVEF of 0.30 or less.[36] Restrictive mitral annuloplasty is burdened by a high rate of MR recurrence of 30% to 40% at 6 to 12 months and approximately 60% at 5 years.[10,12,22] Several causal factors of MR are identifiable on preoperative echocardiography: symmetric leaflet tethering, posterior leaflet tethering angle exceeding 45 degrees, tenting height exceeding 11 mm, presence of a basal aneurysm/dyskinesis, greater degree of LV dilation, and LV sphericity index.[22] MR recurrence is more frequent with use of partial annuloplasty bands or flexible complete rings.[37,38] High rates are also noted with complete rigid ring insertions.[10,12,39]

Observational, nonrandomized, and single-center experiences are heterogenous in nature and contain many confounders that limit the quality of evidence. They lack robustness in study design, including nonrigorous definitions of the degree of MR, especially in patients with moderate and severe degrees.[35,40,41] Michler and colleagues[11] published a Cardiothoracic Surgical Trials Network (CTSN) RCT[11] of 301 patients with moderate IMR undergoing CABG, revealing a mortality rate of 10.0% in the group undergoing CABG plus mitral valve repair vs 10.6% after CABG alone at 2 years of follow-up (hazard ratio [HR] in the combined-procedure group, 0.90; 95% confidence interval [CI], 0.45-1.83; $P = .78$). The rate of moderate or severe residual MR was higher in the CABG-alone group (32.3% vs 11.2%; $P < .001$), despite similar LV reverse remodeling. Although hospital readmission and serious adverse event rates were similar, neurologic events and heart rhythm disorders were more frequent in patients undergoing CABG plus mitral valve

repair, suggesting that current evidence to support concomitant mitral valve repair for moderate IMR at the time of CABG is weak.[11]

Two other RCTs are of particular interest: the Randomized Ischemic Mitral Evaluation (RIME) trial[32] and the POINT (Efficacy of adding mitral valve restrictive annuloplasty to coronary artery bypass grafting in patients with moderate ischemic mitral valve regurgitation) trial.[34] In these RCTs, the authors demonstrated that the addition of restrictive mitral annuloplasty to CABG in patients with severe IMR resulted in improvements in LV reverse remodeling, LVEF, NYHA, and MR grade, but not in survival. In the POINT trial, 102 patients were randomly assigned to undergo CABG alone or CABG plus restrictive mitral annuloplasty. The CABG plus valve repair arm had significantly reduced LV end-systolic dimension. In the RIME trial, 73 patients were randomly assigned to undergo CABG alone or CABG plus valve repair. Their CABG plus restrictive mitral annuloplasty cohort demonstrated a 28% reduction in LVESV index (LVESVI) compared with baseline.

The 3 randomized trials highlight that improvements in global and regional wall motion, as well as reverse LV remodeling after CABG, with and without mitral valve repair, are indicative of viable myocardium. Penicka and colleagues[42] noted that patients with moderate IMR who underwent CABG alone and experienced resolution of MR after surgery had more viable LV segments and less dyssynchrony at baseline. Michler and colleagues[11] similarly noticed that patients with resolution of IMR showed greater reverse remodeling and better wall motion scores than those who did not, regardless of the treatment group. Given the importance of myocardial viability in ensuring good outcomes, the 3 RCTs deserve a more detailed analysis.

First, the number of patients enrolled in the studies differ widely, especially in CTSN, which enrolled 3 times the number of patients included in the other RCTs (CTSN, 301; RIME, 73; and POINT, 102).

Second, the clinical end points adjudicated in the studies were different. CTSN used the LVESVI as the primary measure of outcome, but POINT used the LV end-systolic and end-diastolic diameters, and LVEF as measures to elucidate reversal of LV remodelling. RIME's primary end point was derived from cardiopulmonary exercise testing. POINT also assessed the tolerability to exercise in patients with residual MR of grade 2+ or less alongside variability of the MR grade during exercise and its effect on dyspnea and systolic pulmonary artery pressure, whereas CTSN focused on echocardiographic measures using a wall motion score and questionnaires and patient-reported outcomes to evaluate quality of life.

