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Review Article

Multiple Valvular Heart Disease in the Transcatheter Era: A State-of-the-Art Review

Craig Basman, MD *, David Landers, MD, Yuriy Dudiy, MD, Sung-Han Yoon, MD, George Batsides, MD, Haroon Faraz, MD, Mark Anderson, MD, Ryan Kaple, MD

Department of Cardiology and Cardiothoracic Surgery, Hackensack University Medical Center, Hackensack, New Jersey, USA

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ABSTRACT

Although existing guidelines offer strong recommendations for single valvular dysfunction, the growing prevalence of multiple valvular heart disease (MVHD) in our aging population is challenging the clarity of clinical guidance. Traditional diagnostic modalities, such as echocardiography, face inherent constraints in precisely quantifying valvular dysfunction due to the hemodynamic interactions that occur with multiple valve involvement. Therefore, many patients with MVHD present at a later stage in their disease course and with an elevated surgical risk. The expansion of transcatheter therapy for the treatment of valvular heart disease has added new opportunities for higher-risk patients. However, the impact of isolated valve therapies on patients with MVHD is still not well understood. This review focuses on the etiology, diagnostic challenges, and therapeutic considerations for some of the most common concomitant valvular abnormalities that occur in our daily clinic population.

ABBREVIATIONS

AI, aortic insufficiency; AS, aortic stenosis; CIED, cardiac implantable electronic device; LV, left ventricular; LVOTO, left ventricular outflow tract obstruction; MAC, mitral annular calcification; MACE, major adverse cardiovascular events; MR, mitral regurgitation; MS, mitral stenosis; m-TEER, mitral transcatheter edge-to-edge repair; MVA, mitral valve area; MVHD, multiple valvular heart disease; PHT, pressure half-time; pHTN, pulmonary hypertension; PBMV, percutaneous balloon mitral valvuloplasty; PVL, paravalvular leak; RV, right ventricular; TAVR, transcatheter aortic valve replacement; THV, transcatheter heart valve; TMTVR, transcatheter mitral and tricuspid valve repair; TR, tricuspid regurgitation; t-TEER, tricuspid transcatheter edge-to-edge repair; TTVI, transcatheter tricuspid valve intervention; US, United States; ViMAC, valve-in-MAC.

Introduction

The prevalence of multiple valvular heart disease (MVHD) is on the rise in our aging population.[1,2] Following rigorous validation through numerous randomized controlled trials, both transcatheter aortic valve replacement (TAVR) and mitral transcatheter edge-to-edge repair (m-TEER) have been officially incorporated as treatment choices in our valvular heart disease guidelines.[3] However, while the current guidelines provide robust recommendations for isolated valve therapy, the management of MVHD is less clear.[3] The utility of traditional diagnostic modalities, such as echocardiography, may be limited in these patients due to the hemodynamic interactions that occur with multiple valve involvement. Therefore, many patients with MVHD present at a later stage with an elevated surgical risk. Surgical correction of multiple valve lesions in a single operation can be performed; however, this strategy portends an operative mortality up to three times higher than isolated-valve surgery.[4,5] Transcatheter approaches are often safer, but their effectiveness may be constrained if all the functionally significant lesions are not addressed. While transcatheter approaches are generally effective for aortic stenosis (AS) or mitral regurgitation (MR), other valvular pathologies such as aortic insufficiency (AI), calcific mitral stenosis (MS), and tricuspid regurgitation (TR) may be left untreated. As we continue to understand the clinical and echocardiographic response of secondary valvular pathology after isolated valve therapy, heart-team

* Address correspondence to: Craig Basman, MD, Division of Cardiology, Hackensack University Medical Center, 30 Prospect Avenue, Hackensack, NJ 07601.
E-mail addresses: craigbasman@gmail.com, craig.basman@hmhn.org (C. Basman).

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discussions must incorporate the benefits and risks. Thus, our review explores the different combinations of some of the most common simultaneous valvular issues present in our daily practice.

Aortic Stenosis and Mitral Regurgitation

Background

Prevalence of severe AS and MR may occur in up to one-third of the population that is referred for TAVR,[6,7] and the co-existence of these valvulopathies is associated with worsened clinical outcomes both in the short term and over the long term as compared to isolated AS or MR.[8,9] The causes of MR in conjunction with AS are multifaceted. MR etiology may be functional, degenerative, or mixed. Functional MR may arise from progressive cardiac deterioration due to severe AS,[10] the coexistence of ischemic heart disease (highly prevalent among TAVR patients),[11] or mitral annular dilation stemming from comorbid conditions such as atrial fibrillation.[12] Degenerative MR often co-exists with AS in the aging population, occurring due to age-related "wear and tear."

The presence of MR results in lower transaortic stroke volume and will thus result in lower transaortic gradients, akin to those of low-flow, low-gradient AS. This phenomenon may delay the diagnosis of severe AS and, thus, the referral for intervention. As AS progresses, the secondary increase in afterload can further exacerbate MR/regurgitant volume, thereby masking AS severity. Abolishment of AS should have immediate effects to reduce the regurgitant volume.[13] TAVR has indeed been shown to reduce MR grade $\geq$1+ in ~50% to 70% of patients.[7,14] The possibility of reverse left ventricular (LV) remodeling following aortic valve replacement may also improve cases of functional MR over time.[15] However, predicting which patients will have significant improvement in MR remains challenging.[16–18] Figure 1 displays factors for expected MR improvement after aortic valve replacement (Figure 1: Factors for expected MR improvement after TAVR).

Therapy Considerations

For patients who may struggle to tolerate double-valve surgery, an alternative approach may involve staged interventions, commencing with TAVR and closely monitoring MR through clinical follow-up. Should MR persist, m-TEER[19] or isolated mitral valve surgery would be treatment options.[20,21] m-TEER has proven to be a viable choice, albeit with the caveat that not all patients possess suitable anatomical criteria for the procedure.[22] Isolated mitral valve surgery is associated with a lower surgical risk than double-valve surgery and allows the surgical team to perform a mini-thoracotomy rather than sternotomy. This staged approach may especially be more favorable in patients when a reduction of MR is expected after TAVR, possibly obviating the need for mitral therapy. For example, a patient with 3+ functional MR would be more likely to have MR improvement after aortic valve replacement than a patient with 4+ degenerative MR due to a flail leaflet. Figure 2 suggests an algorithm for AS/MR in patients with elevated surgical risk (Figure 2: Treatment algorithm for severe AS and MR).

Aortic Stenosis and Mitral Stenosis

Background

Among patients that underwent TAVR in the Transcatheter Valve Therapy registry, ~11% had combined AS/MS.[23] The majority of MS cases among elderly patients are from degenerative MS, generally associated with mitral annular calcification (MAC).[24] The addition of MS heralds a worse prognosis among patients that undergo TAVR with a three-fold increased risk of cardiovascular adverse events at just 1 year compared to those without MS.[24] The combination of stenoses across the mitral and aortic valves induces a low-flow state. It is usual to have an underestimation of aortic valve gradients due to a reduction in LV preload (i.e., low-flow, low-gradient AS).[25] Thus, the combination of MS and AS may lead to delayed therapy, progressive cardiac damage, and subsequently higher procedural risks.

