Transcatheter Aortic Valve Replacement in Patients With Multivalvular Heart Disease

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ABSTRACT

As transcatheter aortic valve replacement becomes a more dominant treatment option across all risk profiles, the frequency of encountering patients with multivalvular disease will increase. Furthermore, percutaneous interventions to treat other valvular lesions are also evolving. Understanding the clinical implications and treatment options for a second valvular lesion is becoming increasingly important to guide heart team decisions, and this paper aims to review the evidence around these situations. Diagnosis of multivalvular disease can be challenging because of changes in physiology. There are little randomized data to guide therapy in multivalvular disease. Multidisciplinary heart team decisions can be invaluable in integrating the plethora of clinical, hemodynamic, and imaging data on which an optimal management strategy can be planned. Prospective studies to assess the role of structural valve interventions in the transcatheter aortic valve replacement era would greatly help improve outcomes for structural heart patients.


Multivalvular heart disease presents a challenge in terms of diagnosis and treatment. Although the prevalence of rheumatic heart disease has declined in the Western world as the traditional cause of multivalvular disease, the prevalence of degenerative valve disease is increasing as a result of the demographic transition (1). For example, in a population-based study of elderly patients in the United Kingdom, multiple valve involvement was detected in more than one-half of all patients with valvular lesions (2). An increase in primary valvular lesions with advancing age is paralleled by a growing interest in secondary valvular lesions resulting from changes of ventricular geometry and dimension in patients with heart failure.

Treatment of multivalvular disease is associated with an increased risk of adverse outcome. Therefore, the number of patients undergoing multivalvular surgery may underestimate the true burden of disease due to a positive selection of surgical candidates. In the Euro Heart Survey, 1 in 10 surgical valve procedures involved multiple valves, more than half of which included the aortic and the mitral valves (3).
Transcatheter aortic valve replacement (TAVR) is becoming a dominant treatment modality for symptomatic severe aortic stenosis (AS) after iterative advances in both evidence and technology. Treatment of multivalvular disease becomes increasingly complex as a wider range of patients may be potentially eligible for transcatheter interventions. The recommendation for a heart team discussion to decide the most appropriate treatment plan on an individual basis will take into account a wide range of anatomical and clinical factors. This review aims to lay out the evidence for various strategies when managing symptomatic severe AS and additional valvular lesions.

### Highlights
- MR is the most common valvulopathy in TAVR patients, followed by TR, MS, and AR.
- Both coexistent MR and MS may result in underestimation of AS and portends a worse outcome after TAVR.
- AR at baseline may be protective against the deleterious effects of post-TAVR paravalvular leak.
- Further research is needed to define the timing and role of tricuspid intervention.

### Abbreviations and Acronyms
- AR = aortic regurgitation
- AS = aortic stenosis
- CI = confidence interval
- HR = hazard ratio
- LV = left ventricle/ventricular
- PAR = paravalvular aortic regurgitation
- MR = mitral regurgitation
- MS = mitral stenosis
- MVA = mitral valve area
- RV = right ventricle/ventricular
- TAVR = transcatheter aortic valve replacement
- TR = tricuspid regurgitation

### TAVR in Patients with Combined Aortic Stenosis and Aortic Regurgitation

#### Pathophysiological Considerations
Mixed AS and regurgitation represents a complex pathophysiology and diagnosis of this entity using conventional methods may have caveats. The stenotic component increases afterload, causing concentric LV hypertrophy, while the regurgitant component creates a state of volume overload, resulting in LV enlargement. Both pathologic remodeling processes, namely LV hypertrophy and LV enlargement, are frequently observed and are associated with increases in LV filling pressures. The summative hemodynamic sequelae may not be accurately represented by the traditional thresholds for severe AS such as aortic valve area <1 cm² or severe AR (regurgitant volume >60 ml). Furthermore, the AR pressure halftime method, which is conventionally used to quantify the severity of AR, is not reliable in the context of mixed aortic disease. Therefore, a peak aortic jet velocity >4 m/s and a Doppler mean gradient ≥40 mm Hg have been proposed as important hemodynamic cutoffs in mixed AS and AR as they not only indicate an increased flow state of both lesions but have also been shown to correlate with outcomes (4,5). At this juncture, patients with both moderate AS and moderate aortic regurgitation (AR) should be referred for intervention if the criteria for increased flow are met, namely peak aortic jet velocity >4 m/s and Doppler mean gradient ≥40 mm Hg, even if the aortic valve area is ≥1 cm² and pressure half-time is ≥200 ms.

Concomitant AR increases the end-diastolic volume and stroke volume, potentially overestimating

the transvalvular gradient. Chronic volume overload of the left ventricle (LV) ultimately enlarges ventricular size, which preconditions the LV and may have a protective effect in patients with paravalvular AR (PAR) after TAVR (6). Additionally, the presence of baseline AR increases the rate of PAR after TAVR, although the latter risk is lower with the advent of newer-generation transcatheter heart valves (Table 1).