Third, the CTSN study used different analytical statistical approaches, which included patients who died as treatment failures in the primary end point analysis, whereas the other studies used simple survival analyses.

Fourth, in the CTSN trial, recipients of surgical treatment had a significantly lower prevalence of prior myocardial infarction, potentially resulting in less LV scar tissue burden.

Fifth, and perhaps most importantly, patients in the CTSN trial had a baseline LV size that was less dilated and remodeled compared with the POINT and RIME trials, respectively.

All of these variables favor CABG plus restrictive mitral annuloplasty, especially in the presence of extensive myocardial scar tissue (Figure 5). In fact, in these patients CABG alone would less likely result in an improvement in the LV wall motion and reverse remodeling, which favor a reduction in the burden of IMR.[43] As highlighted in the RIME trial, CABG plus restrictive mitral annuloplasty reduced the LV size by 28% from baseline, whereas in the CTSN trial, CABG plus restrictive mitral annuloplasty was associated with only a 9% reduction. Patients in the CTSN trial had smaller ventricles at baseline and, as the evidence suggests, more viable myocardium—precisely the clinical substrate that is likely to benefit most from CABG alone.

Other factors such as the predicted probability of significant functional improvement should lead to the provision of a mitral valve reparative procedure. This category includes patients with documented scar tissue or basal aneurysm or dyskinesia in the inferoposterior lateral LV, large ventricles (LVESVI >60 mL/m^2 with LV end-diastolic diameter >50 mm), and poor coronary targets in the left circumflex and right coronary distributions, all of which reduce the likelihood that revascularization will provide significant enhancement of LV contractility and LV reverse remodeling.[12,22,43]

In patients presenting with severe IMR, mitral valve replacement or repair combined with CABG is suitable (Figures 4, 5). The 2017 AHA/ACC Focused Update on Valvular Heart Disease considered severe secondary MR an EROA exceeding 0.4 cm^2, a regurgitant volume of 60 mL or more, and a regurgitant fraction of 50% or more, whereas the 2017 European Society of Cardiologists Guidelines consider severe secondary MR an EROA of 0.2 cm^2 or more or a regurgitant volume of 30 mL or more.

A CTSN randomized trial of surgical mitral valve repair vs replacement in 251 patients with severe IMR showed a mortality rate of 19.0% in the repair group and 23.2% in the replacement group ($P = .39$) at 2 years, with similar degrees of LV reverse remodelling.[10] The rate of recurrence of MR over 2 years was higher in the repair group (58.8% vs 3.8%, $P < .001$), leading to a higher incidence of heart failure and repeat hospitalizations.

Several valvular measures (eg, tenting area, anteroposterior annular diameter, coaptation length) and ventricular measures (eg, LVESVI, LV sphericity index, and interpapillary muscle distance) have been identified as possible predictors of recurrent MR in patients who undergo restrictive mitral annuloplasty alone using rings with a predefined geometry, which overcorrects for the increased tethering of the P2 and P3 segments of the posterior mitral leaflet.[10,39,44]

The high mortality rate at 2 years in both groups[10] emphasizes the poor prognosis of IMR, which clearly differs from primary MR—the former being due to myocardial and coronary disease and the latter a purely valvular condition. In patients with advanced NYHA class

III or IV symptoms, isolated mitral replacement or repair may be considered for patients who have persistent symptoms despite optimal guideline-directed medical and CRT in appropriate candidates (Class IIb; LOE, B).[1,10] The experience of the surgeon, alongside consultation with the heart valve team, is critical in the decision making for surgical mitral valve repair vs replacement[10,12,22,39-43]; however, it is reasonable to perform a chordal-sparing mitral valve replacement or repair in combination with a subvalvular procedure (Class IIb; LOE, B-R)[1,10,12,22,45,46] (Figures 4, 5). Surgical decision making for patients with IMR therefore could be enhanced by preoperative identification of those who would most likely have an improvement in regional wall motion and global LV function with combined CABG. Despite this, preoperative assessment of myocardial viability is often scarce in RCTs.[47] Viability assessment can predict the effectiveness of revascularization in specific patient populations, particularly within the present context.[38]

