

## HOW TO USE IMAGING

# Multiple and Mixed Valvular Heart Diseases Pathophysiology, Imaging, and Management

**M**ultiple valvular heart disease (VHD), ie, the combination of stenotic or regurgitant lesions occurring on  $\geq 2$  cardiac valves, and mixed VHD, ie, the combination of stenotic and regurgitant lesions on the same valve, are highly prevalent conditions. Yet, there is only limited data in the literature and current guidelines to support and guide clinical decision-making. This paradox is, at least partly, explained by the heterogeneity of these conditions in terms of combinations, pathogenesis, severity, surgical risk, reparability, and suitability for transcatheter therapies.

The aims of this article are (1) to provide a state-of-the-art review with respect to the pathophysiology, diagnosis (with an emphasis on pitfalls), and management strategies of multiple and mixed VHD and (2) to propose a standardized framework for the clinician.

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## PATHOGENESIS AND PREVALENCE

Multiple and mixed VHD are highly prevalent conditions. In the Euro Heart Survey, multiple VHD, as defined by at least 2 moderate VHDs, was observed in 20% of the patients with native VHD and in 17% of those undergoing intervention.<sup>1</sup> In the American Society of Thoracic Surgeons Database including 290 000 patients who underwent surgery between 2003 and 2007, 11% had double valve procedures (replacement or repair), most often aortic and mitral,<sup>2</sup> and triple valve surgery has been performed in 1% of cases. In a Swedish nationwide study based on hospital discharge codes without quantification of valvular dysfunction, multiple VHD accounted for 11% of patients.<sup>3</sup> The most frequent associations were aortic stenosis (AS) plus aortic regurgitation (AR), AS plus mitral regurgitation (MR) and AR plus MR.

Multiple valve disease is most often acquired.<sup>4</sup> In the Euro Heart Survey,<sup>5</sup> rheumatic fever was the predominant pathogenesis (51%), but degenerative VHD was also highly prevalent (41%). Other acquired pathogeneses, which include infective endocarditis, radiation therapy, drug-induced VHD, and inflammatory diseases, were by far less frequent. As in single VHD, a shift from rheumatic toward degenerative pathogenesis is currently observed in industrialized countries reflecting aging and the overall decreased incidence of rheumatic fever. Degenerative mitral annulus and leaflet calcifications often coexist with AS in the elderly patients and may, when severe, cause significant mitral stenosis (MS). This multiple VHD entity is often associated with worse prognosis and poses specific therapeutic challenges<sup>6</sup> because balloon commissurotomy or surgical mitral valve replacement is often not an option in these patients. Secondary MR and tricuspid regurgitation (TR) may develop in patients with aortic VHD and in patients with right ventricular volume or pressure overload because of left-sided or pulmonary VHD. Significant pulmonary

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regurgitation is unusual, and acquired pathogeneses include endocarditis, carcinoid disease, and, rarely, left-sided VHD-related pulmonary hypertension. Because of the high prevalence of coronary artery disease with previous myocardial infarction in patients with degenerative VHD, associated ischemic MR is not uncommon in this setting. Congenital pathogeneses are far less frequent causes of multiple VHD.

Congenital (mainly bicuspid aortic valve) and degenerative VHDs are currently the most frequent pathogeneses of mixed aortic VHD among patients undergoing aortic valve replacement (37%–49% and 53%, respectively) in industrialized countries, whereas rheumatic (9%–13%) and endocarditis (1%) are less frequent.<sup>4,5</sup> Mixed mitral VHD mainly results from rheumatic and degenerative processes, the latter being found almost exclusively in the elderly. Although the prevalence of adult congenital heart disease is constantly increasing and many of these individuals have multiple or mixed VHD,<sup>7</sup> this review will focus on noncongenital multiple/mixed VHD.

## **PATHOPHYSIOLOGY, DIAGNOSIS, AND IMAGING**

The hemodynamic and clinical consequences of any given valvular lesion may be modulated by the concomitant presence of another stenotic or regurgitant lesion on the same valve (mixed VHD), or on another valve (multiple VHD). These consequences depend on the complex interplay of several factors, including the specific combination of VHD, the severity and timing of onset of each individual lesion, the loading conditions, and the ventricular systolic or diastolic performance. The main hemodynamic interactions that may impact on the diagnosis of multiple and mixed VHDs are (1) low-flow, low-gradient stenosis is frequent; (2) mixed valve disease may be associated with increased antero-grade flow and gradient; (3) the continuity equation is inapplicable when transvalvular flows are unequal; (4) any severe valvular lesion may induce or increase upstream secondary MR or TR; (5) pressure half-time-derived methods may be invalid in the presence of altered left ventricular (LV) compliance/relaxation or abnormal LV filling in the presence of mixed VHD.