### Prevalence of Concomitant AR in Patients Undergoing TAVR
Although trivial and mild AR frequently accompany severe degenerative AS, data from observational studies documented a prevalence of more than mild AR at baseline in 17% to 47% of patients (Table 1). Concomitant AR is frequently observed in patients with bicuspid anatomy and patients with rheumatic heart disease.

### Peri-Procedural Challenges of Concomitant AR in Patients Undergoing TAVR
Relevant concomitant AR may complicate visualization and positioning of the transcatheter heart valve, while calcification of the aortic cusps facilitates anchoring within the annulus. In cases of a hyperdynamic jet, rapid ventricular stimulation may also be required for self-expanding valves to stabilize the prosthesis for positioning and deployment.

### Clinical Impact of Concomitant AR
Although the effect of moderate or severe PAR post TAVR is well established, data regarding the effect of concomitant baseline AR on outcomes in patients undergoing TAVR for AS are limited (Table 1). A retrospective study by Egbe et al. (5) found that patients with combined moderate AR and moderate AS had worse outcomes than did those with a single isolated
moderate lesion, and in fact, had similar adverse outcomes to patients with asymptomatic severe AS.

In patients with PAR after TAVR, Hayashida et al. (7) reported increased mortality among those without baseline AR compared with patients with pre-existent AR. Similarly, Jerez-Valero et al. (8) reported that any worsening of the severity of AR (even by 1 grade) relative to baseline with a final severity of moderate to severe was a strong independent predictor of mortality. Moreover, they showed patients with chronic moderate or severe AR (no severity changes compared with baseline AR) had a similar mortality as compared with patients with none or trace PAR at 2-year follow-up (41.0% [acute moderate-to-severe AR] vs. 26.7% [chronic moderate-to-severe AR] vs. 24.5% [none to mild AR]; hazard ratio [HR] comparing none to mild AR: 2.37; 95% confidence interval [CI]: 1.53 to 3.66; HR comparing chronic moderate-to-severe AR: 2.24; 95% CI: 1.17 to 4.30) (8). Van Belle et al. (9) demonstrated that PAR = mild was associated with a 3-fold increase in mortality in patients without baseline AR (HR: 2.94; 95% CI: 2.25 to 3.82) but was not associated with an increased mortality in patients with baseline AR = mild (HR: 0.60; 95% CI: 0.25 to 1.41) at 1-year follow-up. Grayburn et al. (10) reported that patients with = mild baseline AR had improved survival at 1 year as compared with patients without baseline AR in the CoreValve US Pivotal High Risk Trial (9.4% vs. 18.6%; p = 0.008), and this advantage disappeared when excluding patients with = mild PAR (12.4% vs. 18.2%; p = 0.820). Chieffo et al. (11) did not document a beneficial effect of = mild baseline AR in patients with = mild PAR (p = 0.270). Colli et al. (12) also showed no survival advantage of baseline AR in patients with mild or moderate PAR, whereas they demonstrated that LV dilatation in patients with = moderate baseline AR had a protective effect on long-term survival.

Further studies are needed to investigate the possibility of the protective effect of baseline AR and