The optimal valvular prosthesis for mitral valve replacement is unclear. Patients with IMR who undergo mitral valve replacement with conventional stented prostheses may have worse hemodynamic performance and reduced functional capacity compared with patients who have a mechanical prosthesis implanted. However, these data require prospective validation with long-term follow-up.[48] Prospective trials on subvalvular repair techniques are currently insufficient to derive definitive conclusions.[12,22,44] However, in patients with dilated ventricles (especially in those with scar tissue, dyskinesia, or a basal aneurysm) in whom surgical mitral valve repair is feasible, a subvalvular procedure, such as papillary muscle approximation, should be considered.

Our previous analysis of patients who underwent CABG plus restrictive mitral annuloplasty with papillary muscle approximation identified echocardiographic preoperative symmetric tethering, the presence of a LV lateral wall dysfunction, persistent LV dyskinesis, and predominant apical tethering of both leaflets as independent predictors of recurrent MR.[45] In addition, IMR recurrence after restrictive mitral annuloplasty, with and without papillary muscle approximation, is determined by persistent tethering of the posterior leaflet.[12,22,49-52] Aggressive annuloplasty ring undersizing causes a mismatch of the LV dimension and ring size, increasing the risk recurrent IMR. Meticulous ring sizing may prevent IMR recurrence after MV repair and correctly identify patients in whom combined restrictive mitral annuloplasty and subvalvular intervention or chordal-sparing mitral valve replacement may be preferable. A recent post hoc analysis by the CTSN authors noted that an LV end-systolic diameter/ring size ratio exceeding 2 was associated with an increased risk of persistent or recurrent IMR. Therefore, avoidance of smaller annuloplasty rings and incorporation of the LV size into surgical planning is prudent to improve repair durability and avoid iatrogenic mitral stenosis.[53]

Our current decision algorithms for managing IMR focus on 5 preoperative factors that help determine the surgical plan. In conjunction with echocardiography and cardiac catheterization, cardiac magnetic resonance imaging is useful for evaluating the following:

1. Severity of IMR
2. Severity of LV dysfunction
3. Severity of LV remodeling (LVESVI)
4. Presence and extent of LV scar tissue
5. Quality and distribution of the left circumflex and right coronary artery circulation (Figures 4, 5)

Two extremes to the decision algorithms must be noted. First, when medical treatment of IMR does not improve symptoms or quality of life or when progressive LV remodeling with increased LV dysfunction occurs, then heart transplantation or destination LV assist device therapy is a more effective treatment strategy than mitral valve surgery.[10,12,44] Second, in patients who have isolated inferobasal myocardial infarction and severe IMR occurs due to posterior leaflet tethering, despite normal LV size and function, the MR is the cause of heart failure and mitral valve surgery may be indicated for symptomatic relief.[10-12,39,43,44,54] The grey area consists of patients in between the described extremes. Particular attention is directed at patients with moderate to severe IMR with evolving symptoms for which CABG is not indicated, representing a potential benchmark for transcatheter mitral valve therapy[19,20] (Figures 2, 5).

Nonsurgical Intervention for Secondary Ischemic Mitral Regurgitation

The aim of transcatheter mitral valve therapy is to develop a lower-risk procedure that effectively reduces the severity of MR and improves clinical outcomes. The increasing prevalence of MR in the elderly population with significant comorbidities has driven the attractiveness for transcatheter interventions. The transcatheter procedure is based on the surgical edge-to-edge mitral valve repair using a clip to approximate scallops of the anterior and posterior leaflets (Figure 6).

