Aortic Stenosis with Other Concomitant Valvular Disease

Aortic Regurgitation, Mitral Regurgitation, Mitral Stenosis, or Tricuspid Regurgitation

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KEYWORDS

• Aortic stenosis • Mitral regurgitation • Tricuspid regurgitation • Mitral stenosis
• Multiple valve disease • Mixed aortic valve disease

KEY POINTS

- Multiple valve disease involving aortic stenosis and mixed aortic valve disease are frequent clinical scenarios.
- Multiple valve disease and mixed aortic valve disease may be associated with diagnostic pitfalls as a result of hemodynamic interactions.
- Mixed aortic valve disease should be managed according to the predominant lesion; however, combined moderate aortic stenosis and regurgitation may have significant clinical impact requiring surgery.
- There is currently no evidence-based management strategy for multiple valve disease, and a case-by-case approach should be adopted by the heart valve team.
- Decision making should include assessment of each individual lesion, global repercussions, operative risk, life expectancy, natural history of the untreated valvular lesion, and suitability for valve repair and/or transcatheter valve procedures.

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[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.[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.[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.[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.[4–6] Among patients undergoing TAVR, MS was observed in 11.6% of cases, and was severe in 2.7% of cases.[7] In another series, MS was observed in 18.1% of patients undergoing TAVR and was classified as moderate/severe in 2.9%.[8] Mixed aortic valve disease was observed in 106 (13.4%) of 793 consecutive patients undergoing TAVR.[9] 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.[10]

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.[11] 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.[12] Occasionally, when noninvasive evaluation remains inconclusive or discordant with clinical findings, cardiac catheterization may be required.[13,14] 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.[15]

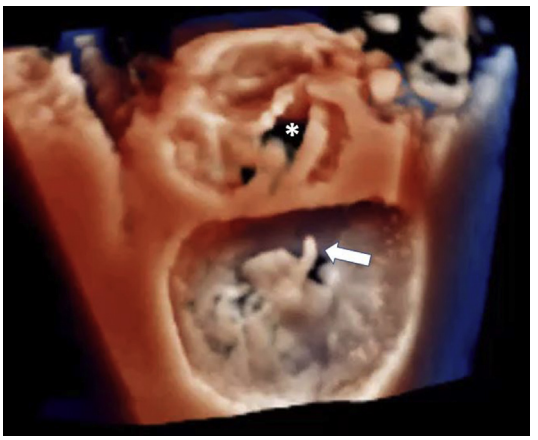

Fig. 1. Degenerative AS and severe MR caused by chordal rupture. Volumetric three-dimensional echocardiography en-face view of the mitral and the aortic valves in a patient with AS (*asterisk*) and ruptured chordae tendineae (*arrow*).

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.[16] 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).[16] MR may be primary, mainly as a result of the high prevalence of mitral annular calcification in the elderly population.[17] Mitral valve chordal rupture occasionally occurs in patients with AS.[18] Coronary artery disease and ischemic MR are also common among patients with AS.[19] 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