### **Role of Imaging Modalities for Assessment of Multiple/Mixed VHD**

#### **Doppler Echocardiography**

Doppler echocardiography is the cornerstone of the diagnosis of multiple and mixed VHD. As in single-valve/single-lesion disease, echocardiography will allow establishing the pathogenesis, mechanisms, severity, progression, and repercussions of each valvular lesion.

Echocardiography is critical in determining the indication and timing for surgery and the likelihood of successful valve repair or of transcatheter valve intervention. However, the hemodynamic consequences of multiple and mixed VHD on blood flow, ventricular size, and function may affect the echocardiographic diagnosis. Several methods routinely used to assess VHD have not been validated in this subset of patients and may be misleading if not correctly interpreted in the context of the multiple/mixed VHD. The main diagnostic caveats in the echocardiographic diagnosis in multiple and mixed VHD are presented in Table 1.<sup>4</sup> An integrative approach is even more needed than for single VHD.

#### **Cardiac Catheterization**

Cardiac catheterization is currently recommended in situations where noninvasive evaluation is inconclusive or discordant with clinical findings<sup>8</sup> and remains commonly performed in patients with multiple VHD.<sup>1</sup> However, cardiac output assessment by either the thermodilution or the Fick method, which is an essential component of the Gorlin formula for the calculation of aortic or mitral valve area, may be inaccurate in patients with severe TR and among those with low cardiac output, which are both common in multiple and mixed VHD. Moreover, because right heart flow does not equal the transvalvular flow in patients with mixed aortic and mixed mitral VHD, the Gorlin formula is inherently inaccurate and should not be used in this setting.

There is growing evidence that other imaging modalities can be helpful in VHD when conventional echocardiography is inconclusive. However, there is currently no data on their potential role in the specific assessment of patients with multiple VHD. Yet, an accurate determination of the severity of stenotic and regurgitant lesions is critical, and imaging techniques other than standard echocardiography may prove helpful in difficult cases, particularly in the setting of low-flow situations.

#### **Three-Dimensional Echocardiography**

Three-dimensional echocardiography can be used to obtain more accurate assessment of aortic valve area, by allowing direct measurement of LV outflow tract area (the which is usually not circular). Using a trans-thoracic or transesophageal approach, it may also be used to measure mitral valve area in rheumatic MS.<sup>9</sup>

#### **Stress Echocardiography**

Low-dose ( $\leq 20$   $\mu\text{g}/\text{kg}$  per min) dobutamine stress echocardiography may be helpful to distinguish true severe from pseudosevere AS and to assess LV flow reserve, when the pressure gradient is low and LV ejection fraction is reduced. Although there is limited (if any) specific data on multiple and mixed VHD, treadmill or preferably bicycle stress echocardiography may be indicated when

**Table 1. Main Diagnostic Caveats in the Echocardiographic Assessment of Multiple and Mixed Valvular Diseases and Proposed Solutions Using Multimodality Imaging**

Combination of Valve Lesions	AS	AR	MS	MR
AS		C: AR pressure half-time method unreliable	C: MS pressure half-time method unreliable	C: increased mitral regurgitant volume
		S: peak aortic jet velocity and Doppler mean gradient reflect severity of both AR and AS	C: low-flow, low-gradient MS can occur	C: Increased area of MR jet using color-flow mapping. Mitral effective regurgitant orifice less affected than MR volume and color-flow mapping parameters
			S: 3D echocardiography to measure mitral valve anatomic area and confirm MS severity	S: CMR may be used to quantify MR volume and fraction and corroborate MR severity
AR	C: simplified Bernoulli equation for gradient determination might not be applicable if LV outflow tract velocity is elevated		C: aortic regurgitant jet can be mistaken for MS jet	C: Doppler volumetric method using left-sided assessment of net forward flow invalid
	C: Gorlin formula using thermodilution/Fick method is invalid		C: continuity equation is unreliable to calculate mitral valve area if aortic valve is used as the reference flow	C: mitral-to-aortic velocity time integral ratio unreliable
	S: Continuity equation is applicable to assess AVA		C: MS pressure half-time method unreliable	S: the PISA method remains accurate for the assessment of MR
	C: most echo parameters only reflect the severity of only one component of the disease: AS (AVA) or AR (regurgitant orifice area or volume)		S: 3D echocardiography to measure mitral valve anatomic area and confirm MS severity	
	S: peak aortic jet velocity and Doppler mean gradient reflect severity of both AS and AR		S: consider using pulmonic flow as the reference for the continuity equation	
MS	C: low-flow, low-gradient AS is common	C: MS can blunt the increase in pulse pressure and the LV dilation associated with AR		C: mitral-to-aortic velocity time integral ratio unreliable
	S: DSE or aortic valve calcium scoring by MDCT can be used to confirm AS severity			S: Doppler mitral gradient reflects severity of both MS and MR
MR	C: mitral regurgitant jet should not be mistaken for the AS jet	C: Doppler volumetric method using left-sided assessment of net forward flow invalid	C: continuity equation unreliable	
	C: low-flow, low-gradient AS is common	C: pressure half-time method can be unreliable	C: pressure half-time method may not be reliable	
	S: DSE or aortic valve calcium scoring by MDCT can be used to confirm AS severity	S: CMR may be used to quantify AR and MR volumes and fractions and corroborate both AR and MR severity	C: Gorlin formula using thermodilution invalid	S: Doppler mitral gradient reflects severity of both MS and MR

