Transcatheter Treatment of Mitral Valve Regurgitation in the Setting of Concomitant Coronary or Multivalvular Heart Disease: A Focused Review

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KEYWORDS

• Mixed valvular heart disease • Percutaneous intervention • Tricuspid regurgitation
• Mitral regurgitation • Aortic stenosis • Aortic regurgitation • Transcatheter edge-to-edge repair

KEY POINTS

- This article summarizes the current literature and guidelines on transcatheter treatment of mitral valve regurgitation in the setting of other coronary or multivalvular heart disease in inoperable patients.
- All patients should be evaluated by a heart team on a case-by-case basis.
- When percutaneous intervention is indicated, a staged approach with serial reevaluation is generally favorable to a single-session approach.
- The order of which valve to intervene on first should take into account the hemodynamic interactions of each valvulopathy.

INTRODUCTION

The function and anatomy of the mitral valve apparatus are complex. The mitral valve is responsible for passively allowing left ventricular (LV) filling during diastole and, more impressively, preventing regurgitation under the high LV pressures of systole.[1] The valve competency owes to the intricate, harmonious coordination of the mitral annulus, leaflets, chordae, and papillary muscles of the mitral apparatus and ideal left atrium and ventricle anatomy and function. When the valve becomes dysfunctional, clinical consequences are serious. In particular, those with mitral valve disease with other valvular pathologies or concomitant coronary artery disease are at high risk of developing heart failure and have high mortality rates.[2–6] Treatment of mixed valve disease has historically been limited, often surgery being the only option. Fortunately, with the recent advancement of transcatheter technology, less invasive percutaneous approaches are quickly becoming viable therapeutic considerations. However, with the emergence of many novel technologies targeting the aortic, mitral, and tricuspid valves, finding the ideal permutation of treatment strategy for those with mixed valvular disease is

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Intervent Cardiol Clin 13 (2024) 279–289
https://doi.org/10.1016/j.iccl.2023.12.005
2211-7458/24/

daunting. Guidelines on managing this particularly complex set of patients are sparse because of insufficient data, discrepancies among available data, and significant patient heterogeneity. In addition, multiple interventions of mixed valvular disease in a single session may introduce logistical hurdles in the catheterization laboratories and health care systems without established long-term benefits.

This review summarizes the current literature on percutaneous interventions (PCI) of mitral regurgitation (MR) in the setting of mixed valvular or coronary artery disease, with a focus on pathophysiology, and the timing and order of interventions.

AORTIC STENOSIS AND MITRAL REGURGITATION

Up to 20% of patients with severe aortic stenosis (AS) have concomitant severe MR.[5,7] Patients with moderate-to-severe MR and severe AS have higher mortality than those with severe AS alone.[8] Evaluation of patients with mixed AS and MR is made difficult by the hemodynamic relationship between the two valvular lesions. AS causes increased LV afterload, leading to LV hypertrophy and concentric remodeling. As the disease advances, the LV and mitral annulus dilate causing secondary MR (Fig. 1). However, the regurgitant volume of MR decreases forward flow through the left ventricle, lowering the forward stroke volume, which can underestimate the severity of AS by relatively lowering aortic valve gradient.[9,10] Historically, patients undergoing cardiac surgery for concomitant MR and AS face a 15.5% in-hospital mortality rate and median lifespan of 7.3 years.[11] The advent of transcatheter aortic valve replacement (TAVR) and percutaneous mitral valve therapies, such as mitral transcatheter edge-to-edge repair (M-TEER), opened the possibility of intervention to many who pose a prohibitive surgical risk and otherwise had no options and with unprecedented results. Unlike surgery where intervention on the aortic and mitral valve should clearly be done in the same session, these transcatheter approaches introduce the option to intervene in series.[12,13]