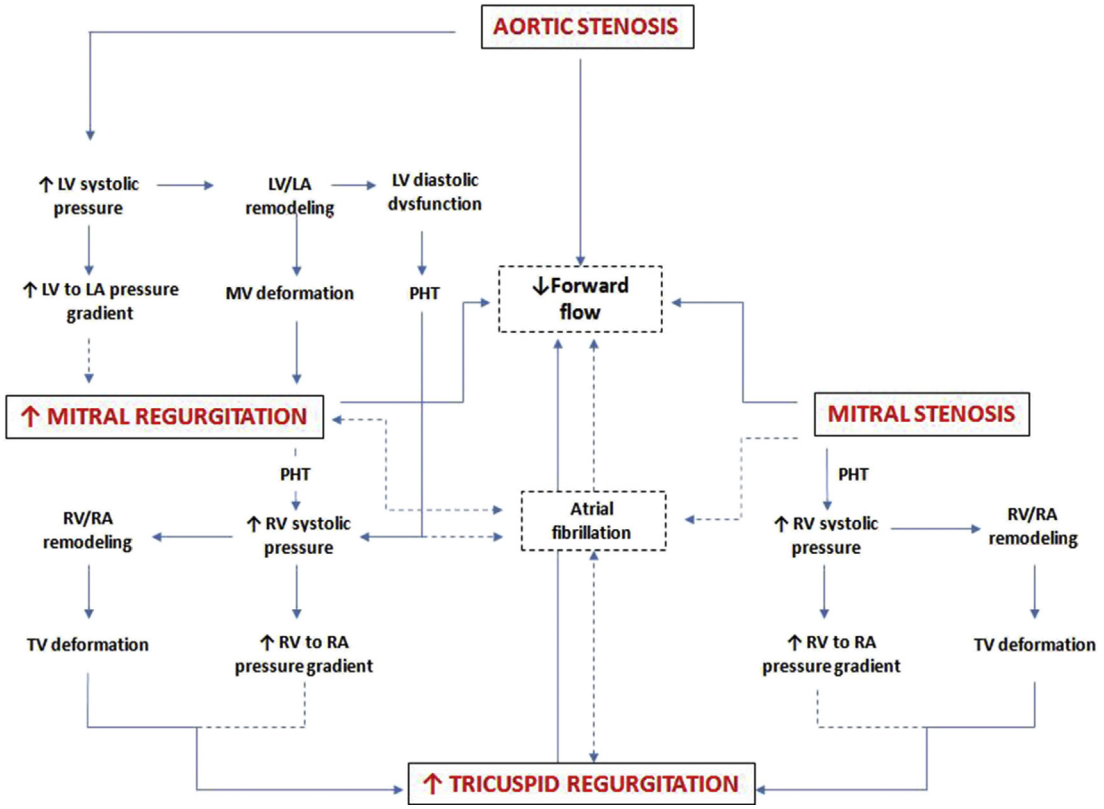

Fig. 2. Pathophysiology of valvular heart disease associated with AS. AS may induce or exacerbate MR by increasing the LV to left atrial (LA) pressure gradient and by mitral valve (MV) deformation. AS may induce or exacerbate TR by inducing pulmonary hypertension either directly or as a result of MR. MR, TR, and MS may all contribute to reducing forward flow and the development of atrial fibrillation (*dotted lines*). Reduced forward flow may prevent the diagnosis of AS (low-flow, low-gradient AS), and atrial fibrillation may also further reduce flow and functional tolerance because of loss of the atrial kick. PHT, pulmonary hypertension; RA, right atrial; RV, right ventricular; TV, tricuspid valve.

affected by aortic valve replacement.[20] 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**),[21,22] 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.[22] 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.[23]

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.[24] 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.[25,26] These changes are instrumental in the improvement in MR observed in most patients after isolated SAVR or TAVR (**Fig. 4**).[27] 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

Table 1
Diagnostic difficulties resulting from the combination of aortic stenosis with another valve disease

	AR	MS	MR	TR
AS Influences the Diagnosis of	AR pressure half-time method is unreliable Peak aortic velocity and mean gradient reflect the severity of both AR and AS; they reflect the severity of the combined disease rather than just the severity of AS	MS pressure half-time method is unreliable Low-flow, low-gradient MS is common	AS increases mitral valve regurgitant volume AS increases MR jet area on color-flow mapping Mitral effective regurgitant orifice is less markedly affected than MR volume and color-flow mapping parameters	—
The Diagnosis of AS is Influenced by the Concomitant Presence of	Simplified Bernoulli equation for gradient determination may not be applicable when left ventricular outflow tract velocity is increased because of high flow Gorlin formula using thermodilution/Fick method is invalid Continuity equation remains applicable to assess AVA, but AVA might be increased at high flow rates	Low-flow, low-gradient AS is common	Mitral regurgitant spectral Doppler signal should not be mistaken for AS spectral Doppler signal Low-flow, low-gradient AS is common	Low-flow, low-gradient AS is common In the presence of severe TR, thermodilution may underestimate cardiac output and consequently overestimate AS severity

Abbreviation: AVA, aortic valve area.