The severity of MS using echocardiographic transmitral gradients and mitral valve area (MVA) may be inaccurate in patients with severe AS. MVA is often overestimated with the use of pressure half-time (PHT) due to impaired LV diastolic function prolonging the PHT. Conversely, the continuity equation is flow-dependent, and in the context of severe AS may result in an overestimation of MS degree.[26] Planimetry of the mitral valve is considered a more reliable parameter; however, the presence of

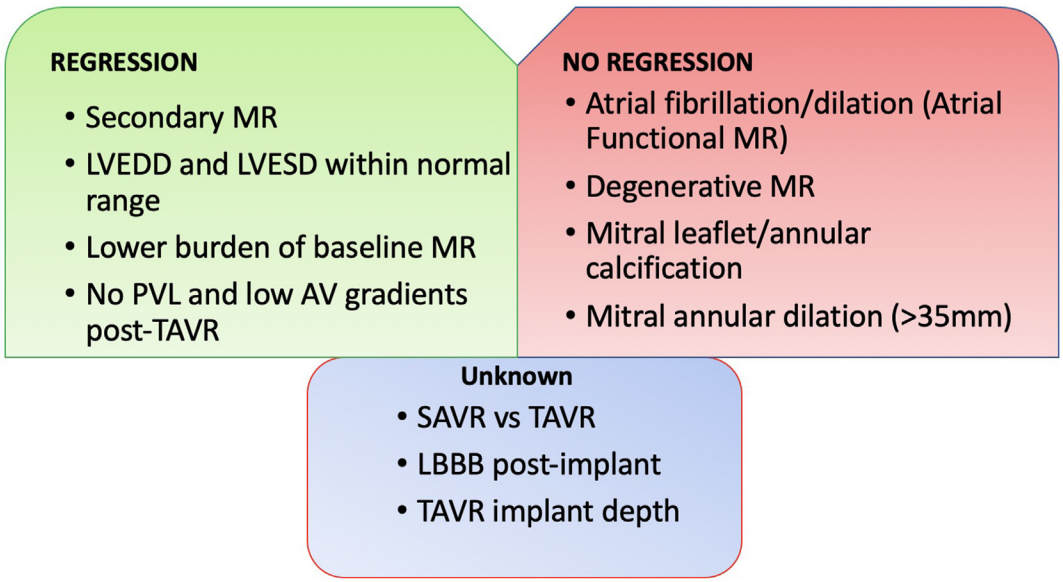

Figure 1. Factors for expected MR improvement after isolated aortic valve replacement. This figure lists factors that are associated with MR regression (and lack of regression) after isolated aortic valve therapy in patients with combined aortic stenosis and mitral regurgitation. The blue box lists certain features that require more investigation (i.e., Do post-TAVR conduction disturbances increase risk of MR persistence?).
Abbreviations: AV, aortic valve; LBBB, left bundle branch block; LVEDD, left ventricular end diastolic diameter; LVESD, left ventricular end systolic diameter; MR, mitral regurgitation; PVL, paravalvular leak; SAR, surgical aortic valve replacement; TAVR, transcatheter aortic valve replacement.

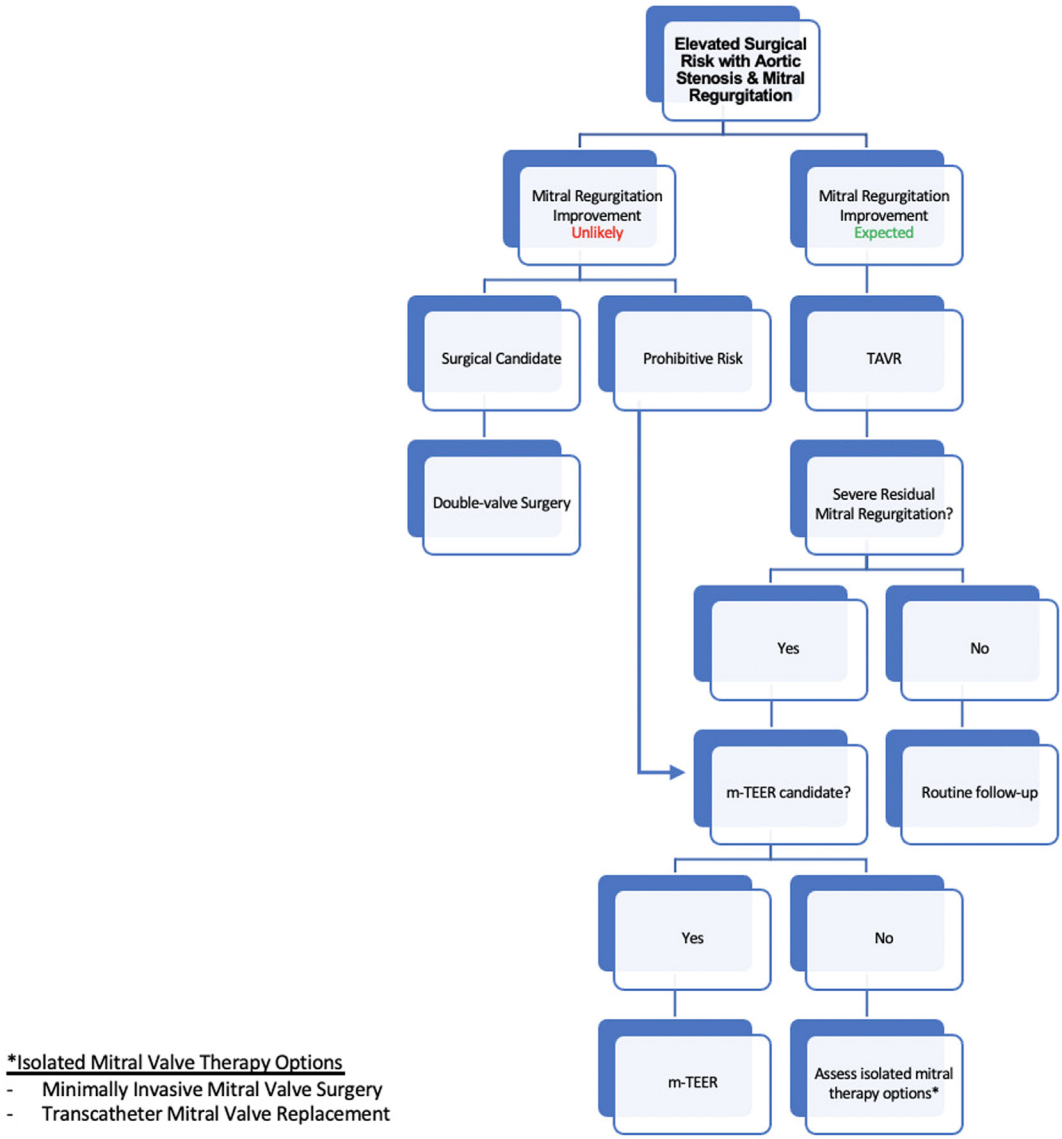

Figure 2. Treatment algorithm for severe AS and MR. This figure describes an algorithm for the management of combined aortic stenosis and mitral regurgitation in the high-risk surgical patient. When MR is not expected to improve after TAVR, the option is for double-valve surgery (high-risk) vs. the TAVR first approach. In cases where TAVR is performed and there is severe residual MR, there are options for m-TEER (preferred) vs. other isolated mitral valve therapy options (i.e., transcatheter mitral valve replacement or minimally invasive mitral valve surgery).
Abbreviations: AS, aortic stenosis; MR, mitral regurgitation; TAVR, transcatheter aortic valve replacement; m-TEER, mitral transcatheter edge-to-edge repair.