Although the optimal order of procedures needs to be individualized, and the ideal wait time between procedures is still unclear, the sequence of interventions should prioritize the downstream aortic valve. If the MR is treated first, the AS-induced LV afterload might cause LV failure. Both the 2020 American College of Cardiology/American Heart Association (ACC/AHA) and 2021 European Society of Cardiology/European Association for Cardiothoracic Surgery (ESC/EACTS) guidelines recommend that prohibitive-risk patients with severe AS and severe MR should undergo staged TAVR first followed by M-TEER if symptomatic MR persists.[12,13] Of note, the guidelines do not differ on primary versus secondary MR. Although MR improves approximately half of the time after TAVR,[5,8,14] data show that secondary MR is more likely to improve after TAVR than primary MR.[14,15] Factors associated with a lower likelihood of MR improvement include atrial fibrillation, mitral annular calcification, left atrial diameter greater than 5 cm, LV end-systolic diameter less than 45 mm, and preoperative peak aortic valve gradient less than 60 mm Hg.[16–20] Witberg and colleagues[14] also showed in the retrospective Aortic + Mitral TRAnsCatheter (AMTRAC) Registry that patients whose MR persisted after TAVR carried significantly higher 4-year mortality than those whose MR improved after TAVR (43.8% vs 35.1%). Of those whose MR persisted, staged M-TEER post-TAVR was associated with a better 1-year New York Heart Association (NYHA) functional class (82.4% vs 33.3% NYHA I/II) and trended toward lower 4-year mortality (64.6% vs 37.5%; hazard ratio, 1.66; $P = .097$).[14] Interpretation of these data is limited by different grading methods used to assess MR severity, lack of centralized and adjudicated echocardiography data, and variable follow-up periods among the studies.

There are no clear data on the optimal time to proceed with M-TEER after TAVR, and the decision should ultimately be based on each patient's specific clinical needs. A retrospective analysis of 626 patients undergoing M-TEER and TAVR compared outcomes of those who had the procedures done during separate verse the same admission.[21] After adjusting for age, sex, and comorbidities, they found that although the overall mortality rates between the two groups were similar, those who had both procedures during the same admission had higher rates of acute kidney injury, vascular complications, need for PCI, mechanical support, and pacemaker insertion. Although the study did not quantify the number of days between procedures, it is safely assumed patients who had both interventions during the same admission had fewer days between interventions than those who were treated in two separate hospitalizations. The AMTRAC registry reported a median of 61 days from TAVR to M-TEER.[14] Even less data exist on single-session TAVR and M-TEER. Rudolph and colleagues[22]