(Table 2), 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

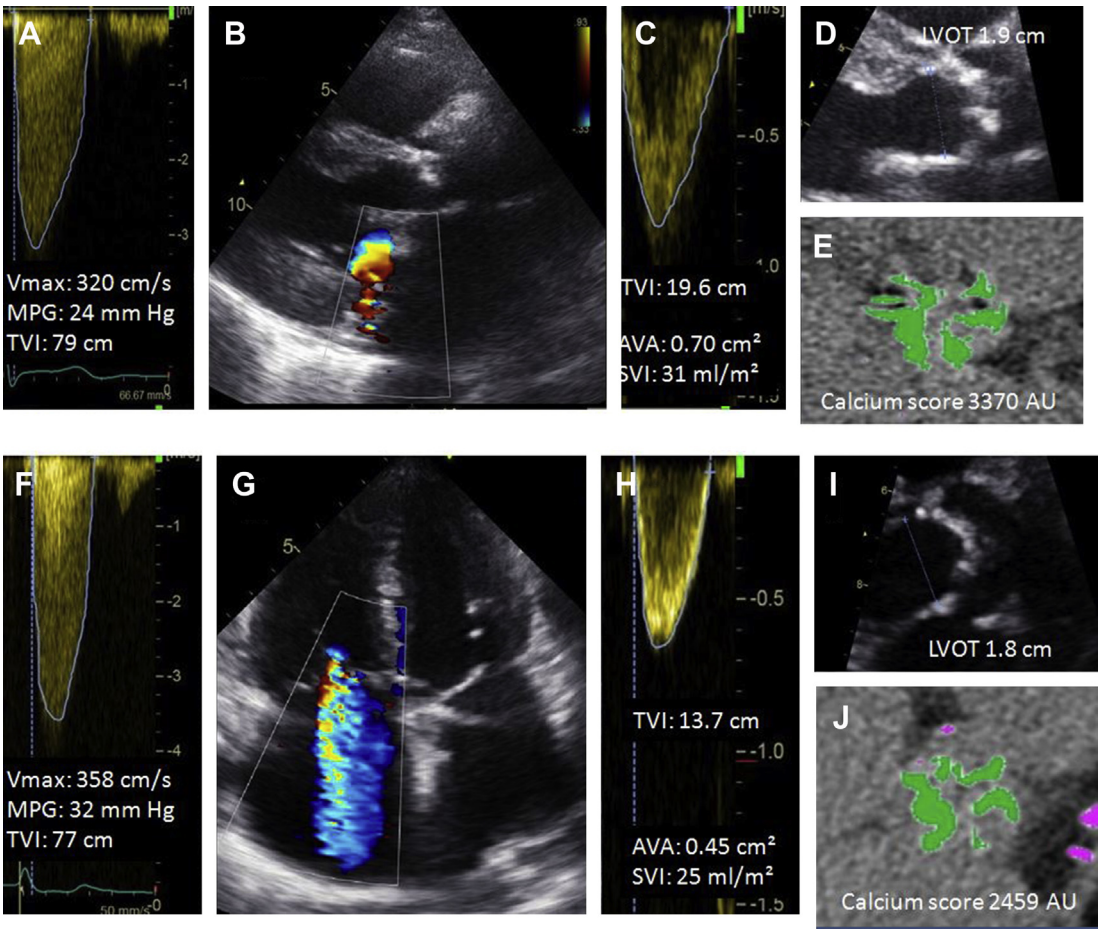

Fig. 3. Low-flow, low-gradient AS associated with other valve disease. (*A–E*) Elderly woman with AS, severe MR, and preserved ejection fraction. (*A*) The mean transaortic pressure gradient (MPG) is 24 mm Hg and the maximal transaortic velocity (Vmax) is 320 cm/s. The large convergence zone of the mitral regurgitant jet is consistent with severe MR. Left ventricular outflow tract (LVOT) pulsed wave Doppler velocity-time integral (TVI) and diameter are 19.6 cm and 1.9 cm, respectively. Calculated stroke volume index (SVI) is 56 mL (31 mL/m^2) and aortic valve area (AVA) is 0.70 cm^2. The aortic valve calcium score is 3370 AU on multidetector computed tomography. (*F–J*) Elderly woman with AS, TR, and preserved ejection fraction. (*A*) The MPG is 32 mm Hg and the Vmax 358 cm/s. Color Doppler flow is consistent with severe TR. LVOT pulsed wave Doppler TVI and diameter are 13.7 cm and 1.8 cm, respectively. Calculated SVI is 35 mL (25 mL/m^2) and AVA is 0.45 cm^2. The aortic valve calcium score is 2459 AU on multidetector computed tomography. These 2 patients have severe AS with a paradoxic low-flow low-gradient pattern, associated with MR (first patient) and TR (second patient). In both cases, quantification of aortic valve calcification confirmed the presence of true severe AS.

may induce pulmonary hypertension, right ventricular remodeling, tricuspid tethering, and annular dilatation, resulting in secondary TR.[29] 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.[21]

Secondary TR is associated with poor prognosis in the presence of severe AS, particularly in patients with concomitant MR.[30,31] 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.[5,32] The sensitivity of TR to changes in loading