MAC renders planimetry difficult in many patients. Yet, elevation in transmitral gradients can be multifactorial, and up to half of patients that present with combined MS in the context of severe concomitant AS are actually "pseudo-severe," whereby the transmitral gradients and MVA calculation improve after TAVR.[26]

Therapy Considerations

Double valve surgery is recommended for patients that undergo aortic valve surgery with MVA <1.5 cm^2.[3] However, the mortality risk with combined mitral and aortic replacement increases significantly compared to single-valve intervention.[4,27] Additionally, many of the combined MS/AS in the elderly population are due to calcific MS, which is associated with higher surgical risks.[28] In select anatomies amenable to percutaneous balloon mitral valvuloplasty (PBMV), a fully transcatheter approach with both TAVR and PBMV could be an option.[29,30] However, presently, there are no federal drug administration (FDA)-approved transcatheter treatments for calcific MS, which is the most frequently encountered pathology accounting for MS in elderly patients with calcific AS.[28] There is emerging data on balloon-expandable transcatheter heart valves (THVs) in MAC, which has been performed off-label with THVs indicated for the aortic space. Unfortunately, this technique is associated with high rates of mortality, paravalvular leak, acute valve embolization during deployment, and iatrogenic LV outflow tract obstruction.[31,32] Development of dedicated transcatheter mitral valve replacement systems for MAC have shown early promise, though some devices require transapical access and many patients are not candidates for these devices due to anatomical constraints.[33,34] Table 1 summarizes some of the current options for the treatment of calcific mitral disease (Table 1: Transcatheter options for calcific MS in development). Since a significant proportion of patients may exhibit "pseudo-severe" MS following aortic valve intervention, it might be reasonable to perform TAVR and consider a staged procedure for MS if still clinically indicated.[26]

Table 1
Transcatheter options for calcific MS in development

Transcatheter therapy	Description	Notes
ViMAC (Valve-in-MAC)	A balloon-expandable THV is deployed in the mitral space.	High rates of mortality/PVL/valve embolization, and iatrogenic LVOTO
Tendyne (Abbott, Minneapolis, MN)	Bioprosthetic valve with apical tether, i.e., deployed transapically via a left lateral thoracotomy without the need for CPB	Feasibility Study of the Tendyne Mitral Valve System in Mitral Annular Calcification. (NCT03539458)
Intrepid (Medtronic, Minneapolis, MN)	Bioprosthetic valve with 35Fr delivery, available via TSP or transapical approach without the need for CPB	>50% excluded from the trial due to high risk of LVOTO APOLLO Trial (NCT03242642) accepting patients in the "MAC arm" No published cases of TSP approach for MAC

Notes. This table lists transcatheter options for calcific mitral valve disease. THV in MAC has been performed, albeit at high rates of PVL, LVOTO, and embolization. The other transcatheter approaches in trial are available via transapical or TSP approach and avoid the need for CPB.
Abbreviations: CPB, cardiopulmonary bypass; LVOTO, left ventricular outflow obstruction; MAC, mitral annular calcification; MS, mitral stenosis; PVL, paravalvular leak; THV, transcatheter heart valve; TSP, transseptal; ViMAC, valve-in-MAC.

Aortic Stenosis and Tricuspid Regurgitation

Background

The combination of AS with significant TR occurs in ~10% to 30% of patients that undergo TAVR[35–38] and is associated with increased mortality compared to patients without significant TR.[39] Functional TR most often arises from volume and pressure overload due to left-sided valve disease and myocardial dysfunction. As the stage of AS advances, right-sided myocardial remodeling and further exacerbation of TR may occur.[10] Hence, it is unclear if worsened clinical outcomes with AS/TR compared to isolated AS are directly related to the TR or due to a complex interplay of underlying pathologies.[36,38]

According to the literature, ~15% to 50% of patients have TR regression after TAVR.[36–40] Thus, the majority of patients will experience no reduction in regurgitation, with an additional small percentage (~5%) experiencing worsening of TR.[38,40] Other factors, such as the possibility of pacemaker insertion after TAVR, may impact TR grade.[41] Risk factors such as the presence of atrial fibrillation, tricuspid annular dilation (>40mm), LVEF <40%, and massive TR have been associated with persistent/symptomatic TR after TAVR.[3,36–40]

Therapy Considerations

Combined SAVR with tricuspid valve repair would be favored in a lower-risk surgical patient.[3] Otherwise, a TAVR-first strategy with clinical reassessment of TR may be reasonable, especially among patients when TR regression is likely.[42] With multiple transcatheter tricuspid valve intervention (TTVI) devices showing promising data, future transcatheter intervention for TR is an option.[43,44] If TR fails to regress after TAVR, TTVI may present itself as a plausible alternative.[45] Therefore, it is essential to thoroughly evaluate the mechanism of TR and consider potential transcatheter options before proceeding (Table 2: A summary of TTVI options). Typically, the preoperative workup for AS does not involve transesophageal echocardiography, which is a vital component of the TR workup when considering transcatheter options. However, preoperative cardiac computed tomography angiography and transthoracic echocardiography are standard for TAVR workup, in which important information for TTVI may be obtained.[43,46] Figure 3 describes factors that could help the decision for surgical treatment (including aortic valve replacement and tricuspid valve repair) vs. a transcatheter approach (TAVR-first strategy, followed by clinical reassessment of the TR and possible TTVI downstream) (Figure 3: Factors favoring surgery or transcatheter approach in patients with severe aortic stenosis and tricuspid regurgitation).

Mitral Regurgitation and Tricuspid Regurgitation

Background

Functional TR commonly develops secondary to the long-term sequalae of increased left atrial pressure in patients with MR. Among patients that undergo m-TEER, the presence of >moderate TR is ~15-40%,[47–50] and is associated with decreased survival and quality of life

Table 2
Transcatheter tricuspid valve intervention options

Transcatheter tricuspid valve intervention	Lead devices	Optimal candidate	Concerning anatomic features
Edge-to-edge repair	TriClip (Abbott, Minneapolis, MN) PASCAL (Edwards Lifesciences, Irvine, CA)	Degenerative or functional TR with small coaptation gap	• Large coaptation gap • Poor imaging windows • CIED-induced TR • Complex leaflet morphology
Orthotopic valve replacement	EVOQUE (Edwards Lifesciences, Irvine, CA) LuX-Valve (Ningbo Jenscare Biotechnology Co, Ningbo, China) GATE (NaviGate Cardiac Structures, Lake Forest, CA, USA)	Able to treat large coaptation gaps Feasible to perform with CIED-induced or CIED-related TR	• Significant IVC/SVC to tricuspid annulus angulation • Severe right ventricular dysfunction • Excessive tricuspid annular dilation • CIED lead without sufficient slack
Annuloplasty	Cardioband (Edwards Lifesciences, Irvine, CA)	Atrial functional TR	• Course of the RCA in proximity to the annular plane • Severely tethered leaflets • CIED-induced, primary, or ventricular functional TR
Caval valve implantation (heteroteopic replacement)	TricValve (P + F Products, Vienna, Austria) Tricento (Medira AG, Balingen, Germany)	Patients that are not good candidates for repair or replacement (coaptation gap, annular dimensions, and CIED presence are not anatomical issues for CAVI)	• Severe right ventricular dysfunction (TAPSE <16 mm) • Small distance from hepatic vein to cavo-atrial junction • Extremely large caval dimensions

Notes. This table lists transcatheter tricuspid valve intervention options, including lead devices, optimal candidates, and features that may preclude their use.
Abbreviations: CAVI, caval valve implantation; CIED, cardioimplantable electronic device; IVC, inferior vena cava; RCA, right coronary artery; SVC, superior vena cava; TAPSE, tricuspid annular plane systolic excursion; TR, tricuspid regurgitation.