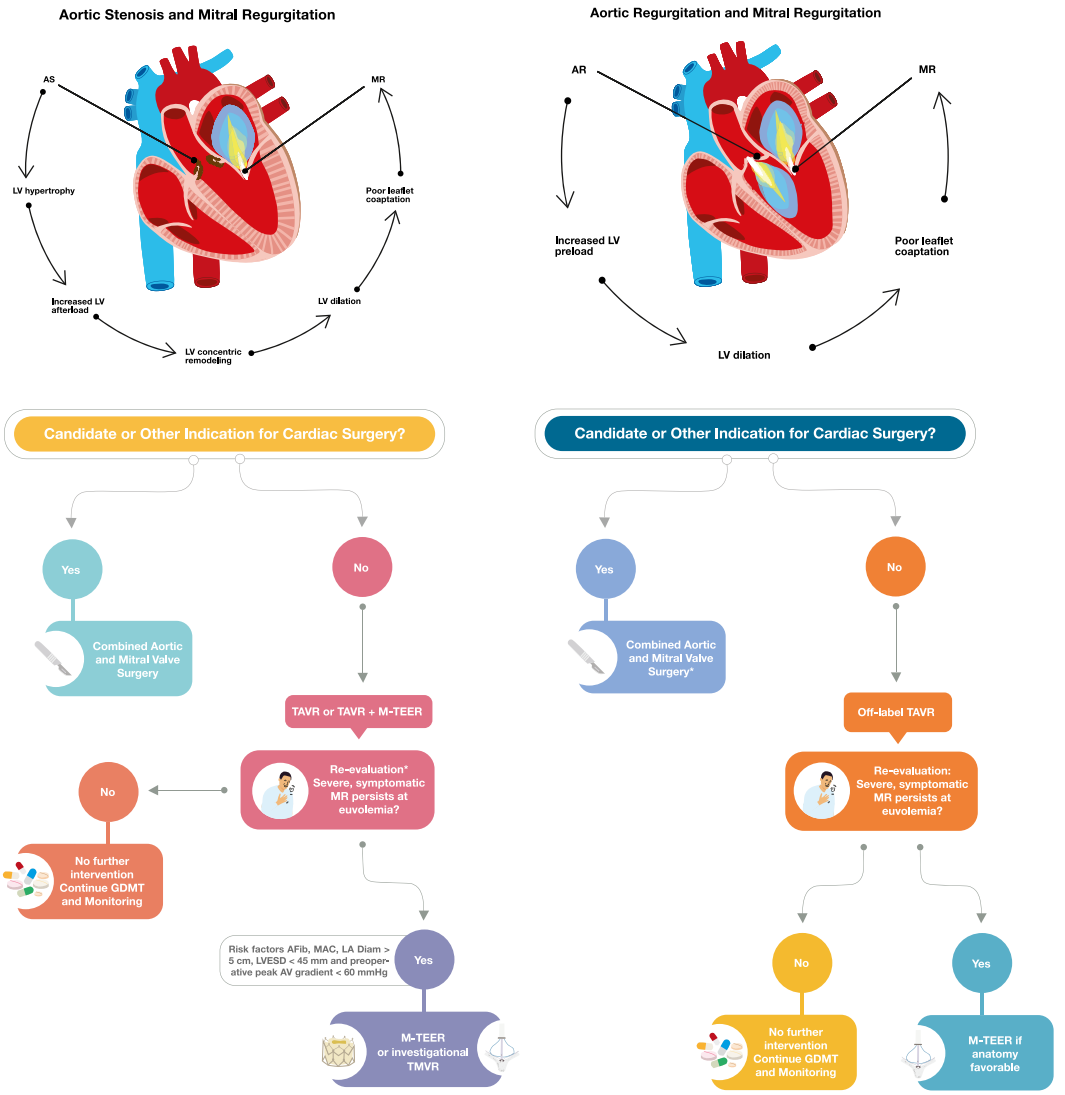


Fig. 1. Pathophysiology and management of aortic stenosis causing mitral regurgitation and aortic regurgitation causing mitral regurgitation. * Surgery for severe aortic regurgitation when it is symptomatic (1B-NR), causing LV systolic dysfunction (1B-NR), already undergoing cardiac surgery (1C-EO), or when LV is severely enlarged (2a B-NR). A Fib, atrial fibrillation; AV, aortic valve; LA, left atrium; LVESD, left ventricle end-systolic dimension; MAC, mitral annular calcification.

reported their experience with three patients, showing that a single-session TAVR and M-TEER is feasible. In all three cases, TAVR preceded the M-TEER. They also reported one case of M-TEER 10 days before TAVR. Witberg and colleagues[23] reported 100% technical success of concomitant TAVR and transcatheter mitral intervention (2 M-TEER, 3 mitral valve-in-valve, and 1 transcatheter heart valve in the mitral position) from the German transcatheter mitral valve interventions (TRAMI) registry. The outcomes of the six patients who had TAVR and transcatheter mitral valve replacement/repair (TMVR/r) were comparable with those who underwent staged intervention from the same registry, although data are susceptible to small sample bias.[23] More research is needed to further assess the benefits and risks of single-session TAVR and TMVR/r.

In summary, evidence supports that symptomatic patients with severe AS and greater than or equal to 2+ MR who are deemed appropriate for transcatheter intervention first undergo TAVR with close reevaluation of the MR post-TAVR, then proceed with staged M-TEER if significant MR persists (see Fig. 1). Optimal timing between

the two interventions is yet to be established. Given scant data, it is yet difficult to draw a firm conclusion on the benefits of concomitant TAVR and M-TEER in a single session.

AORTIC REGURGITATION AND MITRAL REGURGITATION

The prevalence of combined aortic regurgitation (AR) and MR varies wildly across populations.[24,25] Up to a quarter of patients with severe AR also have moderate-to-severe MR.[26,27] The increased preload in chronic AR can result in LV remodeling and dilation (see Fig. 1). This then impacts the mitral apparatus, leading to poor coaptation of the mitral leaflets and secondary MR.[28] When the aortic valve is replaced surgically, the secondary MR improves by at least one grade in most (~90%) patients.[29] Guidelines currently recommend surgical intervention for severe AR causing symptoms, LV systolic dysfunction, during concomitant cardiac surgery, or when LV is severely enlarged.[12] For patients who are not candidates for surgery, TAVR is an off-label option with results comparable with surgical aortic valve replacement.[30,31] TAVR for AR is technically challenging, and size selection must weigh the risks of dislocation and oversizing. A predominantly regurgitant aortic valve may lack significant calcification the standard TAVR valves depend on for stable anchoring.[12,30] Recently, novel technologies, such as the percutaneous leaflet-capturing Trilogy system that does not require calcification for anchoring, received a CE (European Conformity) mark for the treatment of AR.[32] Prospective data of the Trilogy system will soon be available from the Align AR trial.[33]