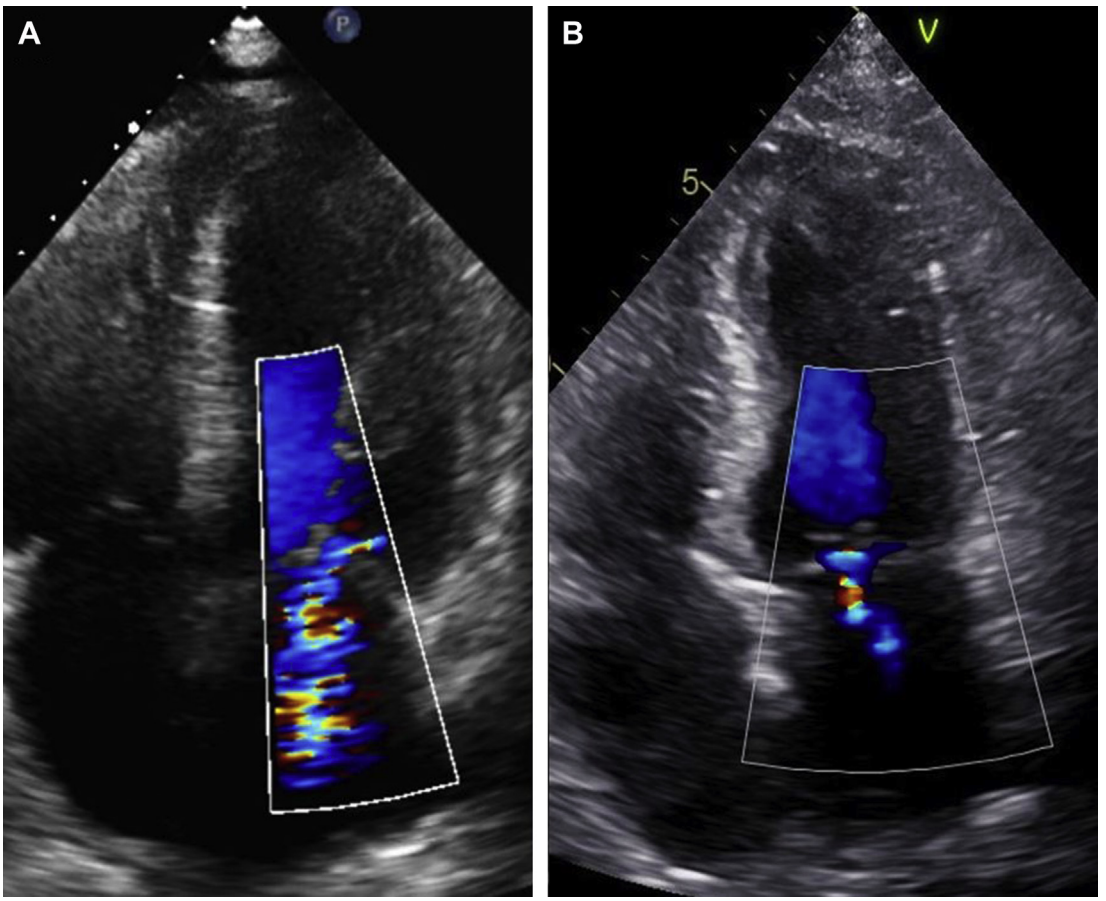

Fig. 4. Downgrading of MR severity following aortic valve replacement. Patient with severe AS undergoing aortic valve replacement. (*A*) Moderate secondary MR is observed preoperatively, but only trivial MR is observed 1 month (*B*) after aortic valve replacement.

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/m^2) 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 paradoxic low-flow low-gradient AS is commonly observed. Paradoxic 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

Table 2
Factors associated with postoperative changes in mitral regurgitation severity after surgical or transcatheter aortic valve replacement

Improvement	No Improvement, Deterioration
Secondary MR	Primary MR
Dilated left ventricle, reduced LVEF	Nondilated left ventricle, normal LVEF
Mean transaortic pressure gradient ≥40 mm Hg	Mean transaortic pressure gradient <40 mm Hg
Peak transaortic pressure gradient ≥60 mm Hg	Peak transaortic pressure gradient <60 mm Hg
Absence of prosthesis-patient mismatch	Prosthesis-patient mismatch
Absence of left atrial or mitral annulus dilatation	Left atrial or mitral annulus dilatation
Absence of atrial fibrillation	Atrial fibrillation
Absence of pulmonary hypertension	Pulmonary hypertension
No or mild residual AR	≥ Moderate residual AR
Balloon-expandable prosthesis	Self-expanding prosthesis (particularly when deeply implanted)
Coronary artery disease or previous myocardial infarction	—

Abbreviation: LVEF, left ventricular ejection fraction.

determining mitral valve area.[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,[36] and MS is an independent risk factor for adverse clinical events following TAVR.[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

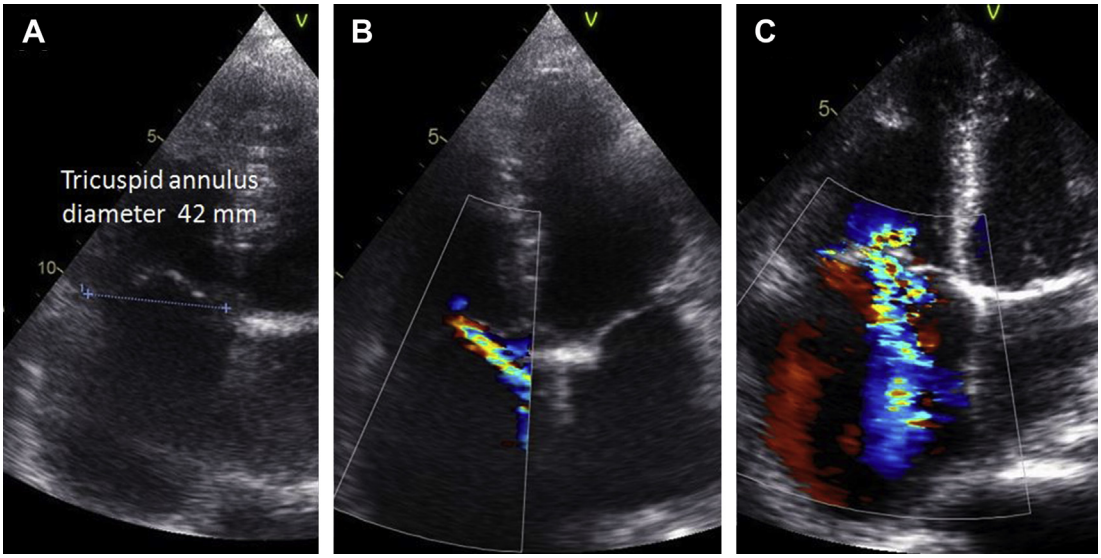

Fig. 5. Development of severe TR following aortic valve replacement. Patient with severe AS undergoing aortic valve replacement without tricuspid annuloplasty. Tricuspid annular dilatation (42 mm, apical 4-chamber view) and mild-to-moderate TR were observed (*A*, *B*) preoperatively. (*C*) Severe TR 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 disproportionally 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 cm^2 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 guidelines[14,43,44] (**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