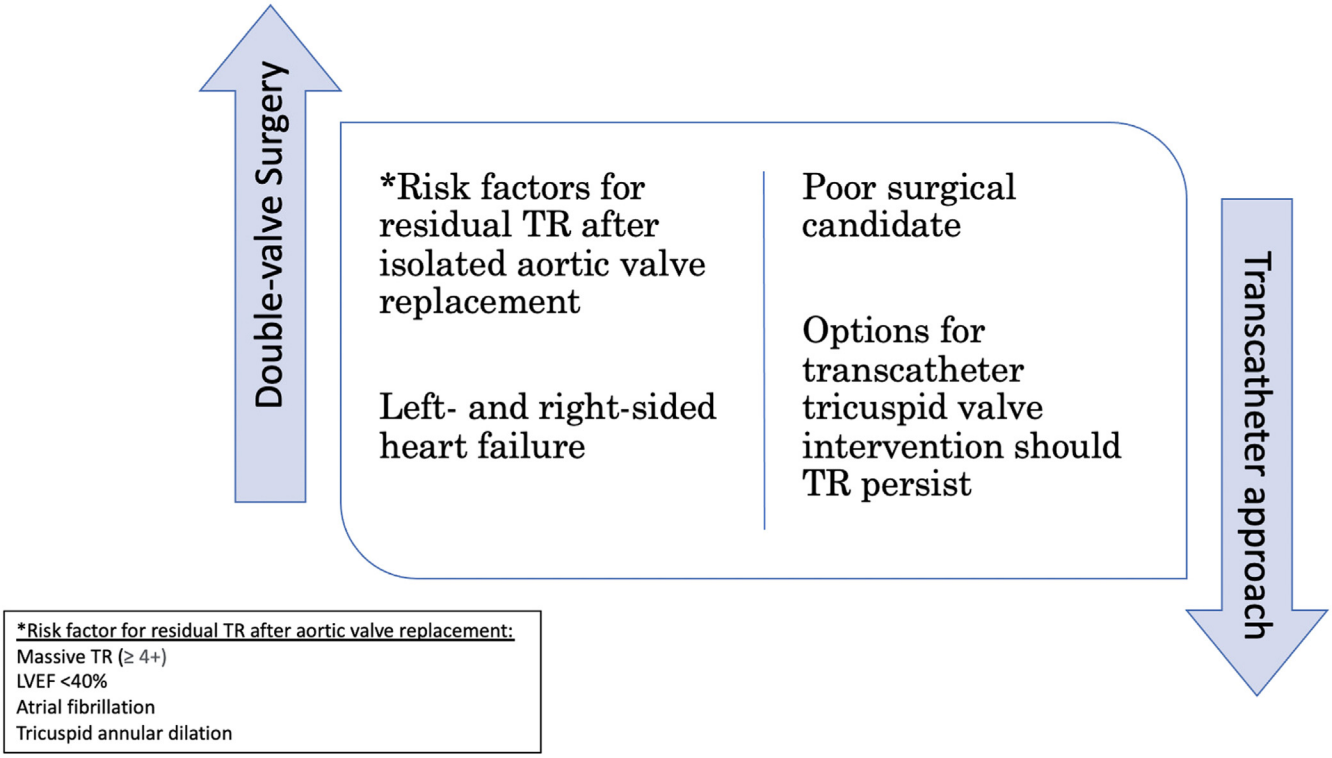

Figure 3. Factors favoring surgery or transcatheter approach in patients with severe aortic stenosis and tricuspid regurgitation. This figure illustrates the major factors favoring surgery or transcatheter approach in patients with severe aortic stenosis and TR.
Abbreviations: LVEF, left ventricular ejection fraction; TR, tricuspid regurgitation.

compared to those without.[51–53] An increase in pulmonary pressure from MR backflow gradually triggers the process of pulmonary arteriolar remodeling resulting in increased pulmonary vascular resistance. In the early stages of MR/TR, pulmonary pressures are likely to be lower with isolated postcapillary pulmonary hypertension (pHTN). However, long-standing valvular regurgitation leads to precapillary and postcapillary pHTN, which may complicate the clinical scenario. As TR develops, the impact of concomitant regurgitation increases the global regurgitant load on the heart, which has a deleterious long-term effect.[53]

There are multiple mechanisms by which chronic MR can induce significant TR, including a gradual increase in pulmonary pressures resulting in right ventricular (RV) dilation/dysfunction. The presence of

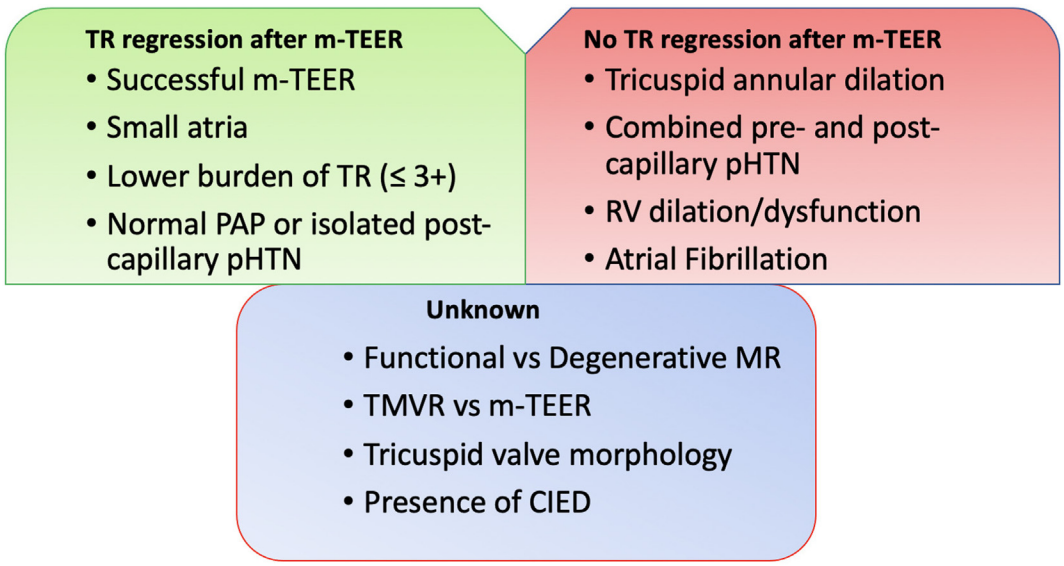

Figure 4. Clinical and echocardiographic predictors for tricuspid regurgitation regression after m-TEER. This figure illustrates some of the known and unknown predictors for having residual tricuspid regurgitation after m-TEER.
Abbreviations: CIED, cardiac implantable electronic device; MR, mitral regurgitation; m-TEER, mitral transcatheter edge-to-edge repair; PAP, pulmonary artery pressure; pHTN, pulmonary hypertension; RV, right ventricular; TMVR, transcatheter mitral valve replacement; TR, tricuspid regurgitation.