### TABLE 1 Prevalence of Pre- or Post-Procedural AR in Patients Undergoing TAVR and Impact on Mortality

<table>
<thead>
<tr>
<th>First Author, Year (Ref. #)</th>
<th>n</th>
<th>Baseline AR</th>
<th>Post-Procedural AR</th>
<th>Valve</th>
<th>Duration of Follow-Up</th>
<th>All-Cause Mortality</th>
<th>Baseline AR Increases PAR Rate</th>
<th>Protective Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hayashida et al., 2012 (7)</td>
<td>400</td>
<td>NR</td>
<td>Grade 2 = 22.2%</td>
<td>SAPIEN</td>
<td>2 yrs</td>
<td>28.0% (grade 0–1) vs. 40.4% (grade 2) vs. 75.0% (grade 3–4)</td>
<td>NR</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Grade 3–4 = 3.0%</td>
<td>CoreValve</td>
<td>Median 297 days</td>
<td>Grade 3: HR: 1.68 (95% CI: 1.21–1.44; p &lt; 0.01)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jerez-Valero et al., 2014 (8)</td>
<td>1,735</td>
<td>NR</td>
<td>Grade 2 = 43.9%</td>
<td>SEV, BEV</td>
<td>30 days</td>
<td>4.3% (grade 0–1) vs. 4.6% (grade 2) vs. 11.7% (grade 3–4)</td>
<td>NR</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Grade 3–4 = 14.2%</td>
<td></td>
<td></td>
<td>Grade 3: HR: 2.69 (95% CI: 1.34–5.38; p = 0.005)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Van Belle et al., 2014 (9)</td>
<td>2,769</td>
<td>Grade ≥2 = 17.1%</td>
<td>Grade 2 = 14.7%</td>
<td>SAPIEN</td>
<td>306 days</td>
<td>6.1% (grade 0–1) vs. 5.7% (grade 2–4); p = 0.820</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Grade 3–4 = 11.1%</td>
<td>CoreValve</td>
<td></td>
<td>Grade 2: HR: 2.24 (95% CI: 1.83–2.34; p &lt; 0.0001)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chieffo et al., 2015 (11)</td>
<td>1,062</td>
<td>Grade 2 = 28.4%</td>
<td>Grade 3 = 8.9%</td>
<td>SAPIEN</td>
<td>30 days</td>
<td>12.3% (grade 0–1) vs. 18.1% (grade 2–4); p = 0.032</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Grade 4 = 2.2%</td>
<td>CoreValve</td>
<td>2 yrs</td>
<td>Grade 2: HR: 2.24 (95% CI: 1.517–2.259; p &lt; 0.001)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Colli et al., 2017 (12)</td>
<td>1,708</td>
<td>Grade 2 = 42%</td>
<td>Grade 3–4 = 18%</td>
<td>SAPIEN</td>
<td>Median 827 days</td>
<td>23% (grade 0–1) vs. 29% (grade 2–4); p = 0.05</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Grayburn et al., 2018 (10)</td>
<td>386</td>
<td>Grade ≥1 = 47.2%</td>
<td>Grade ≥1 = 42.2%</td>
<td>CoreValve</td>
<td>1 yr</td>
<td>18.6% (grade 0) vs. 9.4% (grade ≥1); p = 0.008</td>
<td>No</td>
<td>Yes</td>
</tr>
</tbody>
</table>

AR grade: 0 = none, 1 = trace, 2 = mild, 3 = moderate, 4 = severe.

AR = aortic regurgitation; BAR = baseline aortic regurgitation; BEV = balloon-expandable valve; CI = confidence interval; HR = hazard ratio; NR = not reported; OR = odds ratio; PAR = post-procedural aortic regurgitation; SEV = self-expandable valve; TAVR = transcatheter aortic valve replacement.
compensatory LV changes to better understand their complex interplay.

**TAVR IN PATIENTS WITH AS AND MITRAL REGURGITATION**

**PATHOPHYSIOLOGICAL CONSIDERATIONS.** Aortic stenosis increases afterload, resulting in LV hypertrophy and remodeling. As the disease progresses, increasing fibrosis causes worsening LV function and cavity dilatation resulting in mitral annular dilation, leaflet tethering and secondary mitral regurgitation (MR). Coexistent coronary artery disease or alternative pathologies including primary leaflet abnormalities can also contribute to MR.

Elevated LV afterload in the setting of AS exacerbates the transmitral pressure gradient for a given effective orifice area and increases the mitral regurgitant volume. On transthoracic echocardiography, this may manifest with an increased area of MR jet using color flow mapping. Therefore, adjunctive imaging modalities such as cardiac magnetic resonance (CMR) may be used to corroborate the severity of MR. Another important consequence of an increased regurgitant volume across the mitral valve is a decrease in forward flow across the aortic valve. This
low-flow state that can underestimate the degree of AS may manifest as classical low-flow, low-gradient AS or paradoxical low-flow, low-gradient AS in the case of preserved LV systolic function. Dobutamine stress echocardiography might not be an effective means of uncovering the true severity of AS in this clinical context, and computed tomography determination of aortic valve calcium may be a useful way to differentiate pseudosevere AS with severe MR and truly severe AS with low-flow and low-gradient (13,14).

PREVALENCE OF CONCOMITANT MR IN PATIENTS UNDERGOING TAVR. The prevalence of concomitant significant MR (moderate or severe) in TAVR recipients ranges between 11.5% and 36.8% (Table 2). Observational data suggest that the etiology of concomitant MR is degenerative in two-thirds of patients undergoing TAVR (15).

CLINICAL IMPACT OF CONCOMITANT MR. Concomitant MR in patients undergoing TAVR has been well studied, mainly focusing on the prognostic impact and the changes of severity after TAVR. Although concomitant MR has been suggested to increase mortality in patients undergoing TAVR, the data are conflicting (Table 2). Recently, 2 different meta-analyses demonstrated increased short- and long-term mortality in TAVR patients with significant MR (16,17). However, there are several underlying limitations that make it difficult to reach a definitive conclusion.