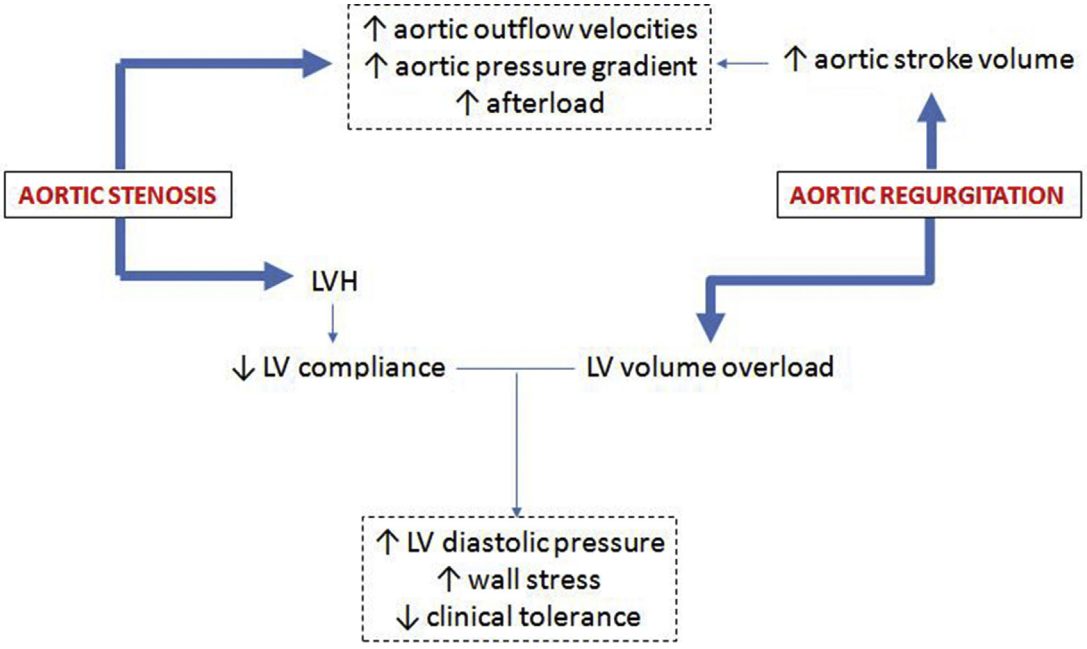

Fig. 6. Pathophysiology of mixed aortic valve disease. In the presence of left ventricular hypertrophy (LVH) and reduced LV compliance secondary to AS, the aortic regurgitant flow disproportionately increases LV diastolic pressure, thereby reducing clinical tolerance. Moreover, AR increases forward stroke volume, which further increases the pressure gradient and LV afterload.