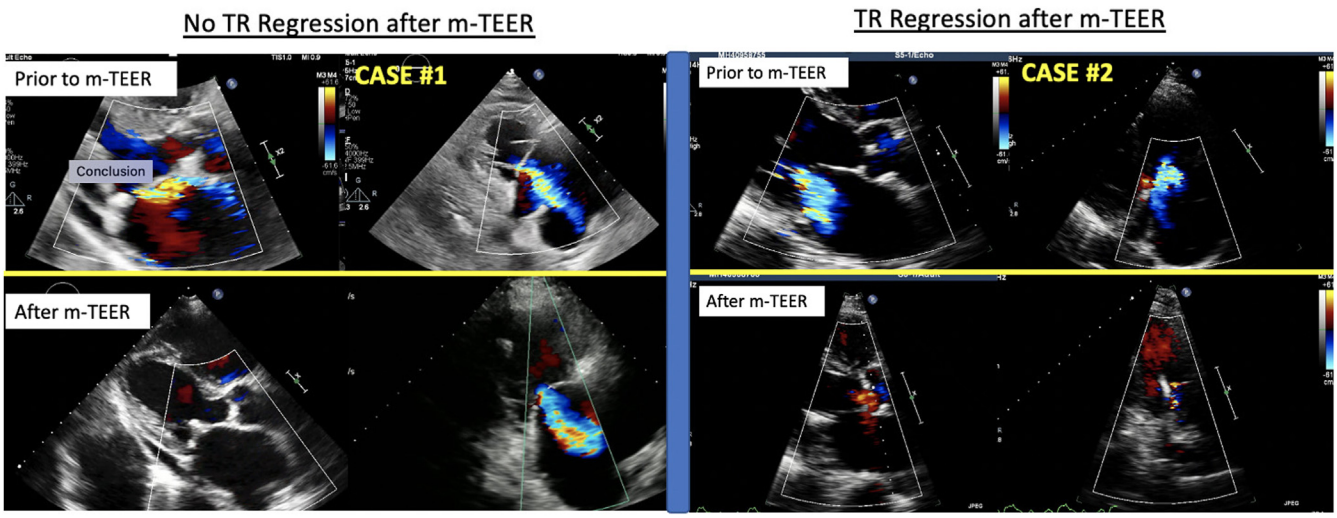

Figure 5. Example of combined mitral and tricuspid regurgitation cases. This figure illustrates variable cases of TR regression after m-TEER. Case #1 is an 80-year-old female with degenerative MR and severe TR with no resolution of TR despite successful m-TEER. Images on the left side show parasternal long-axis on transthoracic echocardiography with Doppler imaging showing severe mitral regurgitation prior to m-TEER (upper) and no MR after m-TEER (lower). On the right side is Doppler imaging of the tricuspid valve showing tricuspid regurgitation prior to m-TEER (upper) and no improvement in TR after m-TEER (lower). Case #2 is a 70-year-old male with functional MR, defibrillator, and severe TR who experienced improvement in TR after successful m-TEER. Images on the left side show parasternal long-axis on transthoracic echocardiography with Doppler imaging showing severe mitral regurgitation prior to m-TEER (upper) and trace MR after m-TEER (lower). On the right side, Doppler imaging of the tricuspid valve reveals severe tricuspid regurgitation prior to m-TEER (upper) and significant improvement in TR after m-TEER (lower).
Abbreviations: MR, mitral regurgitation; m-TEER, mitral transcatheter edge-to-edge repair; TR, tricuspid regurgitation.

TR itself leads to further RV and tricuspid annular remodeling that may continue to worsen TR, a dysfunctional cycle.[54] Additionally, chronic atrioventricular valve regurgitation may stimulate the occurrence and/or development of atrial fibrillation leading to annular dilation, which may further promote atrial functional regurgitation. When the MR is treated, improvement of left-sided volumes could result in the reduction of TR. However, the amount of TR reduction after isolated m-TEER is variable, and most patients do not have significant echocardiographic improvement in TR.[47,55] (Figure 4: Clinical and echocardiographic predictors for TR regression after m-TEER) Additionally, clinical and echocardiographic predictors of TR improvement after isolated mitral valve therapy are still not well understood[47,48,56,57] (Figure 5: Example of combined mitral and tricuspid regurgitation cases).

Table 3
Simultaneous vs. staged transcatheter mitral and tricuspid intervention

Therapy	Simultaneous m-TEER/t-TEER	Staged m-TEER/t-TEER
Advantage	No delay in TR therapy and further structural right heart remodeling Avoids a second invasive procedure under general anesthesia	Avoids possible overtreatment of patients that would have TR regression "Prehab" prior to TR may be better tolerated with abolishment of MR, further reduction of coaptation gap prior to t-TEER
Disadvantage	Possible higher risk of MACE and/or esophageal injury due to longer esophageal intubation duration Operator/Imager fatigue Additional use of dedicated t-TEER device	Additional hospitalization Delay in TR therapy with subsequent clinical and/or structural repercussions.

Notes. This table describes the advantages and disadvantages associated with performing TEER simultaneously on the mitral and tricuspid valves compared to employing a staged approach, wherein m-TEER is performed first, followed by t-TEER at a later time.
Abbreviations: MACE, major adverse cardiovascular events; m-TEER, mitral TEER; TEER, transcatheter edge-to-edge repair; TR, tricuspid regurgitation; t-TEER, tricuspid TEER.

Therapy Considerations

As the field of transcatheter mitral and tricuspid interventions is still growing, much of our understanding derives from the surgical literature. In patients that undergo mitral valve surgery with ≥ moderate TR or tricuspid annular dilation (>4cm), guidelines support concomitant tricuspid valve repair to improve long-term outcomes.[3] Performing simultaneous tricuspid valve repair during mitral valve surgery has not been associated with an increase in procedural morbidity and mortality (albeit an increase in pacemaker implants exists among those that receive tricuspid therapy).[58,59] Consequently, managing concomitant MR and TR within the surgical population is more straightforward with the ability to simultaneously repair both valves.[58–62] However, until recent FDA approval of transcatheter treatments for the tricuspid valve, transcatheter therapy was limited to isolated mitral treatment which is likely less effective than dual-valve therapy.[60–62] Fortunately, the mounting data in favor of TTVI, specifically tricuspid transcatheter edge-to-edge repair (t-TEER), may lead to the approval of commercially available devices soon.[44,45] Transcatheter mitral and tricuspid valve repair (TMTVR) should improve outcomes in this patient cohort, as suggested in retrospective literature.[63] Nevertheless, t-TEER is not suitable for all patients, and outcomes may differ depending on individual anatomical considerations.[64] Therefore, careful transesophageal echocardiography evaluation is required to assess tricuspid leaflet morphology, possible cardiac implantable electronic device-induced disease, and right-sided dimensions before assuming that t-TEER is an option. Atrial functional regurgitation is a widely recognized mechanism of MR and TR. Medical management and rhythm control are essential for such patients before valvular intervention.[12]

As TMTVR becomes more widely adopted, it will be essential to assess the conversation surrounding concomitant MR/TR repair vs. a staged approach. For patients whose isolated m-TEER has a better chance of promoting TR regression, a staged approach might be a more reasonable choice. If TR regression is not anticipated in these patients, it may be advisable to perform concurrent TMTVR rather than postponing tricuspid intervention. Table 3 discusses the advantages and disadvantages of simultaneous vs. staged TMTVR (Table 3: Simultaneous vs. staged