First, the major limitation is the difficulty of reliable assessment of MR by echocardiography, especially in AS patients (as described previously). Although echocardiographic assessment is the gold standard for MR, any single parameter is insufficient to grade MR, and multiple quantitative and qualitative parameters are recommended. Moreover, the assessment can be more difficult when AS coexists because the color Doppler jet size tends to be larger and overestimates MR severity because of the increased LV pressure in AS patients. Furthermore, temporary changes of MR severity because of patients’ hemodynamics makes this assessment more challenging (13,18-20). For these reasons, multiple diagnostic modalities such as CMR cardiac catheterization, and transesophageal echocardiography should be utilized in patients with AS and MR, with particular attention given to the hemodynamic consequences of these valvular lesions, such as chamber enlargement and LV systolic dysfunction.

Second, the prognosis, evaluation, and management are known to be different between primary and secondary MR (21). In most studies, etiology of MR and the effects on outcomes have not been well studied (Table 2). Although Kiramijyan et al. (22) reported similar short- and long-term survival between secondary and primary MR, Vollenbroich et al. (15) reported increased mortality at 30 days and at 2 years in primary MR as compared with secondary MR in cohorts that were considerably larger than the former study. Primary and secondary etiologies of MR are further subdivided into multiple mechanisms (Table 3), which could also contribute to a variety of clinical courses. Moreover, in some cases, multiple mechanisms are mixed.

Third, dynamic changes of MR severity after TAVR have also been reported and this might affect the impact on mortality. Khawaja et al. (23) reported that patients who had MR deterioration had a poorer outcome than those with an improvement in MR (log-rank \( p = 0.005 \)). Furthermore, Mavromatis et al. (24) reported that patients with improved MR had similar outcomes as patients with no or mild MR at baseline (HR: 0.98; \( p = 0.71 \)). There are limited data regarding the association of incremental severity of post-procedural MR with mortality. Boerlage-van Dijk et al. (25) showed numerically increased risk of mortality in post-procedural MR (=mild) as compared with none or trace MR (25% vs. 18%; \( p = 0.07 \)). In previous studies, 47% to 78% of significant MR improves more than 1 grade after TAVR (Table 2). On the other hand, 1% to 6.5% of significant MR and 8% to 17% of =mild MR were reported to worsen after TAVR (25-28). Resolution of AS immediately reduces LV pressure, which directly improves MR severity. Subsequent reversed LV remodeling or regression of LV hypertrophy might also improve MR severity especially in functional MR. Although several factors have been related to the improvement of MR (Table 4), there are conflicting results; therefore, prediction of MR improvement is still challenging.

INTERVENTIONS FOR CONCOMITANT MR. When surgical aortic valve replacement is performed, concomitant mitral valve repair or replacement is
recommended in the presence of severe MR. If the severity is moderate, the decision becomes case-dependent (29). There is limited evidence supporting this strategy, and data are required to evaluate whether double valve intervention, which is known to be associated with increased operative mortality (30,31), is justifiable, considering the clinical impact and possibility of MR improvement after isolated aortic valve intervention. Furthermore, in light of emerging transcatheter interventions for mitral valve repair or replacement, surgical candidates with severe AS and concomitant moderate MR may be well served with isolated surgical aortic valve replacement and the option of future transcatheter treatment of MR. A list of available devices for transcatheter mitral repair or replacement is provided in Supplemental Table 1.

In surgical high-risk patients, it might be optimal to undergo isolated TAVR and subsequently consider transcatheter treatment of MR depending on the residual severity and anatomical features. Given the shift toward TAVR, a more detailed assessment of the possibility of MR improvement, clinical impact of MR, and anatomical features are required to decide whether double valve intervention should be performed simultaneously or whether subsequent percutaneous or surgical treatment after TAVR can be considered. Although open surgery may be preferable for concomitant primary MR in operable candidates, a transcatheter approach may be favorable in the setting of concomitant secondary MR. Moreover, the timing of the procedure should be carefully determined because the data regarding subsequent treatment of MR after TAVR is limited (32,33). Cortés et al. (34) reported that 14 of 1,110 patients who underwent TAVR were deemed to be potentially suitable for percutaneous mitral valve intervention at 1 month follow-up. However, 12 (86%) of them had died at 6 months after TAVR (34). Another study by Abdelghani et al. (35) found that moderate-to-severe MR at baseline ameliorated at 30 days post-TAVR in 60% of cases, although etiology of MR (i.e., primary vs. functional) was not specifically assessed. Nevertheless, additional MR improvement after 30 days was observed, particularly in patients who underwent cardiac remodeling. A prospective study with core laboratory assessment of MR is required to investigate the optimal strategy for severe AS concomitant with significant MR.