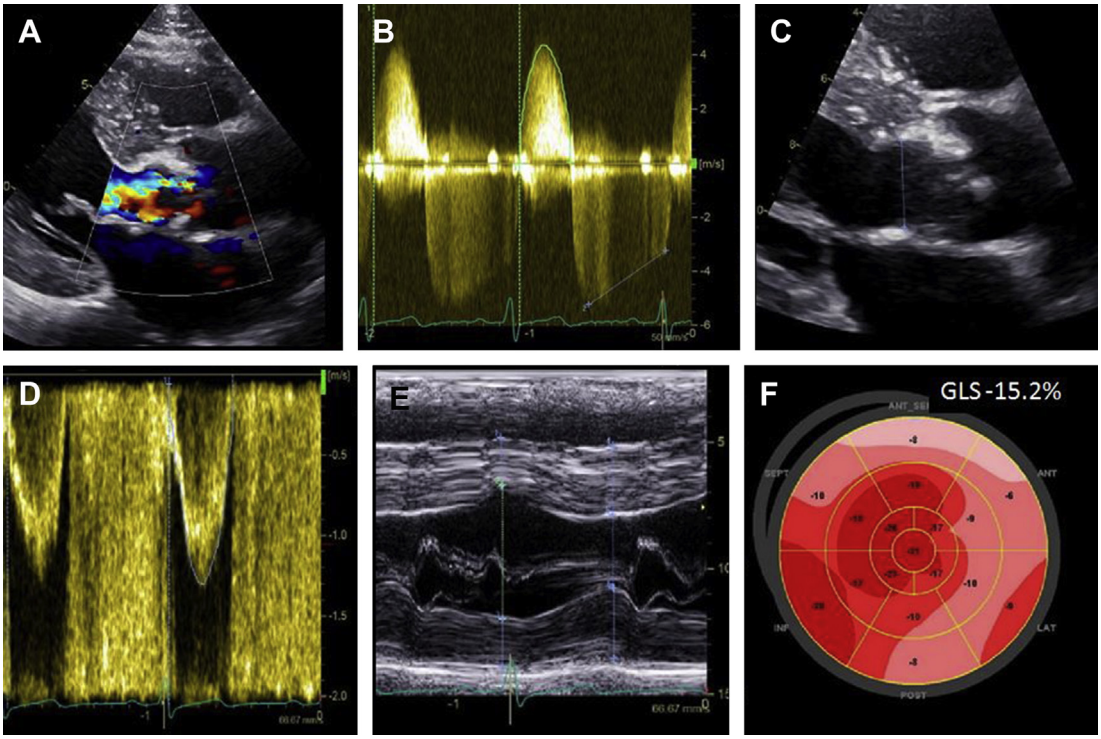

Fig. 7. Example of moderate AS and moderate AR resulting in severe mixed aortic valve disease. (*A*) Parasternal long-axis transthoracic view showing moderate AR (vena contracta, 5 mm). (*B*) Continuous wave Doppler obtained from a right parasternal window showing a maximal forward velocity of 4.15 m/s and a mean gradient of 43 mm Hg. (*C*) The left ventricular outflow tract diameter is 23 mm and the (*D*) velocity-time integral by pulsed wave Doppler is 33.7 cm, giving a calculated stroke volume of 144 mL, and an aortic valve area of 1.35 cm^2, suggesting a nonsevere AS. Although AS and AR are both moderate, the presence of increased aortic forward velocity, which provides an overall assessment of aortic valve disease, is consistent with severe mixed aortic valve disease. In addition, the typical features of this condition are present, (*E*) including severe left ventricular hypertrophy and absence of LV dilatation. (*F*) Ejection fraction is preserved, but the bull's-eye representation of longitudinal strain is consistent with subclinical LV dysfunction. GLS, global longitudinal strain.

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 addressed[14,43,44] (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

Table 3
Indications for mitral and/or tricuspid valve surgery in patients undergoing aortic valve replacement, and indications for aortic valve replacement in patients with nonsevere aortic stenosis undergoing other cardiac surgery

	2014–2017 AHA/ACC Guidelines		2017 ESC/EACTS Guidelines	
	Indication	**Class (Level of Evidence)**	**Indication**	**Class (Level of Evidence)**
(1) Surgery for severe AS is indicated. How should concomitant valvular disease be managed?				
MR	Concomitant mitral valve repair or replacement is indicated in patients with chronic severe primary MR	I (B)	Severe primary MR: not mentioned	
	Mitral valve surgery is reasonable for patients with chronic severe secondary MR	IIa (C)	Severe secondary MR: not mentioned However, mitral valve surgery is indicated in patients with severe secondary MR undergoing CABG and with LVEF >30%	I (C)
	Concomitant mitral valve repair is reasonable in patients with chronic moderate primary MR (stage B)	IIa (C)	Moderate primary MR: not mentioned	
	Mitral valve repair may be considered for patients with chronic moderate secondary MR (stage B)	IIb (C)	The potential impact of mitral valve intervention (surgery and catheter intervention) on survival in patients with secondary MR needs to be evaluated	
MS	Concomitant mitral valve surgery is indicated for patients with severe MS	I (C)	Severe concomitant aortic valve disease is a contraindication to percutaneous mitral commissurotomy In patients with severe MS, mitral valve surgery is preferable, when not contraindicated	
	Concomitant mitral valve surgery may be considered for patients with moderate MS (mitral valve area, 1.6–2.0 cm^2)	IIb (C)	Moderate MS: not mentioned	

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Table 3
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	2014–2017 AHA/ACC Guidelines		2017 ESC/EACTS Guidelines	
	Indication	**Class (Level of Evidence)**	**Indication**	**Class (Level of Evidence)**
TR	Tricuspid valve surgery is recommended for patients with severe TR (stages C and D)	I (C)	Tricuspid valve surgery is indicated in patients with severe primary or secondary TR	I (C)
	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	IIa (B)	Tricuspid valve surgery should be considered in patients with moderate primary TR undergoing left-sided valve surgery	IIa (C)
	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	IIb (C)	Tricuspid valve surgery should be considered in patients with mild or moderate secondary TR with dilated annulus ($\geq$40 mm or >21 mm/m^2) undergoing left-sided valve surgery	IIa (C)
			Tricuspid valve surgery may be considered in patients undergoing left-sided valve surgery with mild or moderate secondary TR, even in the absence of annular dilatation when previous recent right heart failure has been documented	IIb (C)
(2) Surgery is indicated on the mitral or tricuspid valve. How should AS be managed?				
—	AVR is reasonable for patients with moderate AS who are undergoing other cardiac surgery	IIa (C)	Surgical AVR should be considered in patients with moderate AS undergoing surgery of the ascending aorta or another valve, after heart team decision	IIa (C)

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,[48] 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.[49] 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,[50,51] 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.