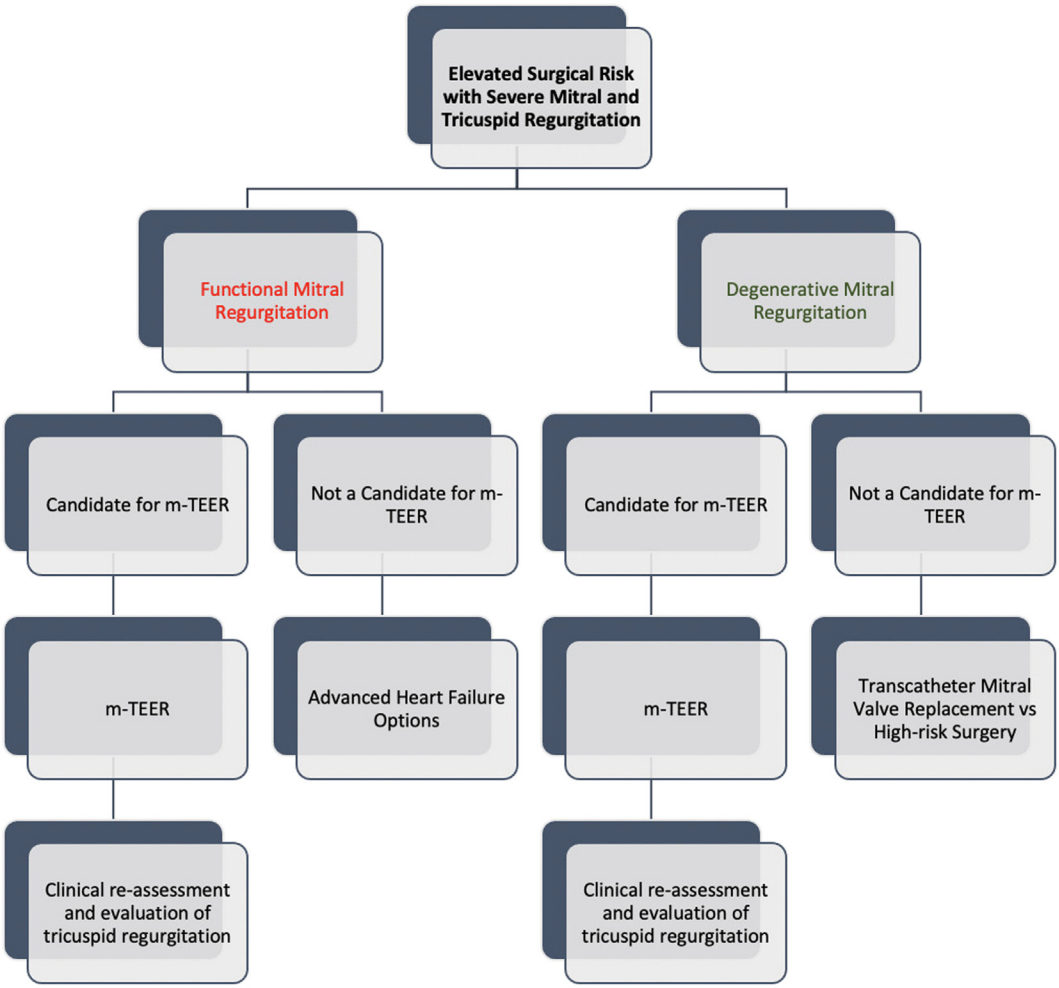

Figure 6. Algorithm for mitral and tricuspid regurgitation. This figure shows an algorithm for the approach to combined mitral and tricuspid regurgitation in a high-surgical-risk patient.
Abbreviation: m-TEER, mitral transcatheter edge-to-edge repair.

transcatheter mitral and tricuspid intervention). Furthermore, etiology of MR (functional vs. degenerative), the impact of pHTN (combined vs. postcapillary), and newer echocardiographic predictors such as right ventricular/pulmonary artery uncoupling[65,66] must be incorporated into heart team discussions prior to decisions for transcatheter, surgical, advanced heart failure, or palliative therapy. Figure 6 suggests an algorithm for the management of MR/TR (Figure 6: Algorithm for mitral and tricuspid regurgitation).

Table 4
Transcatheter options for severe aortic insufficiency

Device	Mechanism	Notes
Off-label use of commercially available THVs	Oversizing an balloon- or self-expandable THV designed for AS	~20% risk of PPM ~20% risk of need for 2nd THV for > mod residual AI
Jenavalve (Jenavalve Technology, Irvine, CA)	Transfemoral, self-expanding valve that anchors between 3 graspers (that attach to the native leaflets) and a sealing ring.	ALIGN-AR EFS trial (NCT04415047) Designed for native trileaflet valves
J-Valve (JC Medical Inc, Burlingame, CA)	Transfemoral, self-expandable THV with 3 U-shaped anatomically orientating claspers.	J-Valve Compassionate Use (NCT03876964) Designed for native trileaflet valves

Notes. This table lists options for transcatheter treatment in patients with severe isolated aortic insufficiency, describes the mechanism of treatment, and notes the progress of the developing technologies.
Abbreviations: AI, aortic insufficiency; AS, aortic stenosis; PPM, permanent pacemaker; THV, transcatheter heart valve.

Mitral Regurgitation and Aortic Insufficiency

Background

The combination of aortic insufficiency (AI) and MR is common and has been associated with worsening clinical outcomes compared to isolated mitral valve disease.[67] Simultaneous degenerative diseases are becoming more commonly recognized in the elderly population. However, secondary MR may also result from the LV compensatory remodeling that occurs with chronic AI.[68] An increase in LV preload from both regurgitant valves may further accelerate LV dilatation and dysfunction.[69]

Echocardiographic volumetric quantification is generally not accurate due to alterations in the mitral and aortic forward flow.[70] For AI quantification, the use of PHT has limited value due to the rapid early diastolic filling from MR. Thus, a cardiac magnetic resonance imaging should be considered if more accurate quantification is desired.[70] There is a paucity of data regarding how treatment of antecedent AI affects the severity of MR. Correction of AS may lead to improvement of MR [18,71]; however, MR improvement after aortic insufficiency treatment is not well understood.

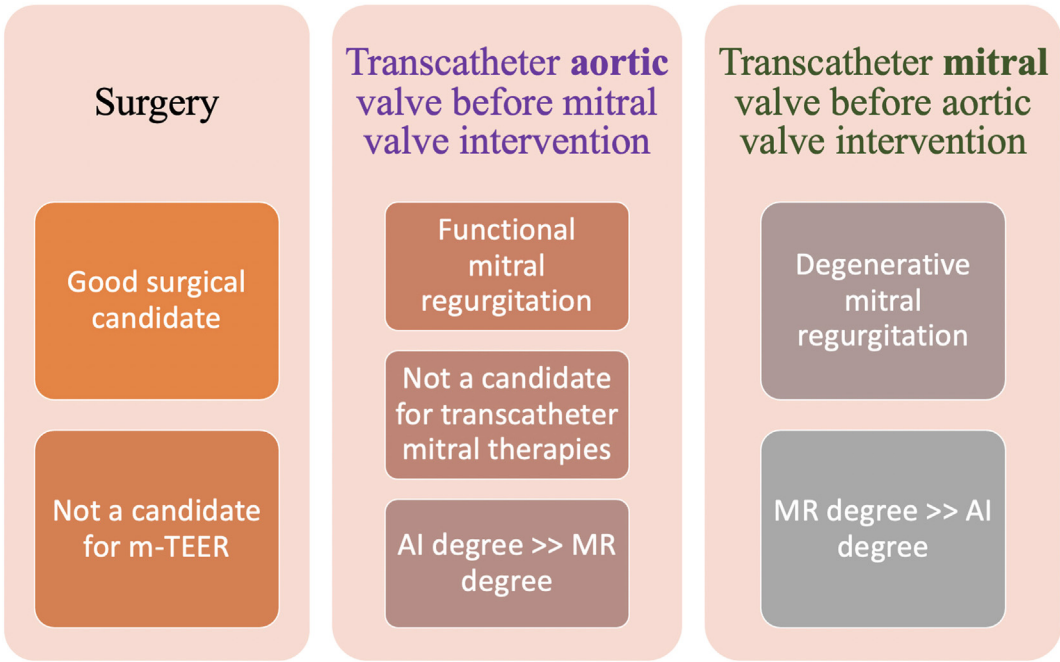

Figure 7. Considerations for surgery vs. transcatheter approach for concomitant aortic and mitral insufficiency. The figure describes factors that favor each approach to combined aortic and mitral insufficiency: 1) double valve surgery; 2) transcatheter aortic valve intervention before addressing the mitral insufficiency; and 3) transcatheter mitral valve treatment before addressing the aortic insufficiency.
Abbreviations: AI, aortic insufficiency; MR, mitral regurgitation; m-TEER, mitral transcatheter edge-to-edge repair.