Results From Transcatheter Mitral Valve Edge-to-Edge Repair From RCTs

To date, 3 RCTs have compared percutaneous transcatheter mitral valve repair to optimal medical therapy or standard mitral valve surgery[16,19,20] (Supplemental Tables 1, 2). COAPT (Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients With Functional Mitral Regurgitation) and MITRA-FR (Percutaneous Repair with the MitraClip Device for Severe Functional/Secondary Mitral Regurgitation) enrolled eligible patients with ischemic or nonischemic cardiomyopathy who had a depressed LVEF, moderate to severe or severe secondary MR despite the administration of stable maximal doses of guideline-directed medical therapy, and CRT. Baseline characteristics and results from these RCTs are reported in Supplemental Tables 1, 2.

The primary effectiveness end point of the COAPT study was all hospitalizations for heart failure within 24 months of follow-up, including recurrent events in

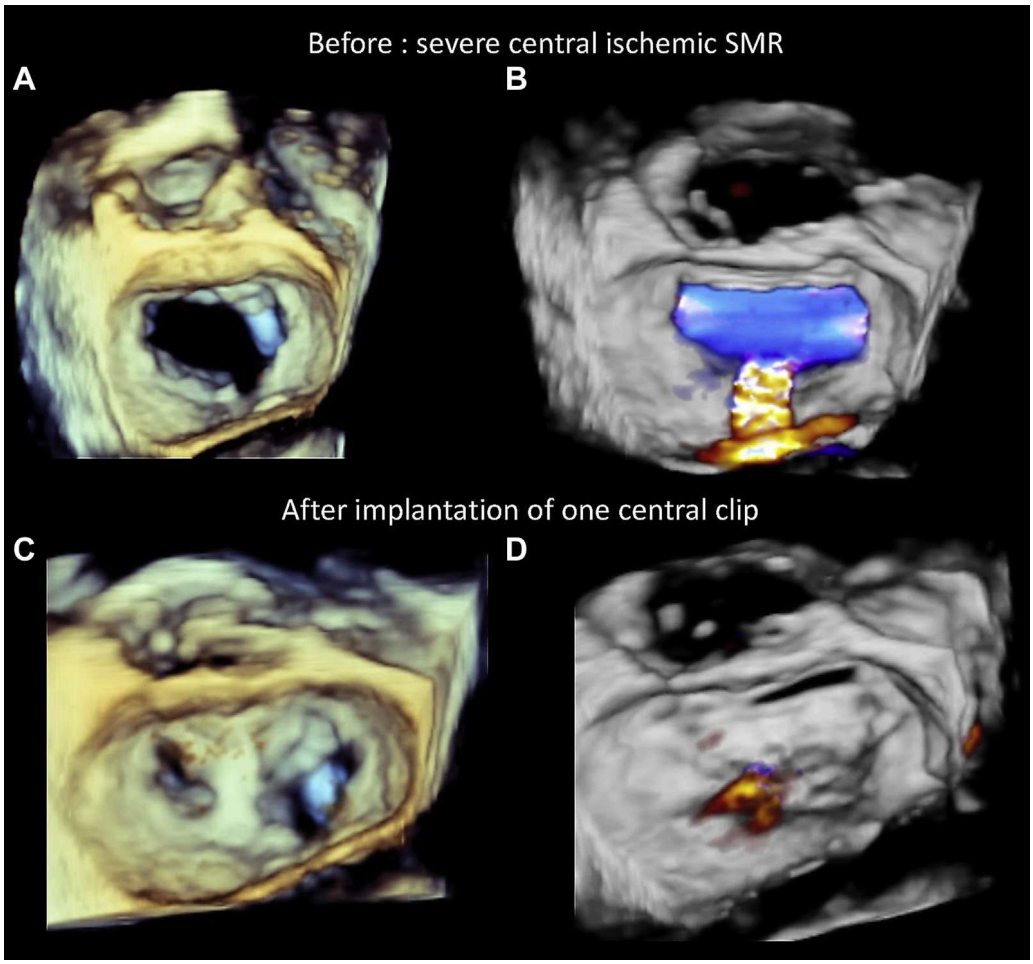

Figure 6. Percutaneous edge-to-edge mitral valve repair of a patient with ischemic secondary mitral regurgitation (SMR) on (A) three-dimensional (3D) transesophageal echocardiography (TEE) and (B) 3D TEE color en-face view showing central SMR. (C) A 3D-TEE en face view after a successful procedure with implantation of 2 central MitraClips (Abbott Vascular, Menlo Park, CA). (D) Transthoracic echocardiographic 3-chamber view shows persistent good results at 1 year with residual mild mitral regurgitation and a gradient at 4 mm Hg.

patients with more than 1 event. In MITR-FR, the primary effectiveness end point was the composite of death from any cause or unplanned hospitalization for heart failure at 12 months after randomization. The baseline LV end-diastolic volume was higher in COAPT (MitraClip [Abbott Vascular, Menlo Park, CA] procedure vs medical therapy: 194.4 ± 69.2 vs 191.0 ± 72.9 mL) than the MITRA-FR study (136.2 ± 37.4 vs 134.5 ± 33.1 mL). There was a marked difference in the rate of data available at 1 year of follow-up (COAPT >94%; MITRA-FR <55%).[19,20] At the 2-year follow-up in the COAPT study, the MitraClip procedure reduced the incidence of all-cause mortality by 38% (HR, 0.62; 95% CI, 0.46-0.92; $P < .001$) and all-cause hospitalizations by 24% (HR, 0.76; 95% CI, 0.6-0.96; $P = .02$) and was associated with significant LV reverse remodelling.[19]

