Aortic Stenosis with Other Concomitant Valvular Disease
Aortic Regurgitation, Mitral Regurgitation, Mitral Stenosis, or Tricuspid Regurgitation

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INTRODUCTION
Prevalence
Aortic stenosis (AS) is often part of multiple valve disease (AS associated with stenosis and/or regurgitation involving 1 or more other heart valves) or mixed valve disease (concurrent AS and aortic regurgitation [AR]). In a Swedish nationwide study, 36,319 patients had a discharge diagnosis of AS based on International Classification of Diseases-10 codes\textsuperscript{1}; among these patients, 6.8% had mixed aortic valve disease, and 7.4% had another concomitant valve disease, consisting of mitral regurgitation (MR) in 5.1% of cases, mitral stenosis (MS) in 1.5% of cases, and tricuspid regurgitation (TR) in 0.6% of cases.\textsuperscript{1} AS was present in 17.9% of patients with AR, in 9.9% of those with MR, and in 28.3% of those with MS.\textsuperscript{1} The prevalence of moderate or severe MR is even higher among patients undergoing transcatheter aortic valve replacement (TAVR) or surgical aortic valve replacement (SAVR), reaching 20% of the patients included in the PARTNER (Placement of Aortic transcatheter Valve Trial) cohort A and B trials.\textsuperscript{2,3}

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Moderate or severe TR was diagnosed in up to 16% of patients with severe AS undergoing aortic valve replacement. Among patients undergoing TAVR, MS was observed in 11.6% of cases, and was severe in 2.7% of cases. In another series, MS was observed in 18.1% of patients undergoing TAVR and was classified as moderate/severe in 2.9%. Mixed aortic valve disease was observed in 106 (13.4%) of 793 consecutive patients undergoing TAVR. Among the 141,905 patients included in the Society of Thoracic Surgeons (STS) database who had undergone isolated primary SAVR between 2002 and 2010, 19.3% had mixed aortic valve disease.

**Cause**

AS and the associated valve disease often have the same underlying cause, mostly degenerative calcification or rheumatic heart disease, but they may also be the result of distinct conditions. For example, chordal rupture, endocarditis, or myxomatous mitral valve disease may occur in patients with degenerative or congenital AS (Fig. 1). Importantly, the chronic left ventricular (LV) pressure overload of severe AS may considerably alter upstream pressures, decrease ventricular function, and remodel ventricles and atria. These morphologic, hemodynamic, and functional changes are instrumental in the development of secondary MR/TR (Fig. 2), with structurally normal valves and with a leaflet coaptation defect mainly resulting from ventricular and/or atrial remodeling.

**Diagnosis**

Doppler echocardiography is the cornerstone technique for diagnosis and allows quantification of each valve disease. However, several methods routinely used to assess valvular heart disease have not been validated in the setting of multiple valve disease. Hemodynamic interactions may result in diagnostic pitfalls. AS may affect the diagnosis of other types of valvular disease; conversely, other valve disease may affect the diagnosis of AS (Table 1). Diagnostic tools other than echocardiography can also be useful, including exercise testing, MRI, and multidetector computed tomography, but limited data are currently available concerning the specific role of these modalities in patients with multiple valve disease. Occasionally, when noninvasive evaluation remains inconclusive or discordant with clinical findings, cardiac catheterization may be required. However, the invasive assessment of cardiac output using thermodilution and Fick methods may prove inaccurate in the presence of severe TR and very low cardiac output, and calculation of aortic valve area by the Gorlin formula may therefore also be inaccurate.

**SPECIFIC COMBINATIONS**

**Aortic Stenosis and Mitral Regurgitation**

Concentric LV hypertrophy as a result of the chronic increased afterload induced by severe AS can lead to diastolic dysfunction, left atrial dilatation, and secondary MR. In addition, impaired LV systolic function may also occur as a result of increased afterload and may be associated with eccentric LV remodeling and mitral annular dilatation, also resulting in secondary MR (see Fig. 2). MR may be primary, mainly as a result of the high prevalence of mitral annular calcification in the elderly population. Mitral valve chordal rupture occasionally occurs in patients with AS. Coronary artery disease and ischemic MR are also common among patients with AS. In addition, elderly patients with AS can have MR of mixed cause, with both LV dysfunction and mitral leaflet and/or annular calcification.