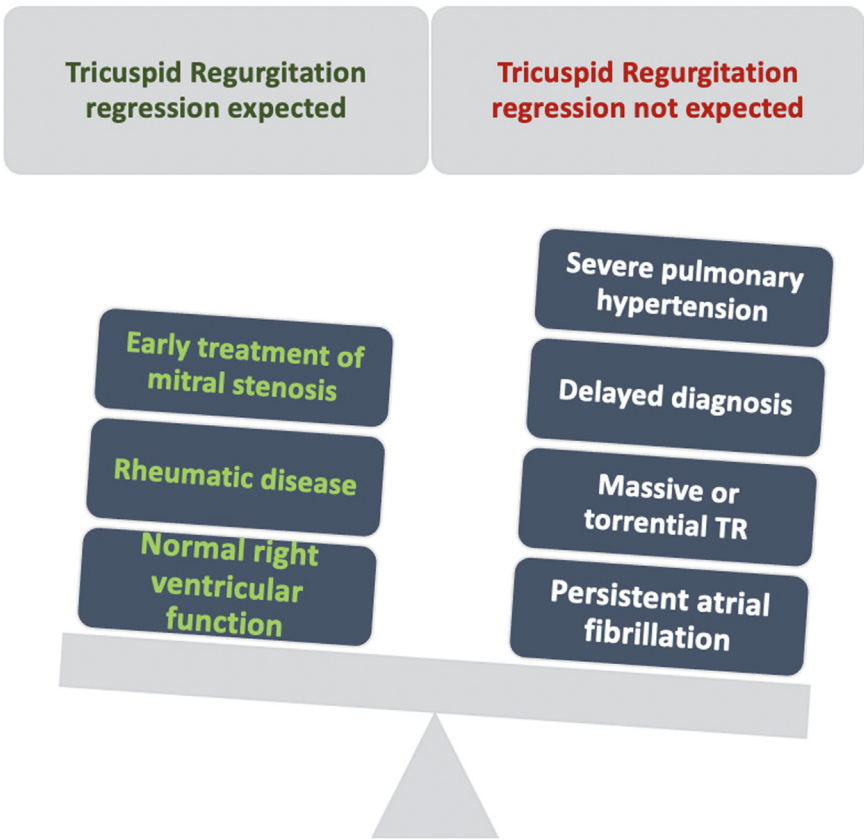

Figure 8. Expected tricuspid regurgitation regression after isolated mitral stenosis treatment. This figure illustrates factors in which tricuspid regurgitation regression is expected vs. not expected after isolated mitral valve therapy in patients with combined mitral stenosis and tricuspid regurgitation.
Abbreviation: TR, tricuspid regurgitation.

Table 5
Overview of common simultaneous valvulopathies encountered in daily practice

Valvular disease	Etiology	Diagnostic challenges	Transcatheter therapy pearls
Aortic stenosis and mitral regurgitation	Etiologies include degenerative MR vs. functional MR. Functional MR may occur from LV remodeling due to AS, concomitant ischemic heart disease, atrial functional MR (commonly from long-standing atrial fibrillation).	Lower transaortic gradients from reduced systolic flow across aortic valve (akin to LFLG AS) may delay diagnosis of severe AS. Higher LV pressure from AS can make MR appear worse (increased afterload).	MR may improve after TAVR by 1+ or greater in ~half of patients. A greater MR reduction is expected for functional MR than degenerative MR.
Aortic stenosis and mitral stenosis	Etiologies include rheumatic, calcific, or radiation-induced. Rheumatic heart disease is more common in nonindustrialized countries. Calcific MS is more prevalent in the elderly population in industrialized countries.	Lower transaortic gradients from reduced systolic flow across aortic valve (akin to LFLG AS) may delay diagnosis of severe AS. Inaccurate MVA calculations; PHT may be impaired due to LV diastology; continuity equation overestimates MVA due to low output.	Transmitral gradients and MVA calculations on echo may improve after TAVR in up to half of patients. MS treatment prior to aortic valve replacement increase the risk of acute decompensated heart failure.
Aortic stenosis and tricuspid regurgitation	Functional TR may be a result of cardiac remodeling due to an advanced stage of AS. Other left-sided heart disease (i.e., diastolic dysfunction, pHTN) may result in functional TR.	TR degree is impacted by volume status; it may be difficult to diurese AS patients' to euvolemia, so true assessment of TR degree is difficult to assess. Low-output state from severe TR could reduce cardiac output/aortic valve gradients (LFLG AS).	TR regression after TAVR occurs in 15%-50% of patients. Risk factors for residual/symptomatic TR after TAVR; atrial fibrillation, tricuspid annular dilation (>40mm), LVEF <40% and massive TR
Mitral regurgitation and tricuspid regurgitation	Functional TR commonly develops from sequalae of chronic MR. Combined precapillary and postcapillary pHTN may complicate long-standing MR with TR.	Pulmonary artery pressure may be underestimated in the presence of severe TR. Volume status may alter severity of both atrioventricular valves.	TR reduction after m-TEER is variable, >1+ TR reduction is uncommon. Simultaneous m-TEER and t-TEER have been performed safely.
Mitral regurgitation and aortic insufficiency	Combined degenerative AI/MR more commonly recognized in the elderly population. Functional MR may occur due to chronic AI and LV remodeling.	Echocardiographic volumetric quantification generally inaccurate with sequential regurgitant lesions. Use of PHT for AI quantification is falsely reduced due to rapid early diastolic filling from MR.	A reduction in MR should not impact AI degree. Correction of AI might improve functional MR due to LV remodeling. Paucity of data on long-term outcomes in this population.
Calcific mitral stenosis and tricuspid regurgitation	Functional TR commonly develops with long-standing calcific MS. Atrial-functional TR may result from development of atrial fibrillation. RV dysfunction results from chronically elevated pulmonary pressures.	Echocardiographic diagnosis of calcific MS limited by multiple factors (i.e., artifacts, inaccurate Doppler gradients from impaired LV compliance). Therefore, calcific MS often recognized at a later stage, when TR has progressed.	>1/2 of patients do not have regression of TR after isolated mitral therapy. The likelihood of TR regression further decreases in patients with long-standing MS.

Abbreviations: AI, aortic insufficiency; AS, aortic stenosis; CIED, cardiac implantable electronic device; LFLG, low-flow, low-gradient; LV, left ventricular; LVEF, left ventricular ejection fraction; MAC, mitral annular calcification; MR, mitral regurgitation; MS, mitral stenosis; m-TEER, mitral transcatheter edge-to-edge repair; MVA, mitral valve area; PHT, pressure half-time; pHTN, pulmonary hypertension; PBMV, percutaneous balloon mitral valvuloplasty; RV, right ventricular; TAVR, transcatheter aortic valve replacement; TEER, transcatheter edge-to-edge repair; TR, tricuspid regurgitation; t-TEER, tricuspid TEER.

Therapy Considerations

With correction of severe AI, LV dimensions and function frequently improve.[72] However, a reduction in LV function is expected after correction of MR due to the change in loading conditions. Therefore, while patients with severe LV systolic impairment are often precluded from mitral surgery, it is unclear if the AI/MR cohort of patients will have fewer issues with postoperative LV function after double-valve surgery. In heart-team discussions, it is crucial to incorporate this information when evaluating the risk of surgery.