**TAVR in Patients with AS and Mitral Stenosis**

**Pathophysiological Considerations.** AS and MS is generally poorly tolerated due to the significantly reduced cardiac output that frequently accompanies these lesions. This low-flow state may result in an underestimation of gradients across both the mitral and aortic valve. Akin to AS with MR, reduced flow across the aortic valve may result in an underestimation of aortic valve stenosis and patients may be diagnosed with a paradoxical low-flow low-gradient AS (or classical low-flow low-gradient AS in patients with LV systolic dysfunction). To clarify the likelihood of severe AS in these clinical contexts, calcium scoring with MSCT should be employed. With respect to the concomitant mitral stenosis (MS), quantification using pressure half-time may be unreliable, and MS severity should be corroborated using 3-dimensional MV planimetry or a multiparametric approach (4). It is important to note that from a procedural perspective, correction of MS may result in pulmonary edema if the AS is not addressed due to the sudden increase in preload in a small and hypertrophied LV.

**Prevalence of Concomitant MS in Patients Undergoing TAVR.** In patients undergoing TAVR, the prevalence of concomitant MS ranges between 11% and 18% (Table 5). The combination of severe MS and AS is typically a sequel of rheumatic heart disease. Conversely, data from central Europe documented degenerative MS in two-thirds of patients with combined AS and MS (36).

**Clinical Impact of Concomitant MS.** Recently, a small number of studies reported the prevalence of MS and its effect on clinical outcomes in patients undergoing TAVR (Table 5). Joseph et al. (37) reported that one-tenth of patients have concomitant MS, and severe MS was independently associated with increased mortality at 1 year, whereas nonsevere MS was not included in the Society of Thoracic Surgeons/American College of Cardiology Transcatheter Valve Therapy Registry. Similarly, a retrospective analysis by Sannino et al. (38) of 928 patients who underwent TAVR in 2 institutions demonstrated that

### Table 4: Suggested Risk Factors of Persistent or Worsening MR

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low baseline aortic gradient</td>
<td>24,26</td>
</tr>
<tr>
<td>Pulmonary hypertension</td>
<td>26,27</td>
</tr>
<tr>
<td>Atrial fibrillation/flutter</td>
<td>24–27,34</td>
</tr>
<tr>
<td>Mitral leaflet calcification</td>
<td>(34)</td>
</tr>
<tr>
<td>Mitral annular calcification</td>
<td>(34)</td>
</tr>
<tr>
<td>Mitral annular diameter (&gt;35.5 mm)</td>
<td>(34)</td>
</tr>
<tr>
<td>Unilateral left ventricular end-diastolic diameter</td>
<td>24,72</td>
</tr>
<tr>
<td>Unilateral left ventricular end-systolic diameter</td>
<td>(72)</td>
</tr>
<tr>
<td>Preserved ejection fraction</td>
<td>(73)</td>
</tr>
<tr>
<td>Self-expandable valve</td>
<td>(74)</td>
</tr>
<tr>
<td>Organic MS</td>
<td>(26,71)</td>
</tr>
<tr>
<td>Moderate or severe residual AR</td>
<td>after TAVR (25)</td>
</tr>
<tr>
<td>Deep positioning of implanted valve</td>
<td>(75)</td>
</tr>
</tbody>
</table>

Abbreviations as in Tables 1 and 2.
patients with severe MS had a 3-fold increased risk of mortality, with no effect on mortality in those with nonsevere MS at a mean follow-up of 40.8 ± 13.9 months. Conversely, Asami et al. (36) reported that one-fifth of patients with any degree of MS was associated with increased risks of mortality and disabling stroke at 1 year, despite MS being mild in the majority of cases. The incremental risk in patients with MS compared with patients without MS was particularly driven by patients with rheumatic MS.

Of note, there is an important difference in assessment methodology of MS among these studies. Joseph et al. (37) defined MS severity based on site-reported mitral valve area (MVA) using variable methodologies potentially affecting assessment. Sannino et al. (38) stratified MS consistently based on mean mitral gradient. Moreover, they demonstrated that severe MS failed to show an increased risk of mortality when applying MVA for the assessment. By contrast, Asami et al. (36) used a multiparametric approach with prioritizing planimetry MVA over calculated MVA when assessable and the assessment was performed in a core lab. This difference in methodology might explain the stronger prognostic impact of MS in the latter study.

The diagnosis of MS is challenging, especially in the presence of AS and its potential effect on pressure half-time because of impaired LV relaxation. Therefore, planimetry is generally considered as the most reliable parameter especially in rheumatic MS assessment (13). However, when the mitral valve is calcified, planimetry is limited by acoustic shadow and blooming artifact of the calcification. Therefore, in clinical practice, a multiparametric assessment is most appropriate for the assessment of MS (39).