Multiple quantitative and qualitative echocardiographic parameters should be integrated in order to assess the severity of MR. However, systolic intraventricular pressure is increased in patients with AS, and concomitant MR is therefore characterized by increased transmitral systolic velocity. The resulting regurgitant volume and color-flow jet area are consequently expected to be higher than in patients without AS. Mitral effective regurgitant orifice area and vena contracta are parameters that are not as afterload dependent as regurgitant volume and color-flow jet area and are therefore more representative of the true severity of MR; these parameters are also less
affected by aortic valve replacement. MR has a net effect on reducing forward flow and is therefore associated with the development of low-flow low-gradient AS (see Fig. 2; Fig. 3) because the combination of volume overload caused by MR and reduced preload reserve caused by LV hypertrophy resulting from AS further reduces the net forward flow. When the ejection fraction is reduced (classic low-flow low-gradient AS), dobutamine stress echocardiography may be used to increase forward flow and thereby confirm AS severity, although this may be impossible or inconclusive in the presence of MR. Alternatively, assessment of the aortic valve calcium score by multidetector computed tomography may help differentiate between true severe and pseudosevere low-flow low-gradient AS (true severe, >2000 arbitrary units (AU) in men and >1200 in women), in both classic and paradoxic (with preserved ejection fraction) low-flow low-gradient AS.

Whether the presence of preoperative moderate or worse MR independently predicts early and/or late outcomes after SAVR or TAVR remains a matter of debate. However, studies designed to assess prognosis have differed markedly with regard to inclusion criteria, particularly in terms of severity, method of assessment, mechanism and cause of MR, and type of prosthesis used. The acute effect of aortic valve replacement is a decrease in LV systolic pressure, and hence a reduction in MR driving pressure. In addition, reverse LV remodeling may occur, with regression of LV hypertrophy/dilatation and improved LV ejection fraction. These changes are instrumental in the improvement in MR observed in most patients after isolated SAVR or TAVR. However, MR does not always improve, and, infrequently, may even worsen. Secondary MR, as opposed to primary MR, is more likely to improve following aortic valve replacement.
because a similar degree of improvement in severe MR caused by flail mitral leaflet is unlikely. Other factors that may predict MR improvement include a potential to reverse LV remodeling, such as dilated LV and reduced ejection fraction, and a large decrease in transaortic pressure gradient, including a high preoperative transvalvular pressure gradient and absence of postoperative prosthesis-patient mismatch (see Table 2). Atrial fibrillation, pulmonary hypertension, and atrial and/or mitral annulus dilatation have been associated with more limited improvement in MR. Balloon-expanded aortic prostheses, as opposed to self-expanded prostheses, may have a more beneficial impact on MR regression.28 Accurate prediction of MR improvement in individual patients is difficult. No randomized trials, and therefore no evidence-based recommendations, are available on whether MR should be addressed at the time of SAVR or TAVR. It also remains unclear whether SAVR or TAVR is more effective at reducing MR.

**Aortic Stenosis and Tricuspid Regurgitation**

The LV hypertrophy and associated diastolic dysfunction present in patients with severe AS
may induce pulmonary hypertension, right ventricular remodeling, tricuspid tethering, and annular dilatation, resulting in secondary TR. In addition, increased right ventricular filling pressure may contribute to the development of right atrial dilatation and atrial fibrillation, both of which can cause and exacerbate TR (see Fig. 2). Alternatively, patients with AS secondary to rheumatic disease may also have primary tricuspid valve involvement. Severe TR is associated with low flow in patients with AS, but the low flow may also be caused by the associated right ventricular impairment.

Secondary TR is associated with poor prognosis in the presence of severe AS, particularly in patients with concomitant MR. TR may be secondary to multiple factors that can have prognostic impact, including LV diastolic dysfunction, pulmonary hypertension, right ventricular dysfunction, and/or atrial fibrillation. It is therefore unclear whether TR per se is an independent prognostic marker or merely a surrogate marker. When left untreated at the time of aortic valve replacement, TR may get worse over time, and can contribute to significant morbidity and mortality. The sensitivity of TR to changes in loading conditions...
conditions has led to the proposal that annular dilatation, rather than the severity of TR, may be predictive of subsequent deterioration. A tricuspid annulus diameter greater than or equal to 40 mm (>21 mm/m²) has been shown to predict the development of moderate to severe TR during follow-up (Fig. 5).³²