Current data on PCI for severe AR and severe MR are limited to case reports in the last 10 years. Most often, it is treated in stages with the TAVR done before M-TEER. Only one case report of a successful single-session TAVR and valve-in-valve TMVR has been reported.[34] A successful single-session TAVR and chord repair for severe AR and MR with mitral annular calcification has also been reported using the Neochord DS 100 device.[35] In another case, a successful single-session TAVR, followed by intra-aortic balloon pump, then M-TEER was reported for a patient with cardiogenic shock from a late-presenting ST segment elevated myocardial infarction with severe AR and MR.[36] In all three of these cases of single-session intervention, the aortic valve was intervened before the mitral valve. Intervening on the downstream aortic valve may decrease LV preload and create a more favorable pressure gradient across the mitral valve.[28] Additionally, the LV reverse remodeling may improve the ventricular geometry and mitral subvalvular apparatus, allowing for better mitral valve coaptation and reduction of MR.[29] To our knowledge, there has only been one case report of M-TEER done before off-label TAVR for AR.[37] The patient had multiple comorbidities including chronic arterial dissection from the carotid arteries to the bilateral femoral arteries. The authors stated that they chose to do M-TEER before TAVR because MR was more severe than the AR initially and the technical difficulties related to the arterial access needed for TAVR in the setting of extensive dissection. AR became more severe on a follow-up echocardiography and a successful TAVR was done in a transapical approach.

In summary, cardiac surgery is still the current standard of care for concomitant severe AR and MR, with TAVR considered as an off-label option for those with favorable anatomy who are not candidates for surgery (see Fig. 1). However, the transcatheter technology is rapidly evolving, and novel devices and valve systems designed specifically for nonsurgical treatment of AR are being tested. Completion of these trials, data publication and analysis, and further research will advance the transcatheter-based treatment of mixed valve disease of MR and AR.

TRICUSPID REGURGITATION AND MITRAL REGURGITATION

Moderate or severe tricuspid regurgitation (TR) has a prevalence of up to 30% in those with severe secondary MR.[2] The presence of secondary TR independently confers a worse prognosis.[38,39] Many severe TR cases are secondary to left-sided heart disease including aortomitral valvular dysfunction, LV cardiomyopathy, and/or pulmonary hypertension.[40] Significant secondary TR develops via several mechanisms, with tricuspid annular dilatation often as the common final pathway. Secondary TR is categorized into either atrial-predominant phenotype, which is typically driven by chronic atrial fibrillation with right atrial dilatation, or ventricular-predominant phenotype, which is caused by pulmonary hypertension or secondary to left-sided valvular or ventricular disease.[41–43] The timing and approach to intervention for both phenotypes remains unclear, especially as it pertains to novel percutaneous therapies. Primary TR etiology is less frequent. It includes degenerative disease, healed endocarditis, traumatic leaflet tear or perforation, and pacemaker lead

impingement. This entity is less likely to change after mitral valve treatment. This section discusses proposed stratification for cases of concomitant secondary TR and MR.

Surgical tricuspid valve repair has existed since Carpentier and colleagues[44] described safety and efficacy of tricuspid ring annuloplasty in 1974. The most recent ESC/EACTS 2021 and ACC/AHA 2020 guidelines recommend that those who are already undergoing left-sided valve surgery should have concomitant surgical intervention for severe secondary TR (class 1) or mild or moderate TR with an annulus greater than 40 mm (class 2a) (Fig. 2).[12,13]

For inoperable patients, there has been a recent expansion of transcatheter options for TR. These include leaflet approximation, annuloplasty, orthotopic valve implantation, and heterotopic valve implantation.[45] Although not mentioned in the 2020 ACC/AHA guidelines, it is a class 2b recommendation by the ESC/EACTS to undergo transcatheter tricuspid valve intervention (TTVI) for severe, symptomatic secondary TR in inoperable patients.[13] This was largely based on the 2019 retrospective analysis of 472 patients in the TriValve registry showing patients who underwent TTVI had lower 1-year all-cause mortality (23% vs 36%) and fewer rehospitalizations for heart failure (26% vs 47%).[46] Subsequently, a 2022 meta-analysis of 1216 patients undergoing TTVI showed that those who had a reduction in the TR grade to 2+ or less had a 58% risk reduction in 1-year mortality.[47] Prospective data from tricuspid TEER (Triluminate Pivotal study,[48] CLASP TR trial[49]), tricuspid replacement (TriSCEND trial[50,51]), and TRI-REPAIR study[52] showed that TTVI is safe, improves quality of life, and improves TR severity in 72% to 98% of patients. However, these prospective randomized studies did not show a significant reduction in mortality or heart failure hospitalizations observed in nonrandomized studies, at least up to 1-year follow-up. Additionally, it is important to mention that patients with concomitant severe MR were excluded in the Triluminate, CLASP TR, and TRISCEND Pivotal studies.[48–50] Further prospective data are needed to shed light on the efficacy of TTVI, particularly as it pertains to patients with multivalvular lesions.