### INTERVENTION FOR CONCOMITANT MS
Concomitant mitral valve surgery is indicated for patients with MVA ≤1.5 cm² when undergoing surgical aortic valve replacement for severe AS (39). In current and future practice, transcatheter mitral valve intervention combined with TAVR may also be considered as TAVR expands to lower-risk populations (40,41). Mitral balloon valvuloplasty may be appropriate in patients with rheumatic valvular disease. Conversely, excessive calcification of the valvular apparatus and concomitant MR may mitigate reasonable chances of success of mitral balloon valvuloplasty in patients with degenerative mitral valve disease. Transcatheter mitral valve implantation has recently evolved as an alternative option when the anatomical features are not suitable for percutaneous mitral balloon commissurotomy (42,43), and it is already being applied at the same time as TAVR or as a subsequent procedure after TAVR (44-46). Okuno et al. (47) reported that mitral annular calcification is associated with significant mitral valve disease in half of all patients. Off-label use of transcatheter aortic valve devices in the mitral position have been evaluated in a pooled analysis of selected cases from 40 centers. Yoon et al. (48) showed that transcatheter heart valve implantation in mitral annular calcification was associated with a significantly increased risk of valve embolization and conversion to surgery as compared with valve-in-valve mitral valve (valve in valve) or valve-in-mitral ring interventions (valve-in-ring). In addition,

### TABLE 5 Prevalence of MS, Etiology of MS, and the Association of MS and Short- and Long-Term Mortality

<table>
<thead>
<tr>
<th>First Author, Year ([Ref. #])</th>
<th>n</th>
<th>MS</th>
<th>MS Etiology</th>
<th>Duration of Follow-Up</th>
<th>Mortality Rate</th>
<th>Time</th>
<th>Mortality Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Joseph et al., 2018 (37)</td>
<td>44,755</td>
<td>11.6% (severe: 2.7%)</td>
<td>NA</td>
<td>In-hospital</td>
<td>3.9% (no) vs. 4.1% (nonsevere) vs. 5.6% (severe); p = 0.02</td>
<td>1 yr</td>
<td>21.3% (no) vs. 21.0% (nonsevere) vs. 24.5% (severe); p = 0.093</td>
</tr>
<tr>
<td>Asami et al., 2019 (36)</td>
<td>971</td>
<td>18.1% (moderate/severe 2.9%)</td>
<td>Degenerative 62.5% Rheumatic 37.5%</td>
<td>30 days</td>
<td>3.3% (no MS) vs. 9.7% (any MS)</td>
<td>1 yr</td>
<td>12.3% (no MS) vs. 28.8% (any MS)</td>
</tr>
<tr>
<td>Sannino et al., 2019 (38)</td>
<td>928</td>
<td>18.2% (severe 1.9%)</td>
<td>NA</td>
<td>30 days</td>
<td>3.1% (no) vs. 1.4% (nonsevere) vs. 5.9% (severe); p = 0.390</td>
<td>Mean follow-up = 40.8 ± 13.9 months</td>
<td>8.1% (no MS) vs. 8.2% (nonsevere) vs. 17.6% (severe); p = 0.573</td>
</tr>
</tbody>
</table>

MS = mitral stenosis; other abbreviations as in Table 2.
TABLE 6  Prevalence of TR, Change of TR Severity Over Time and Prognostic Impact of TR Following TAVR

<table>
<thead>
<tr>
<th>First Author, Year (Ref. #)</th>
<th>n</th>
<th>TR (Moderate)</th>
<th>RV Dysfunction</th>
<th>Changes Following TAVR</th>
<th>Short-Term</th>
<th>Long-Term Mortality</th>
<th>Multivariate Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hutter et al., 2013 (28)</td>
<td>268</td>
<td>22.4%</td>
<td>18.5%</td>
<td>34.5% (PAP &gt;60 mm Hg)</td>
<td>6 months</td>
<td>30 days</td>
<td>96.6% vs. 11.2% (log-rank p = 0.028)</td>
</tr>
<tr>
<td>Barbanti et al., 2015 (55)</td>
<td>518</td>
<td>15.2%</td>
<td>NA</td>
<td>37.9% (PAP &gt;60 mm Hg)</td>
<td>30 days</td>
<td>30 days</td>
<td>5.7% vs. 10.1% (log-rank p = 0.001)</td>
</tr>
<tr>
<td>Lindman et al., 2015 (49)</td>
<td>507</td>
<td>26.6%</td>
<td>54%</td>
<td>Mean PAP 31 mm Hg</td>
<td>30 days</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Schwartz et al., 2017 (56)</td>
<td>519</td>
<td>11%</td>
<td>50%</td>
<td>Mean systolic pulmonary pressure 61.2 ± 14 mm Hg</td>
<td>6 months</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>McCarthy et al., 2018 (57)</td>
<td>34,576</td>
<td>24%</td>
<td>NA</td>
<td>Mean RVSP 53.0 ± 16 mm Hg</td>
<td>30 days</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