**Aortic Stenosis and Mitral Stenosis**

MS associated with AS has a degenerative and calcific cause in most cases, and a rheumatic cause in the remaining cases.⁷,⁸

In patients with concomitant MS and AS, the reduction in cardiac output related to severe MS may be severe and is usually more pronounced than in isolated AS. The aortic and/or mitral pressure gradient may therefore be lower than expected and paradoxical low-flow low-gradient AS is commonly observed. Paradoxical low-flow low-gradient MS (severe MS with a mean pressure gradient <10 mm Hg) may also be present. It is therefore important not to underestimate the severity of AS and/or MS, which may require aortic valve calcium quantification by multidetector computed tomography and/or mitral planimetry by transesophageal echocardiography. LV filling is altered by the presence of AS, and use of the pressure half-time method to determine mitral valve area should be avoided in this setting. Planimetry of the mitral valve orifice is the method of choice for mitral valve area assessment, but its feasibility is usually limited to rheumatic MS. By providing better alignment of the image plane at the mitral tips, three-dimensional guided planimetry may allow more accurate determination of the mitral valve orifice area.³³ In degenerative MS, mitral valve area assessment using the continuity equation, provided it is not associated with more than mild AR or MR,³⁴ and direct planimetry with three-dimensional echocardiography and color-flow Doppler are acceptable techniques for

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**Fig. 4.** Downgrading of MR severity following aortic valve replacement. Patient with severe AS undergoing aortic valve replacement. (A) Moderate secondary MR is observed preoperatively, but only trivial MR is observed 1 month (B) after aortic valve replacement.
determining mitral valve area.\textsuperscript{35} In selected cases, catheterization using the Gorlin-derived method may be used for AS and MS valve area determination, in the absence of concomitant regurgitation. Severe mitral annular calcification has been associated with conduction abnormalities and increased mortality following TAVR,\textsuperscript{36} and MS is an independent risk factor for adverse clinical events following TAVR.\textsuperscript{7,8}

### Mixed Aortic Valve Disease

Pure AR is characterized by LV enlargement with increased compliance, enabling a large volume overload to be accommodated with no significant increase in LV end-diastolic pressure. In the presence of AR, stroke volume needs to be increased in order to maintain forward cardiac output. In the presence of concomitant AS with consequent

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**Table 2**

Factors associated with postoperative changes in mitral regurgitation severity after surgical or transcatheter aortic valve replacement

<table>
<thead>
<tr>
<th>Improvement</th>
<th>No Improvement, Deterioration</th>
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<tbody>
<tr>
<td>Secondary MR</td>
<td>Primary MR</td>
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<tr>
<td>Dilated left ventricle, reduced LVEF</td>
<td>Nondilated left ventricle, normal LVEF</td>
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<td>Mean transaortic pressure gradient (&gt;40 \text{ mm Hg})</td>
<td>Mean transaortic pressure gradient (&lt;40 \text{ mm Hg})</td>
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<tr>
<td>Peak transaortic pressure gradient (&gt;60 \text{ mm Hg})</td>
<td>Peak transaortic pressure gradient (&lt;60 \text{ mm Hg})</td>
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<td>Absence of prosthesis-patient mismatch</td>
<td>Prosthesis-patient mismatch</td>
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<tr>
<td>Absence of left atrial or mitral annulus dilatation</td>
<td>Left atrial or mitral annulus dilatation</td>
</tr>
<tr>
<td>Absence of atrial fibrillation</td>
<td>Atrial fibrillation</td>
</tr>
<tr>
<td>Absence of pulmonary hypertension</td>
<td>Pulmonary hypertension</td>
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<tr>
<td>No or mild residual AR</td>
<td>(\geq) Moderate residual AR</td>
</tr>
<tr>
<td>Balloon-expandable prosthesis</td>
<td>Self-expanding prosthesis (particularly when deeply implanted)</td>
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<td>Coronary artery disease or previous myocardial infarction</td>
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*Abbreviation:* LVEF, left ventricular ejection fraction.