TR often exists as a consequence of MR and improves in 23% to 50% of patients after M-TEER.[53–57] One scenario is that as MR is reduced, left atrial dynamics improve, pulmonary pressures normalize, and ultimately positive right ventricular (RV) remodeling leads to a reduction in tricuspid annulus size and approximation of leaflet coaptation.[58] Risk factors for lack of TR improvement after M-TEER include the presence of atrial fibrillation, chronic RV dysfunction, large tricuspid annulus size, or significant residual MR after M-TEER (see Fig. 2).[59]

There are limited data on the timing and sequencing of TTVI and M-TEER. To date, no prospective studies exist comparing single-session M-TEER plus TTVI versus a staged approach. A retrospective analysis of the TriValve and TRAMI registries showed a higher 1-year survival rate (83.6%) with combined TEER compared with isolated M-TEER (66%).[60] This survival benefit of combined tricuspid and M-TEER should be interpreted with caution, given confounding factors inherent to retrospective analysis. For example, the combined TEER group had significantly worse ejection fraction and lower baseline glomerular filtration rate (GFR). Another retrospective analysis of the TriValve registry found that heart failure exacerbations were similar in those who got TTVI combined with M-TEER, compared with TTVI alone.[46] The conflicting data of these retrospective analyses highlights the need for future prospective randomized controlled studies in this patient population.

In addition to the previously mentioned registry data, studies have been performed to understand the safety and efficacy of specific hemodynamic subtypes within the MR TR population. Stocker and colleagues[61] identified increased mortality following TTVI (T-TEER) for patients with combined precapillary and postcapillary pulmonary hypertension (CpPH) compared with those without pulmonary hypertension or isolated postcapillary pulmonary hypertension (IpcPH). In another interrogation of the TriValve registry by Brener and colleagues,[62] noninvasive estimation of RV–pulmonary artery uncoupling by tricuspid annular plane systolic excursion/pulmonary artery systolic pressure less than a median value of 0.406 was associated with increased risk of all-cause mortality at 1 year after TTVI. These two studies support cautious employment or avoidance of TTVI for patients with advanced pulmonary hypertension with resultant RV failure.

In summary, it is advisable to stratify patients by hemodynamic and anatomic profiling during preprocedural planning for PCI of concomitant MR and TR. Right heart catheterization is underused and crucial for the characterization of CpcPH verse IpcPH in this population. Patients presenting with CpcPH and chronic RV systolic failure represent an advanced disease state that may be less tolerant of valvular intervention and are also less likely to reap long-term benefits because of futility. Similar to surgical patients,