REFERENCES

1. Andell P, Li X, Martinsson A, et al. Epidemiology of valvular heart disease in a Swedish nationwide hospital-based register study. Heart 2017;103:1696–703.
2. Leon MB, Smith CR, Mack M, et al. Transcatheter aortic-valve implantation for aortic stenosis in patients who cannot undergo surgery. N Engl J Med 2010;363:1597–607.
3. Smith CR, Leon MB, Mack MJ, et al. Transcatheter versus surgical aortic-valve replacement in high-risk patients. N Engl J Med 2011;364:2187–98.
4. Amano M, Izumi C, Taniguchi T, et al, CURRENT AS Registry Investigators. Impact of concomitant tricuspid regurgitation on long-term outcomes in severe aortic stenosis. Eur Heart J Cardiovasc Imaging 2018;20:353–60.
5. Jeong DS, Sung K, Kim WS, et al. Fate of functional tricuspid regurgitation in aortic stenosis after aortic valve replacement. J Thorac Cardiovasc Surg 2014;148:1328–33.
6. Worku B, Valovska MT, Elmously A, et al. Predictors of persistent tricuspid regurgitation after transcatheter aortic valve replacement in patients with baseline tricuspid regurgitation. Innovations (Phila) 2018;13:190–9.
7. Joseph L, Bashir M, Xiang Q, et al. Prevalence and outcomes of mitral stenosis in patients undergoing transcatheter aortic valve replacement: findings from the Society of Thoracic Surgeons/American College of Cardiology Transcatheter Valve Therapies Registry. JACC Cardiovasc Interv 2018;11:693–702.
8. Asami M, Windecker S, Praz F, et al. Transcatheter aortic valve replacement in patients with concomitant mitral stenosis. Eur Heart J 2018. https://doi.org/10.1093/eurheartj/ehy834.
9. Abdelghani M, Cavalcante R, Miyazaki Y, et al. Transcatheter aortic valve implantation for mixed versus pure stenotic aortic valve disease. EuroIntervention 2017;13:1157–65.
10. Thourani VH, Suri RM, Gunter RL, et al. Contemporary real-world outcomes of surgical aortic valve replacement in 141,905 low-risk, intermediate-risk, and high risk patients. Ann Thorac Surg 2015;99:55–61.
11. Unger P, Rosenhek R, Dedobbeleer C, et al. Management of multiple valve disease. Heart 2011;97:272–7.
12. Unger P, Pibarot P, Tribouilloy C, et al, On Behalf of the European Society of Cardiology Council on Valvular Heart Disease. Multiple and mixed valvular heart diseases: pathophysiology, imaging, and management. Circ Cardiovasc Imaging 2018;11:e007862.
13. Iung B, Baron G, Butchart EG, et al. A prospective survey of patients with valvular heart disease in Europe: the Euro heart survey on valvular heart disease. Eur Heart J 2003;24:1231–43.
14. Baumgartner H, Falk V, Bax JJ, et al. 2017 ESC/EACTS Guidelines for the management of valvular heart disease: the task force for the management of valvular heart disease of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS). Eur Heart J 2017;38:2739–91.
15. Cigarroa RG, Lange RA, Williams RH, et al. Underestimation of cardiac output by thermodilution in patients with tricuspid regurgitation. Am J Med 1989;86:417–20.
16. Unger P, Dedobbeleer C, Van Camp G, et al. Mitral regurgitation in patients with aortic stenosis undergoing valve replacement. Heart 2010;96:9–14.