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**Fig. 5.** Development of severe TR following aortic valve replacement. Patient with severe AS undergoing aortic valve replacement without tricuspid annuloplasty. Tricuspid annular dilatation (42 mm, apical 4-chamber view) and mild-to-moderate TR were observed (A, B) preoperatively. (C) Severe TR was observed 3 years after surgery.
pressure overload, LV hypertrophy, and reduced LV compliance, the AR-induced volume overload leads to LV filling over a steeper portion of the pressure-volume curve, and thereby disproportionately increases LV diastolic pressure and wall stress, which eventually results in poor clinical tolerance (Figs. 6 and 7).37,38 LV concentric hypertrophy secondary to AS may prevent the development of LV dilatation.38–40 Reduced coronary flow and increased LV filling pressure also contribute to the development of exercise intolerance. The aortic regurgitant volume increases the forward stroke volume and consequently the pressure gradient. In this setting, a significant increase in afterload may occur even in the presence of moderately severe AS.

Several diagnostic pitfalls must be avoided in mixed aortic valve disease. The pressure half-time method is unreliable for the evaluation of AR in the presence of impaired LV relaxation.41 Increased LV outflow tract velocities may prevent use of the simplified Bernoulli equation for calculation of the aortic valve pressure gradient. Invasive determination of the aortic valve area by the Gorlin formula is inherently inaccurate in patients with mixed aortic valve disease. The hemodynamic burden associated with mixed aortic valve disease is only partially characterized by assessment of the aortic valve area, effective regurgitant orifice area, and regurgitant volume. If cardiac output is preserved, the overall severity and prediction of outcome can be reliably characterized by assessment of peak aortic valve velocity and mean gradient, which increase with the severity of both AS and AR (see Fig. 7).37–39 The assessment of aortic valve area remains accurate using the continuity equation; however, aortic valve area may increase at high transvalvular flow rates, and, in some patients, an aortic valve area greater than 1.0 cm² might reflect severe AS.42 In this setting, the assessment of the aortic valve calcium score by multidetector computed tomography might be considered.

**DECISION MAKING**

Current guidelines on medical, surgical, and interventional management of patients with multiple valve disease are based on only limited data, as emphasized by the C level of evidence indicated for most recommendations made by the American Heart Association/American College of Cardiology and European Society of Cardiology/European Association for Cardio-Thoracic Surgery guidelines14,43,44 (Table 3).

Clinicians are faced with 2 main scenarios: (1) aortic valve surgery is indicated because of severe AS in the presence of concomitant mitral and/or...
tricuspid valve disease; and (2) mitral and/or tricuspid surgery are indicated in the presence of concomitant AS. In these 2 scenarios, the clinician should follow the current guidelines applicable to the most severe lesion. When both lesions are severe, there is general consensus that they should both be addressed14,43,44 (see Table 3). The management of less-than-severe associated lesions remains more controversial.

Mixed aortic valve disease may present with predominant stenosis or regurgitation, which should be addressed according to current guidelines. However, even moderate AR combined with moderate AS may induce a clinically relevant hemodynamic burden and, although it has not been specifically addressed in current guidelines, intervention should be considered in symptomatic patients with moderate AS and moderate AR with a peak velocity greater than or equal to 4 m/s and a mean gradient greater than or equal to 40 mm Hg (see Fig. 7).