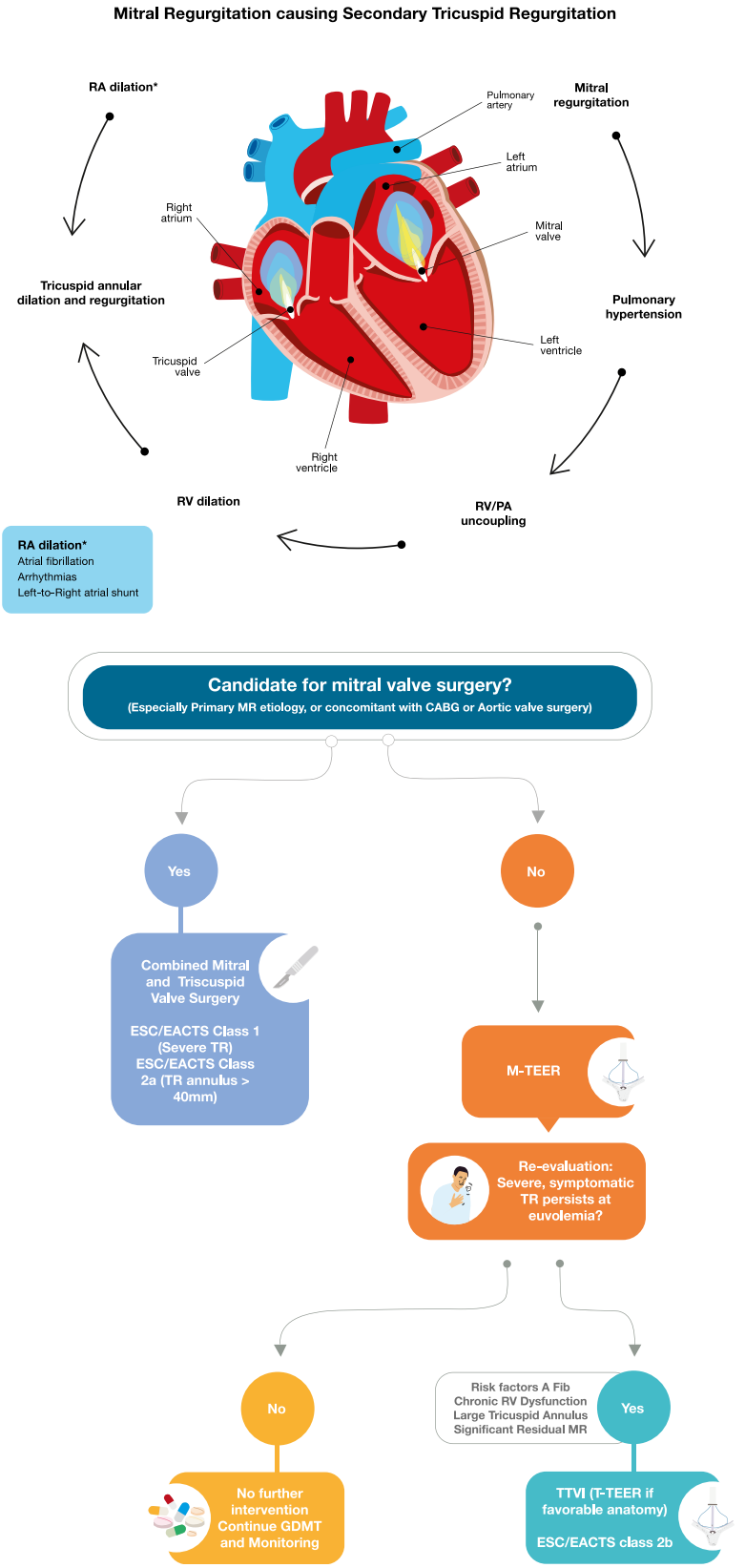
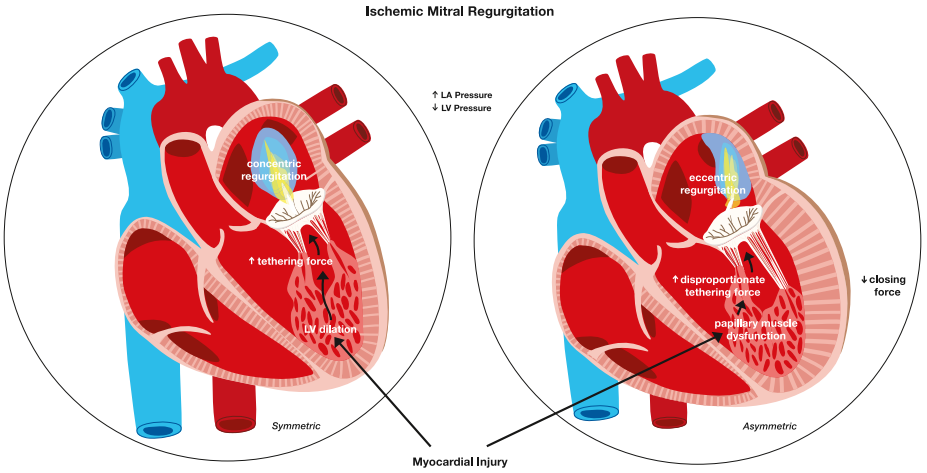


Fig. 2. Pathophysiology and management of mitral regurgitation causing secondary tricuspid regurgitation. * Atrial fibrillation, arrhythmias, and left-to-right atrial shunt. (blue box text). A Fib, atrial fibrillation; CABG, coronary artery bypass graft; PA, pulmonary artery; RA, right atrium; RV, right ventricle; T-TEER, tricuspid transcatheter edge-to-edge repair.