An initial transcatheter strategy in the AI/MR population is difficult since there are no US regulatory approved devices for AI. Development of dedicated transcatheter devices for AI has lagged compared to the AS population due to several factors: 1) lack of calcification that serves as a docking space for THV deployment; 2) larger aortic annuli than the general population/AS population; 3) aortic root dilation. However, optimism exists that transcatheter devices for AI are on the horizon, with Jenavalve (JenaValve Technology, Irvine, CA) and J-Valve (JC Medical Inc, Burlingame, CA) enrolling in pivotal US trials.[73,74] Additionally, THVs designed for AS have been employed "off-label" in patients with AI, though this approach is associated with increased risks of complications such as paravalvular leak and valve embolization[75] (Table 4: Transcatheter options for severe aortic insufficiency).

In patients who are at prohibitive risk for surgery, transcatheter mitral therapy may improve clinical symptoms for degenerative MR but should bear no effect on the degree of AI. Hence, an effective strategy in such patients may involve pursuing isolated mitral therapy with vigilant clinical monitoring while keeping the option open for potential transcatheter aortic valve intervention in the future, using either newly approved devices or "off-label" THV, for patients who do not show clinical improvement. The concern with isolated mitral therapy in the AI/functional MR population is that persistent LV stress from untreated AI may render the isolated mitral therapy ineffective. Therefore, in such patients', aortic intervention would be hypothetically favored as a first step. Figure 7 describes factors that would favor each treatment algorithm for combined MR/AI (Figure 7: Considerations for surgery vs. transcatheter approach for concomitant aortic and mitral insufficiency).

Calcific Mitral Stenosis and Tricuspid Regurgitation

Background

In the aging population, the predominant cause of MS is due to degenerative and calcific changes. Over time, calcific MS and the comorbidities associated with it predispose patients to the development of TR.[76] Individuals diagnosed with calcific MS face a grim long-term outlook, with approximately 50% mortality within 5 years.[77] Furthermore, the presence of both calcific MS and functional TR is associated with an even more pronounced reduction in survival.[77]

The progression of MS often coincides with progressive RV dysfunction and functional TR due to factors including elevated pulmonary pressures and the development of atrial fibrillation.[78–81] Echocardiographic assessment of calcific MS is fraught with difficulties (see AS/MS section above); therefore, many of these patients have a delayed diagnosis.[82] This delay allows for more time to develop sequalae associated with long-standing MS, which is why concomitant calcific MS and severe

TR is so prevalent. Hence, early treatment of MS could prevent the development of TR and right-sided dysfunction. Once TR develops, most patients with concomitant MS do not have TR improvement after isolated mitral valve therapy,[83] and the probability of TR regression diminishes with long-standing MS.[84] Consequently, the combination of mitral and tricuspid surgery has been linked to superior clinical outcomes compared to solely percutaneous mitral valve therapy in patients with concomitant MS/TR.[83] As transcatheter treatment for calcific MS has only recently gained momentum, this data derives from a different population (rheumatic), but the implications are similar. Early treatment of mitral disease improves chances of TR reduction.

Therapy Considerations

Having significant TR is a factor that tends to discourage the use of PBMV in rheumatic heart patients, with surgery often being the preferred option.[3,83] Nonetheless, in cases of calcific MS, the presence of MAC elevates the surgical risks, and many of these patients are not suitable candidates for surgery due to technical and/or clinical limitations.[85,86] Hence, there is a growing emphasis on exploring transcatheter options for calcific MS. When addressing concurrent cases of calcific MS and TR, it is important to consider that calcific MS often represents a chronic, longstanding condition on the left side of the heart, which is typically associated with a lower probability of TR regression.[84] Consequently, if successful isolated MS therapy is achieved, the issue of residual TR is expected. This underscores the motivation to explore TTVI options as we progress toward more comprehensive transcatheter solutions for calcific MS/TR. Figure 8 illustrates a pendulum for when TR regression can be expected after isolated MS treatment (Figure 8: Expected tricuspid regurgitation regression after isolated mitral stenosis treatment).

Discussion

This review paper delves into some of the more common simultaneous valvulopathies seen in daily practice to discuss the diagnostic challenges and therapeutic considerations. Frequently, only one valvular lesion can be treated via transcatheter approach, which may not improve the secondary valvular issue. The clinical benefits of this treatment could be compromised by the persistence of the remaining valvular issue. Therefore, understanding the mechanism of isolated valve therapy and its influence on concomitant valvulopathy is essential. Table 5 provides a comprehensive summary encompassing the etiological factors, diagnostic challenges, and considerations for isolated transcatheter therapy (Table 5: Overview of common simultaneous valvular pathologies encountered in daily practice).

Because there is a paucity of randomized controlled trials data on therapy for MVHD, the existing guidelines primarily rely on non-randomized surgical literature for guidance.[3] The key distinction between the surgical and transcatheter populations lies in the consideration that staged interventions may not be a viable option due to the escalating risks associated with repeat cardiac surgeries.[87] Consequently, the era of transcatheter therapy has introduced an unprecedented opportunity for staged interventions without a concurrent rise in risks. A pathway for the management of secondary valvular dysfunction must be discussed in the heart team for patients that are subject to isolated valvular therapy. Several considerations should be addressed by the heart team in addition to patient/family wishes: 1) the risk of surgery; 2) options for transcatheter therapy; 3) isolated valve therapy and its potential impact on secondary valvular pathology; 4) future treatment options for valvular issues not being initially addressed; and 5) timing of interventions.

MVHD is often underrecognized as many of the valvular interactions will affect the diagnostic interpretation.[88] Hence, many patients may present at a later stage and are subject to worse outcomes with both surgical and transcatheter intervention.[89] These outcomes may in part stem from the diagnostic difficulties that lead to underestimation of valvular severity in the context of MVHD. This delay in diagnosis may be the root cause of a greater amount of surgical turndown and perioperative morbidity/mortality. Hence, particular focus should be enforced in all patients once multiple-valvular involvement is recognized. Advanced diagnostic imaging, such as cardiac magnetic resonance imaging may be additive tools to echocardiography, as the analysis of each valvular lesion is not impacted by concomitant valvulopathy.[82]

Treatment dogma for valvular intervention has historically focused on the classification of "severe" valvular disease prior to intervention.[3] However, paradigm changes have occurred since our initial observations: 1) The procedural risk of valve intervention has decreased; and 2) Potentially irreversible adverse cardiac remodeling changes are noted to occur before valvular disease is classified as "severe."[10] Hence, the timing of valvular intervention (especially for MVHD) may be more favorable at an early stage. There are several clinical investigations underway regarding the benefit of valvular intervention before reaching the classification of severe and/or symptomatic. (EXPAND TAVR II, NCT05149755, and PROGRESS, NCT04889872) While this review paper focuses on the combination of 2 severe valvular lesions, further scrutiny of MVHD with 1 severe/1 moderate and even 2 moderate valvular issues are warranted. Additionally, timing for staged transcatheter procedures is of paramount importance to incorporate into the treatment algorithm. Some secondary valvular pathologies will improve at a quicker rate than others. For example, functional regurgitation improvement requires ventricular remodeling, which may require months. Therefore, the approach to ventricular functional MR after aortic valve intervention should be more delayed than for a patient with degenerative MR. Future studies will need to focus on when to address secondary valvular dysfunction and balance the risk of delaying therapy vs. unnecessary valvular intervention.

Conclusions

MVHD is prevalent in the heart-valve clinic and associated with worsening clinical outcomes. Expansion of transcatheter therapy to the valvular treatment armamentarium has added new opportunities for higher-risk patients; however, the impact of isolated valve therapy is still not well understood. Future research endeavors must focus on the management of MVHD to provide better clinical guidance in this population.

ORCIDs

Craig Basman https://orcid.org/0000-0001-5354-1394

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