Covariates included in each multivariate analysis: *Sex, age, implanted valve type, logistic EuroSCORE (European System for Cardiac Operative Risk Evaluation) and Society of Thoracic Surgeons score, moderate or greater MR, previous cardiac operation, coronary artery disease or cerebral infarction, LVEF ≤35%, atrial fibrillation, renal failure (creatinine >1.5 mg/dl), restrictive or obstructive pulmonary disease, systolic PAP >60 mm Hg. †Prior pacemaker implantation, atrial fibrillation, mean transaortic gradient ≥40 mm Hg, renal insufficiency, age, moderate or greater MR, New York Heart Association functional class II/IV, LVEF ≤40%, systolic PAP >60 mm Hg. ‡Age, sex, body mass index, Society of Thoracic Surgeons score, prior myocardial infarction (MI), prior coronary artery bypass grafting surgery, frailty, permanent pacemaker implantation, atrial arrhythmia, aortic valve mean gradient, LVEF, MR. §Age, sex, pacemaker and atrial fibrillation, EuroSCORE, stroke volume index, deceleration time, systolic PAP, tricuspid annular plane systolic excursion/TR grade, MR. ¶Age, sex, specific body surface area, hemoglobin, platelet count, estimated glomerular filtration rate, bilirubin, procedure date, race (non-Hispanic white vs. other), current dialysis, left main stenosis ≥50%, proximal LAD ≥70%, prior MI, endocarditis, prior stroke or transient ischemic attack, carotid stenosis, prior peripheral artery disease, current/recent smoker, diabetes, New York Heart Association functional class III/IV, atrial fibrillation/flutter, conduction defect, moderate/severe chronic lung disease, home oxygen, hostile chest, porcelain aorta, access site (femoral vs. other), pacemaker, previous implantable cardiac defibrillator, prior percutaneous coronary intervention, prior coronary artery bypass grafting, prior cardiac operations, prior aortic valve replacement/repair, prior mitral valve replacement/repair, valve morphology (tricuspid vs. other), aortic insufficiency (moderate/severe vs. other), acute (elective vs. urgent or shock or instrobes or assist device vs. emergency or salvage or cardiac arrest), right ventricular systolic pressure >40 mm Hg, moderate or severe MR, mitral stenosis, LVEF ≤30%. LAD = left anterior descending coronary artery; LVEF = left ventricular ejection fraction; PAP = pulmonary artery pressure; RVSP = right ventricular systolic pressure; TR = tricuspid regurgitation; other abbreviations as in Tables 1 and 2.

All-cause mortality was 3- to 5-fold higher in patients undergoing transcatheter heart valve implantation in mitral annular calcification as compared with those undergoing valve in ring or valve-in-valve implantation, respectively (48). Because there are no data comparing these strategies, the decision should be case-dependent, with a comprehensive assessment of surgical risk and anatomical features.

Even mild MS might have an increased risk of mortality, as demonstrated in the study by Asami et al. (36), and worsened MS was reported as a rare complication after TAVR in patients with pre-existing impaired transmural flow. Therefore, careful assessment and follow-up of MS is required in patients with mild MS.

TAVR in Patients With AS and Tricuspid Regurgitation

PATHOPHYSIOLOGICAL CONSIDERATIONS. The interplay among tricuspid regurgitation (TR), pulmonary hypertension, and right ventricular (RV) function has been investigated in several studies (49,50). Secondary TR accounts for 90% of all severe TR and occurs predominantly as a result of LV dysfunction, MR, atrial fibrillation, and pulmonary disease. The subsequent pulmonary hypertension results in a cascade of progressive sequelae on the right side of the heart, including RV dysfunction and dilation (51), annular dilatation toward the RV free wall, tricuspid leaflet tethering, and right atrial enlargement (4). In patients with severe AS,
Patients with severe aortic stenosis (AS) with moderate or severe mitral regurgitation (MR) should be assessed for the presence of reduced systolic function, presence of functional MR, absence of atrial fibrillation (AF), and absence of pulmonary hypertension. If this group of criteria is fulfilled, then there is a 50% chance that the functional MR will improve post–transcatheter aortic valve replacement (TAVR), and thus, this approach is recommended in this clinical context. In patients in whom symptomatic severe MR still persists post-TAVR, then a subsequent percutaneous or surgical mitral intervention should be considered. In patients in whom the aforementioned group of 4 criteria is not fulfilled, a double valve procedure is recommended (i.e., open surgical treatment in appropriate candidates or double transcatheter intervention in nonsurgical patients).

In patients with severe AS with moderate or severe mitral stenosis (MS), surgical candidates should be considered for surgical treatment of both valves, as per clinical practice guidelines, whereas nonsurgical candidates should undergo TAVR first, followed by mitral balloon valvuloplasty or transcatheter mitral valve replacement (TMVR), depending on the anatomic features of the MS. It should be noted that there is a 3-fold increased risk of cardiovascular death or disabling stroke at 1 year in TAVR patients with MS.