The extraordinary results from COAPT were beyond the expectations of the authors themselves, because the rate of freedom from device-related complications with MitraClip procedure exceeded their prespecified objective performance goal. Moreover, in the subgroup analysis, the benefits of transcatheter mitral valve therapy were consistent both in ischemic and nonischemic cardiomyopathy as well as in patients who were considered high risk for surgery alongside low-risk patients. This benefit was independent of the MR grade and LV volume and function at baseline.[19] Conversely, Obadia and colleagues[20] reported that patients with severe secondary MR who received transcatheter mitral valve therapy in the MITRA-FR study did not experience a clinical benefit compared with patients randomized to medical treatment alone. This result was consistent across all the subgroups tested. The missing data reported by Obadia and colleagues[20] remains a cause for concern, and results from the 2 trials should be interpreted within their respective contexts. A complete description of the 2 trials is provided in Supplemental Table 2.

The COAPT trial sheds light that an effective and sustainable percutaneous treatment can improve the prognosis and the risk of death of patients with secondary MR.[19] However, the main lesson of the MITRA-FR trial is that not all patients presenting with secondary MR will be improved by the MitraClip procedure.[20] The differences of these results can be explained by the different inclusion criteria of both studies that led to the inclusion of 2 different populations of patients with secondary MR.[19,20]

Patients included in the COAPT study[19] presented with more severe MR (EROA of 0.41 cm^2 vs 0.31 cm^2 in the

MITRA-FR study) and were treated more efficiently by transcatheter mitral valve therapy than in the MITRA-FR study, with early recurrence of severe MR (grade 3/4) of 5% vs 9% and 1-year severe recurrence MR of severe MR (grade 3/4) of 5% vs 17%, respectively. Furthermore, maximally optimized medical treatment was assessed in the COAPT trial before inclusion and randomization by a central adjudication committee, including a heart failure specialist. The rigorous follow-up may have played a role in COAPT, an industry-funded trial, accounting for its improved outcomes compared with the institutional MITRA-FR RCT.