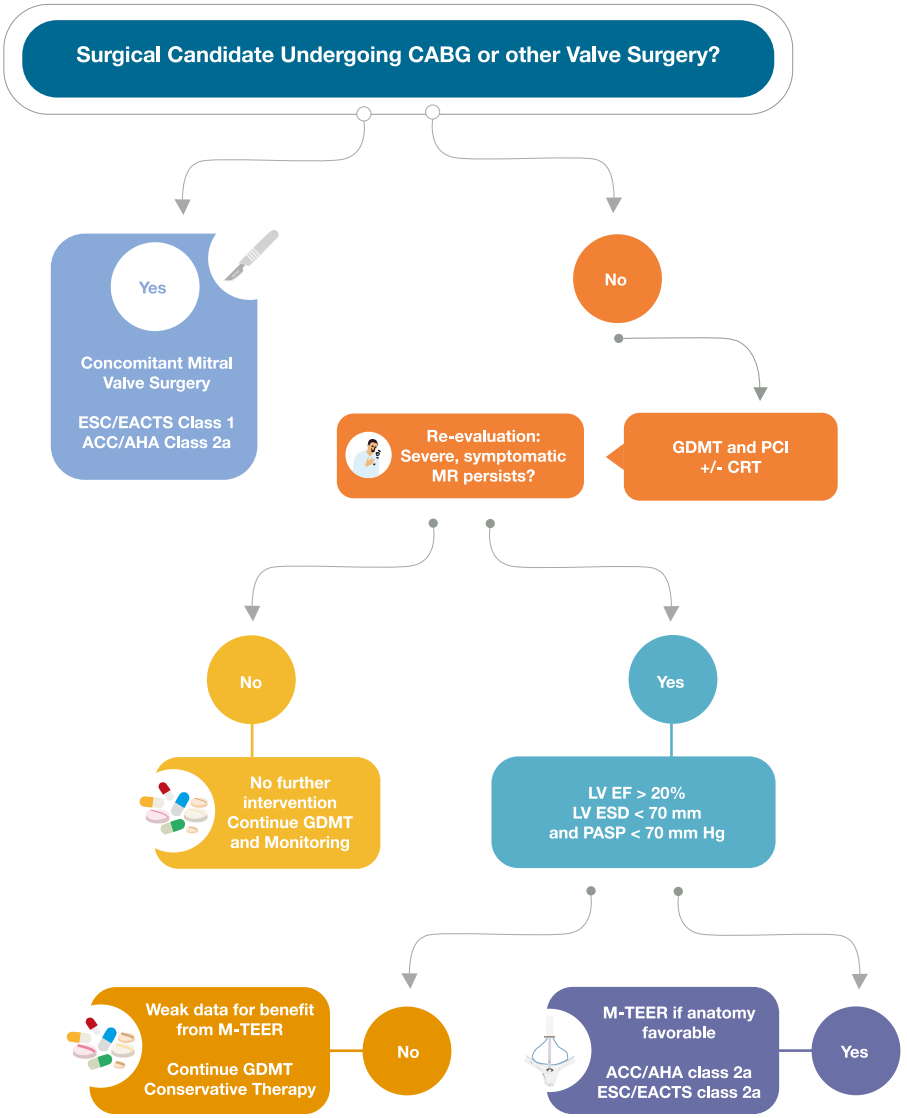


Fig. 3. Pathophysiology and management of ischemic cardiomyopathy causing mitral regurgitation. CABG, coronary artery bypass graft; CRT, cardiac resynchronization therapy; LA, left atrium; LV EF, left ventricular ejection fraction; LV ESD, left ventricle end-systolic dimension; PASP, pulmonary artery systolic pressure.

patients with tenuous RV function may benefit from periprocedural ventricular inotropic drugs, such as milrinone to optimize RV function and reduce the risk of acute RV decompensation that can occur when severe TR improves to less than mild.[63] In contrast, patients with IpcPH may reasonably undergo either concomitant TEER or a staged approach with reassessment of TR following M-TEER. Those with atrial-predominant TR secondary to atrial fibrillation are less likely to achieve a reduction of TR after M-TEER and may gain benefit from a concomitant approach, depending on minimizing procedural time and optimizing resource use. More data on timing, order of interventions, and patient selection regarding transcatheter management of concomitant MR and TR are needed.