Patients with severe AS and TR should be referred for TAVR provided that: 1) there is no history of AF; 2) concomitant functional MR is present; and 3) there is preserved right ventricular (RV) function. Should there be worsening of tricuspid regurgitation (TR) with symptoms or reduced RV function post-TAVR, then transcatheter tricuspid valve (TV) intervention or TV surgery should be considered. In cases in which there is severe AS with greater than mild TR: 1) right atrial dilation; 2) RV failure; and 3) AF, then the patient should be assessed for surgical candidacy. Open treatment of both valves should be considered in surgical candidates, while a strategy of TAVR first followed by tricuspid intervention should be considered in nonsurgical candidates. LVEF = left ventricular ejection fraction.
secondary TR may represent an advanced stage with myocardial fibrosis and stiffness, affecting mortality (52). It should be noted that from a diagnostic perspective, thermodilution derived cardiac output can be erroneously low, which ultimately can result in an underestimation of aortic valve area and over-estimation of AS severity (53).

**PREVALENCE OF CONCOMITANT TR IN PATIENTS UNDERGOING TAVR.** Moderate or more TR has been documented in 11% to 27% of patients in observational registries. Relevant TR has been associated with RV dysfunction in 18% to 54% of patients and with pulmonary hypertension in 34% to 38% of patients (Table 6).

**CLINICAL IMPACT OF CONCOMITANT TR.** Several studies have investigated the clinical impact of concomitant TR in TAVR patients (Table 6). These studies, as well as a meta-analysis (54), suggest that concomitant TR is associated with an increased mortality in an unadjusted analysis. However, when multivariate adjustment with clinical or echocardiographic variables was performed, concomitant TR did not emerge as an independent predictor of mortality in most of the studies (28,55,56). Two studies demonstrated concomitant TR as an independent predictor of mortality despite multivariable adjustment; however, the significance was limited in patients without MR or reduced LV ejection fraction (49,57). TR may not be a direct factor of increased mortality, but rather an important marker of underlying disease that results in higher mortality. There are limited data demonstrating the efficacy of intervention for functional TR as a result of other cardiac conditions, and it is still unknown whether intervention improves clinical outcomes (58).

**INTERVENTION FOR CONCOMITANT TR.** When performing left heart valve surgery, current guidelines (13,39) recommend additional tricuspid valve surgery for concomitant TR because it has been shown to prevent worsening of TR and facilitates reverse remodeling of the RV and improvement of functional status without increasing operative risk (59-62). Concomitant tricuspid valve surgery is indicated even for mild TR in the presence of tricuspid annular dilation or signs of right heart failure, as it may worsen later after left heart valve surgery and possibly cause poor clinical outcomes. Moreover, there is a high mortality after redo surgery for progressive TR (63-65), thus supporting early intervention for concomitant mild or moderate TR. With the rise of TAVR, it may be reasonable to consider an additional intervention for TR depending on the progress of RV function and TR after TAVR. In fact, it has been suggested that TR improves in 15% to 60% (Table 6), and normalization of RV function was observed in more than one-half of the patients after TAVR (50), which seems to be better than in patients undergoing surgical aortic valve replacement (66).

Various devices are now under preclinical and clinical evaluation for transcatheter tricuspid repair (Supplemental Table 2) (67). Further investigation is required to determine the efficacy and the optimal timing of the additional intervention for concomitant TR in the TAVR patient.

**CONCLUSIONS**

Diagnosis of multiple valvular lesions can be challenging due to changes in physiology and echocardiographic parameters, which have been validated for isolated lesions. When tackling multivalvular heart disease, it is important to recognize the sum effect of 2 or more moderate valvular lesions. LV impairment, pulmonary hypertension, and exertional symptoms are clues to the cumulative effect of multivalvular disease and should trigger discussions around earlier intervention (Central Illustration). The use of subtle markers of deteriorating LV function such as LV strain or rising natriuretic peptides and functional assessments with exercise testing can all contribute to deciphering the hemodynamic sequelae from multivalvular lesions. Multidisciplinary heart team decisions can be invaluable in integrating the plethora of clinical, echocardiographic, hemodynamic, and anatomical data, upon which an optimal management strategy can be planned. Prospective studies to assess the role of tricuspid intervention are required. Given the significant prevalence of coexistent MR with severe AS, studies to elucidate the optimal approach to this pair of lesions in the TAVR era would also greatly help improve outcomes for our structural heart patients.

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Multivalvular Disease
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KEY WORDS aortic regurgitation, mitral regurgitation, mitral stenosis, transcatheter aortic valve replacement, tricuspid regurgitation

APPENDIX For an expanded References section and supplemental tables, please see the online version of this paper.