The MITRA-FR study[20] included some patients with less severe MR, more advanced LV disease, with more dilated LV end-diastolic diameter (135 mL/m^2 vs 101 mL/m^2), and increased incidences of pulmonary hypertension. It is possible to surmise that transcatheter mitral valve therapy was performed too late in the course of the heart failure disease in these patients.

Finally, Grayburn and colleagues[55] recently reported that a number of COAPT patients presented with a disproportionate secondary MR (severe MR and few dilated LV), whereas MITRA-FR patients presented with proportioned MR. In patients with disproportionate MR, the mitral disease is in the foreground, explaining that an effective and sustainable treatment may improve the prognosis. In patients with proportionate MR, the secondary MR is linked to the severity of LV disease and prognosis may not be linked to MR treatment.[55]

In the EVEREST (Endovascular Edge-to-Edge Repair) II study,[16] transcatheter mitral valve therapy was compared with conventional mitral valve surgery, although only 27% of the patients had functional MR. Results showed that the 5-year freedom from death, mitral valve surgery or reoperation, and moderate to severe MR was lower in the MitraClip group vs the surgery group (44.2% vs 64.3%, $P = .01$). This was driven by lower rates of MV surgery or reoperation (95% vs 72.1%, $P = .003$) and moderate to severe MR (98.2% vs 87.7%, $P = .02$), as opposed to survival (79.2% vs 73.2%, $P = .36$). Interestingly, a subgroup analysis showed the potential benefits of transcatheter mitral valve therapy were derived in patients aged older than 70 years, with surgery performing better than percutaneous repair in younger patients (interaction $P = .005$).[16] Results from transcatheter mitral valve therapy edge-to-edge repair from observational and registry studies are reported in the Supplemental Material.

Areas of Uncertainty and Future Direction

Areas of uncertainty remain regarding the optimal treatment in both populations with severe IMR because rigorous randomized trials of medical treatment vs surgery are lacking in patients not suitable for CABG with reduced LVEF and moderate to severe MR. Therefore, medical therapy, CRT, and revascularization, when indicated, should be considered the preferred treatment choice. Transcatheter mitral valve therapy for IMR is currently limited to edge-to-edge mitral valve repair, although new techniques could be extended to the annulus or chordae, either exclusively or in combination.

Small studies using novel interventional therapies have demonstrated feasibility and efficiency in reducing MR and improving heart failure symptoms. The Carillon (Cardiac Dimensions, Inc, Kirkland, WA), Cardioband (Edwards Lifesciences, Irvine, CA), and Mitralign (Mitralign, Boston, MA) devices were designed to reduce annular dilatation, a frequent and important perpetuator of secondary MR (Figure 3). Several transcatheter mitral valve replacement systems (Tendyne [Abbott], CardiAQ-Edwards [Edwards Lifesciences], Neovasc [Neovasc, Richmond, BC, Canada], Tiara [Neovasc], Intrepid [Medtronic, Minneapolis, MN], Caisson [LivaNova, Maple Grove, MN], HighLife [HighLife Medical, Inc, Irvine CA], MValve System [MValve Technologies, Herzeliya, Israel], and NaviGate Mitral [NaviGate Cardiac Structures Inc, Lake Forest, CA]) are emerging because transcatheter valve replacement may offer more durability compared with transcatheter valve repair.[56]

Conclusion

There are several options for treatment and management of IMR with differing prognostic benefits; however, patients who manifest IMR with heart failure and LV dysfunction have a worse prognosis. Guideline-directed medical therapy is the first treatment choice for moderate and severe secondary MR, with CRT and coronary revascularization performed in appropriate candidates. The roles of mechanical intervention, conventional surgery, or transcatheter mitral valve therapy are less clear and still evolving. Long-term follow-up of patients with secondary MR and ischemic cardiomyopathy receiving surgical or percutaneous intervention should be guided by consistent evaluations of valve durability, functional outcomes, and survival. Finally, better communication between members of the multidisciplinary heart team will also assist in determining the appropriate intervention.

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