**Role of the Heart Team and Valve Clinics**

The management of each patient must take into account several factors in addition to the patient’s symptoms and the severity and effects of the valvular lesions. These factors include the increased operative morbidity and mortality associated with multiple valve surgery. In the EuroHeart Survey and the STS database, the mean operative mortality of double-valve replacement was 2-fold higher than that of single-valve replacement.13,45–47 In addition, the presence and severity of concomitant coronary artery disease can markedly affect the treatment strategy and operative risk. The expected natural history of a patient with a valve that is left without surgical correction and the risk of redo surgery should be weighed against the patient’s life expectancy. The individual surgical risk profile and comorbid conditions are also important determinants of the treatment strategy. The likelihood of spontaneous changes...
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<tbody>
<tr>
<td>MR</td>
<td>Concomitant mitral valve repair or replacement is indicated in patients with chronic severe primary MR</td>
<td>Severe primary MR: not mentioned</td>
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<tr>
<td></td>
<td>Mitral valve surgery is reasonable for patients with chronic severe secondary MR</td>
<td>Severe secondary MR: not mentioned</td>
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<tr>
<td></td>
<td>Concomitant mitral valve repair is reasonable in patients with chronic moderate primary MR (stage B)</td>
<td>Moderate primary MR: not mentioned</td>
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<tr>
<td></td>
<td>Mitral valve repair may be considered for patients with chronic moderate secondary MR (stage B)</td>
<td>The potential impact of mitral valve intervention (surgery and catheter intervention) on survival in patients with secondary MR needs to be evaluated</td>
</tr>
<tr>
<td>MS</td>
<td>Concomitant mitral valve surgery is indicated for patients with severe MS</td>
<td>Severe concomitant aortic valve disease is a contraindication to percutaneous mitral commissurotomy</td>
</tr>
<tr>
<td></td>
<td>Concomitant mitral valve surgery may be considered for patients with moderate MS (mitral valve area, 1.6–2.0 cm²)</td>
<td>In patients with severe MS, mitral valve surgery is preferable, when not contraindicated</td>
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<td>Moderate MS: not mentioned</td>
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<tbody>
<tr>
<td>TR</td>
<td>Tricuspid valve surgery is recommended for patients with severe TR (stages C and D)</td>
<td>Tricuspid valve surgery is indicated in patients with severe primary or secondary TR</td>
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<tr>
<td></td>
<td>I (C)</td>
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<td></td>
<td>Tricuspid valve repair can be beneficial for patients with mild, moderate, or greater functional TR (stage B) at the time of left-sided valve surgery with either (1) tricuspid annular dilatation or (2) prior evidence of right heart failure</td>
<td>Tricuspid valve surgery should be considered in patients with moderate primary TR undergoing left-sided valve surgery</td>
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<td>IIa (B)</td>
<td>IIa (C)</td>
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<td>Tricuspid valve repair may be considered for patients with moderate functional TR (stage B) and pulmonary artery hypertension at the time of left-sided valve surgery</td>
<td>Tricuspid valve surgery should be considered in patients with mild or moderate secondary TR with dilated annulus (≥40 mm or &gt;21 mm/m²) undergoing left-sided valve surgery</td>
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<td></td>
<td>IIb (C)</td>
<td>IIb (C)</td>
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<td>(2) Surgery is indicated on the mitral or tricuspid valve. How should AS be managed?</td>
<td></td>
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<tr>
<td></td>
<td>AVR is reasonable for patients with moderate AS who are undergoing other cardiac surgery</td>
<td>Surgical AVR should be considered in patients with moderate AS undergoing surgery of the ascending aorta or another valve, after heart team decision</td>
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<td>IIa (C)</td>
<td>IIa (C)</td>
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These indications are according to the AHA/ACC and ESC/EACTS guidelines.

Abbreviations: ACC, American College of Cardiology; AHA, American Heart Association; AVR, aortic valve replacement; CABG, coronary artery bypass grafting; EACTS, European Association for Cardio-Thoracic Surgery ESC, European Society of Cardiology.

Data from Refs. 14, 42, 43
in MR after aortic valve replacement should be taken into account, remembering that, as mentioned earlier, individual responses are difficult to predict. Tricuspid annular dilatation should also be systematically assessed, because it may predict the development of clinically significant TR during follow-up. Surgical reparability as well as the feasibility of transcatheter approaches should be estimated. Multiple transcatheter procedures have been shown to be feasible in several scenarios, but worldwide clinical experience remains limited. Only 13% of patients with significant persistent MR after TAVR were deemed suitable candidates for percutaneous mitral valve repair with either the MitraClip or balloon-expandable valve. Although TAVR is usually performed for the treatment of degenerative AS, mitral balloon valvuloplasty, indicated in patients with rheumatic valve disease, is only rarely feasible in patients undergoing TAVR. Experience of combined therapy with TR is also currently limited. Technical progress that enables the technique to be used for broader indications is needed before multiple transcatheter valve therapies can be incorporated into routine clinical practice.

The management of patients with multiple or mixed valve disease is challenging and requires an integrated diagnostic approach as well as individually tailored decision making, highlighting the critical role of a collaborative approach between cardiac imagers, interventional cardiologists, and cardiac surgeons. For this purpose, a dedicated heart team–based management strategy in the setting of heart valve centers is required, as recommended by current guidelines in order to identify patients likely to benefit from a double-valve procedure, single aortic valve replacement, or a staged procedure, in which clinical status and lesion severity are reevaluated following aortic valve intervention.

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Aortic Stenosis in Multivalvular Disease


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