ISCHEMIC (CORONARY ARTERY DISEASE) MITRAL REGURGITATION

Ischemic MR starts with coronary artery disease causing pathologic remodeling and dilation of the LV and compromised perfusion to the mitral subvalvular apparatus. The LV dilation is either symmetric or asymmetric. In the former, the mitral annular ring becomes dilated and leads to poor leaflet coaptation. In contrast, the displaced papillary muscles of the asymmetrically dilated LV cause a tethering force on the chordae tendinea mitral valve leaflet leading to MR (**Fig. 3**). The resulting regurgitation is self-perpetuating because the volume overload from the MR can further exacerbate LV dilation.[64–68] It is an ESC/EACTS class 1 and ACC/AHA class 2a recommendation to have mitral valve surgery for the coexisting severe MR if a patient is undergoing coronary artery bypass graft or other valve surgery.[12,13] For those not eligible for cardiac surgery, M-TEER is an ACC/AHA and ESC/EACTS class 2a recommendation for patients with severe, symptomatic ischemic MR refractory to optimal goal-directed medical therapy (GDMT), PCI, and cardiac resynchronization therapy if indicated (see **Fig. 3**).[12,13]

These recommendations are largely based on the evidence from the COAPT and MITRA-FR trials.[39,69] In these trials, MitraClip plus GDMT was prospectively compared with GDMT alone for patients with symptomatic MR refractory to optimal GDMT. The COAPT study showed an improvement in survival, hospitalization, symptoms, and quality of life up to 5 years.[70] In contrast to the COAPT trial, the MITRA-FR trial did not show a reduction in the composite end point of death or hospitalization. Because of these differences, and taking into consideration multiple subgroups analysis, the guidelines adopted these additional criteria for the indication for M-TEER (LV ejection fraction between 20% and 50%, LV end-systolic dimension $\leq$70 mm, pulmonary artery systolic pressure $\leq$70 mm Hg, and persistent symptoms [NYHA functional class II, III, or IV] while on optimal GDMT).[12]

The benefits of cardiac surgery for mitral valve replacement or repair for ischemic MR are controversial and outside the scope of this review paper. For high or prohibitive surgical risk patients with primary severe MR in the setting of ischemic cardiomyopathy, M-TEER is reasonable and should not be delayed because the MR is not expected to improve significantly after PCI. Patients should have a life expectancy greater than 1 year and favorable anatomy.[12,13] Ideally, the most favorable anatomy for M-TEER includes a central pathology of the mitral valve, no leaflet calcifications, mitral valve area greater than 4.0 cm^2, posterior leaflet greater than 10 mm, tenting height less than 10 mm, flail gap less than 10 mm, and flail width less than 15 mm.[71] With increasing anatomic challenges, M-TEER, although still feasible, requires more operator skill set, and MR reduction is less optimal in some cases. The farther patients are from this ideal anatomy, the more consideration should be given to mitral valve replacement, which is a fast-growing technology.[72] For patients with severe secondary ischemic MR and high or prohibitive surgical risk, the main points of the guidelines are discussed previously. The underlying cause ischemia and the focus should be first on optimizing revascularization, GDMT, and cardiac resynchronization therapy if indicated. If MR remains severe and symptomatic, then M-TEER is indicated with proven mortality and morbidity benefit.

SUMMARY

Patients with MR with other valvular pathologies or concomitant coronary artery disease are clinically complex. Transcatheter therapies targeting the aortic, mitral, and tricuspid valves introduce the option of permutations on order and timing of treatments, with insufficient data to date to recommend single-stage interventions. In general, the order of treatment should prioritize the downstream valve; aortic before mitral and mitral before tricuspid. Ultimately, each patient should be evaluated by a heart team and management should be individualized based on their unique hemodynamics. Further data from large registries and perhaps randomized controlled trials are needed to establish strong evidence-based guidelines.

CLINICS CARE POINTS

- There has been a recent expansion of percutaneous interventions for valvular heart disease. The heart team decision is important in order to consider all options available for their patients, as well as order and timing of interventions.
- In general, the order of percutaneous treatment should prioritize the downstream valve; aortic before mitral and mitral before tricuspid.
- Until there is more data on the safety and efficacy of single-session multivalvular percutaneous interventions, patients should have their valves intervened in sequence with re-evaluation of valve disease severity and symptoms between each procedure.

DISCLOSURE

None of the authors have disclosures.

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