17. Abramowitz Y, Jilaihawi H, Chakravarty T, et al. Mitral annulus calcification. J Am Coll Cardiol 2015;66: 1934–41.
18. Effron MK. Aortic stenosis and rupture of mitral chordae tendineae. J Am Coll Cardiol 1983;1:1018–23.
19. Beach JM, Mihaljevic T, Svensson LG, et al. Coronary artery disease and outcomes of aortic valve replacement for severe aortic stenosis. J Am Coll Cardiol 2013;61:837–48.
20. Unger P, Plein D, Van Camp G, et al. Effects of valve replacement for aortic stenosis on mitral regurgitation. Am J Cardiol 2008;102:1378–82.
21. Leong DP, Pizzale S, Haroun MJ, et al. Factors associated with low flow in aortic valve stenosis. J Am Soc Echocardiogr 2016;29:158–65.
22. Benfari G, Clavel MA, Nistri S, et al. Concomitant mitral regurgitation and aortic stenosis: one step further to low-flow preserved ejection fraction aortic stenosis. Eur Heart J Cardiovasc Imaging 2018;19: 569–73.
23. Clavel MA, Pibarot P, Messika-Zeitoun D, et al. Impact of aortic valve calcification, as measured by MDCT, on survival in patients with aortic stenosis: results of an international registry study. J Am Coll Cardiol 2014;64:1202–13.
24. Sannino A, Grayburn PA. Mitral regurgitation in patients with severe aortic stenosis: diagnosis and management. Heart 2018;104:16–22.
25. Clavel MA, Webb JG, Rodés-Cabau J, et al. Comparison between transcatheter and surgical prosthetic valve implantation in patients with severe aortic stenosis and reduced left ventricular ejection fraction. Circulation 2010;122:1928–36.
26. Treibel TA, Kozor R, Schofield R, et al. Reverse myocardial remodeling following valve replacement in patients with aortic stenosis. J Am Coll Cardiol 2018;71:860–71.
27. Nombela-Franco L, Ribeiro HB, Urena M, et al. Significant mitral regurgitation left untreated at the time of aortic valve replacement: a comprehensive review of a frequent entity in the transcatheter aortic valve replacement era. J Am Coll Cardiol 2014;63: 2643–58.
28. Unger P, Dedobbeleer C, Vanden Eynden F, et al. Mitral regurgitation after transcatheter aortic valve replacement: does the prosthesis matter? Int J Cardiol 2013;168:1706–9.
29. Taramasso M, Vanermen H, Maisano F, et al. The growing clinical importance of secondary tricuspid regurgitation. J Am Coll Cardiol 2012;59:703–10.
30. Mascherbauer J, Kammerlander AA, Marzluf BA, et al. Prognostic impact of tricuspid regurgitation in patients undergoing aortic valve surgery for aortic stenosis. PLoS One 2015;10(8):e0136024.
31. Lindman BR, Maniar HS, Jaber WA, et al. Effect of tricuspid regurgitation and the right heart on survival after transcatheter aortic valve replacement: insights from the placement of aortic transcatheter valves II inoperable cohort. Circ Cardiovasc Interv 2015; 8(4) [pii:e002073].
32. Dumont C, Galli E, Oger E, et al. Pre- and postoperative tricuspid regurgitation in patients with severe symptomatic aortic stenosis: importance of preoperative tricuspid annulus diameter. Eur Heart J Cardiovasc Imaging 2018;19:319–28.
33. Wunderlich NC, Beigel R, Siegel RJ. Management of mitral stenosis using 2D and 3D echo-Doppler imaging. JACC Cardiovasc Imaging 2013;6:1191–205.
34. Baumgartner H, Hung J, Bermejo J, et al. Echocardiographic assessment of valve stenosis: EAE/ASE recommendations for clinical practice. J Am Soc Echocardiogr 2009;22:1–23.
35. Oktay AA, Gilliland YE, Lavie CJ, et al. Echocardiographic assessment of degenerative mitral stenosis: a diagnostic challenge of an emerging cardiac disease. Curr Probl Cardiol 2017;42:71–100.
36. Abramowitz Y, Kazuno Y, Chakravarty T, et al. Concomitant mitral annular calcification and severe aortic stenosis: prevalence, characteristics and outcome following transcatheter aortic valve replacement. Eur Heart J 2017;38:1194–203.
37. Egbe AC, Poterucha JT, Warnes CA. Mixed aortic valve disease: midterm outcome and predictors of adverse events. Eur Heart J 2016;37:2671–8.
38. Egbe AC, Luis SA, Padang R, et al. Outcomes in moderate mixed aortic valve disease: is it time for a paradigm shift? J Am Coll Cardiol 2016;67:2321–9.
39. Zilberszac R, Gabriel H, Schemper M, et al. Outcome of combined stenotic and regurgitant aortic valve disease. J Am Coll Cardiol 2013;61:1489–95.
40. Rashedi N, Popovic ZB, Stewart WJ, et al. Outcomes of asymptomatic adults with combined aortic stenosis and regurgitation. J Am Soc Echocardiogr 2014;27:829–37.
41. de Marchi SF, Windecker S, Aeschbacher BC, et al. Influence of left ventricular relaxation on the pressure half time of aortic regurgitation. Heart 1999;82:607–13.
42. Blais C, Burwash IG, Mundigler G, et al. Projected valve area at normal flow rate improves the assessment of stenosis severity in patients with low-flow, low-gradient aortic stenosis: the multicenter TOPAS (Truly or Pseudo-Severe Aortic Stenosis) study. Circulation 2006;113:711–21.
43. Nishimura RA, Otto CM, Bonow RO, et al, ACC/AHA Task Force Members. 2014 AHA/ACC guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association task force on practice guidelines. Circulation 2014;129:e521–643.
44. Nishimura RA, Otto CM, Bonow RO, et al. 2017 AHA/ACC focused update of the 2014 AHA/ACC guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association task force

on clinical practice guidelines. Circulation 2017;135: e1159–95.
45. Vassileva CM, Li S, Thourani VH, et al. Outcome characteristics of multiple-valve surgery: comparison with single-valve procedures. Innovations (Phila) 2014;9:27–32.
46. Rankin JS, He X, O'Brien SM, et al. The Society of Thoracic Surgeons risk model for operative mortality after multiple valve surgery. Ann Thorac Surg 2013; 95:1484–90.
47. Lee R, Li S, Rankin JS, et al. Society of Thoracic Surgeons Adult cardiac surgical database. Fifteen-year outcome trends for valve surgery in North America. Ann Thorac Surg 2011;91:677–84.
48. Ando T, Takagi H, Briasoulis A, et al. A systematic review of reported cases of combined transcatheter aortic and mitral valve interventions. Catheter Cardiovasc Interv 2018;91:124–34.
49. Cortes C, Amat-Santos IJ, Nombela-Franco L, et al. Mitral regurgitation after transcatheter aortic valve replacement: prognosis, imaging predictors, and potential management. JACC Cardiovasc Interv 2016;9:1603–14.
50. Lancellotti P, Rosenhek R, Pibarot P, et al. ESC working group on valvular heart disease position paper–heart valve clinics: organization, structure, and experiences. Eur Heart J 2013;34:1597–606.
51. Chambers JB, Prendergast B, Iung B, et al. Standards defining a 'Heart Valve Centre': ESC working group on valvular heart disease and European association for cardiothoracic surgery viewpoint. Eur Heart J 2017;38:2177–83.