This table presents the caveats in the echocardiographic assessment of a given valvular lesion (horizontal rows) in presence of concomitant valvular lesion (vertical columns) and the proposed solutions using multimodality imaging. 3D indicates 3-dimensional; AR, aortic regurgitation; AS, aortic stenosis; AVA, aortic valve area; C, caveat; CMR, cardiac magnetic resonance; DSE, dobutamine stress echocardiography; LV, left ventricular; MDCT, multidetector computed tomography; MR, mitral regurgitation; MS, mitral stenosis; PISA, proximal isovelocity surface area; and S, solution.

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symptoms appear disproportionate in relation to the resting hemodynamics. This test may provide a mechanistic explanation for the symptoms, by revealing, for example, a disproportionate increase in the transvalvular pressure gradient or pulmonary arterial pressure.

When the VHD appears severe on resting echocardiography but the patient claims to be asymptomatic, exercise testing may unmask symptoms, an abnormal blood pressure response to exercise, ST-segment abnormalities, or exercise-induced arrhythmias.<sup>8,10-12</sup>

### Multidetector Computed Tomography

Multidetector computed tomography is increasingly used to assess the aortic valve calcium score when there is evidence of low-flow, low-gradient AS and preserved LV ejection fraction. High calcium scores are consistent with increased likelihood of severe AS (Table 2).<sup>8,13,14</sup>

### Cardiac Magnetic Resonance

In patients with inadequate echocardiographic image quality or in case of discrepant results, cardiac magnetic resonance allows assessing the severity of valvular lesions, particularly of regurgitant lesions and thus of mixed valve disease, as well as ventricular volumes and systolic function.<sup>15</sup> However, the assessment of regurgitant fraction and volume by calculating ventricular volumes may be misleading in the presence of multiple VHD because it assumes that only one valve is affected, and alternative methods, such as phase-contrast velocity mapping, should be preferred for quantifying valvular regurgitation.<sup>16</sup> Using standard imaging sequences, cardiac magnetic resonance allows identifying accurately serial changes in ventricular volumes, mass, and function reflecting the global burden of valvular disease and has, therefore, the potential to contribute to determining the optimal time for surgical or transcatheter valvular intervention. However, there is only limited data on the specific added value of cardiac magnetic resonance in multiple valve disease.

### AS and MR

Long-standing increased afterload, which may eventually result in hypertrophic remodeling, dilatation, or dysfunction of the LV, is a hallmark of severe AS. Consequently, secondary MR may develop as a result of leaflet tethering and mitral annular dilatation. Because of the high prevalence of concomitant coronary artery disease, ischemic MR is also not uncommon in the elderly population. Elderly patients may also present primary MR as a result of mitral annular calcifications or pro-

lapse (Figure 1).<sup>17</sup> The association of severe degenerative AS and MR because of chordal rupture is rare but generally associated with poor LV performance.<sup>18</sup>

As a direct consequence of the increased afterload because of AS, the transmitral systolic pressure gradient increases, therefore, leading, for any given mitral effective regurgitant orifice, to higher regurgitant volume. Moreover, the presence of significant MR may decrease the forward flow across the aortic valve (Figure 1). This MR-induced low-flow state may reduce the transaortic pressure gradient and yield to an underestimation of AS severity (Table 1). This low-flow, low-gradient AS pattern because of coexistent MR may occur with reduced (classical low-flow, low-gradient AS) or preserved (paradoxical low-flow, low-gradient AS) LV ejection fraction.<sup>19</sup> In the presence of MR, dobutamine stress echocardiography may fail to induce a significant increase in LV outflow and may thus not allow the confirmation of AS severity. Quantification of aortic valve calcium score by multidetector computed tomography may be useful to differentiate true versus pseudo-severe AS in these patients with low-flow, low-gradient AS and concomitant significant MR. A typical example is shown in Figure 1.

### AS and MS

This infrequent combination is usually poorly tolerated, and the reduction in cardiac output is usually greater than what is seen in isolated AS or MS. Hence, both aortic and mitral pressure gradients may be lower than expected, which can lead to underestimation of the severity of both AS and MS. Similar to MR, severe MS may lead to low LV outflow and, therefore, result in paradoxical low-flow, low-gradient AS. This highlights the need for a careful quantification of AS severity using an integrative approach, including aortic valve calcium quantification by multidetector computed tomography.

### AR and MS

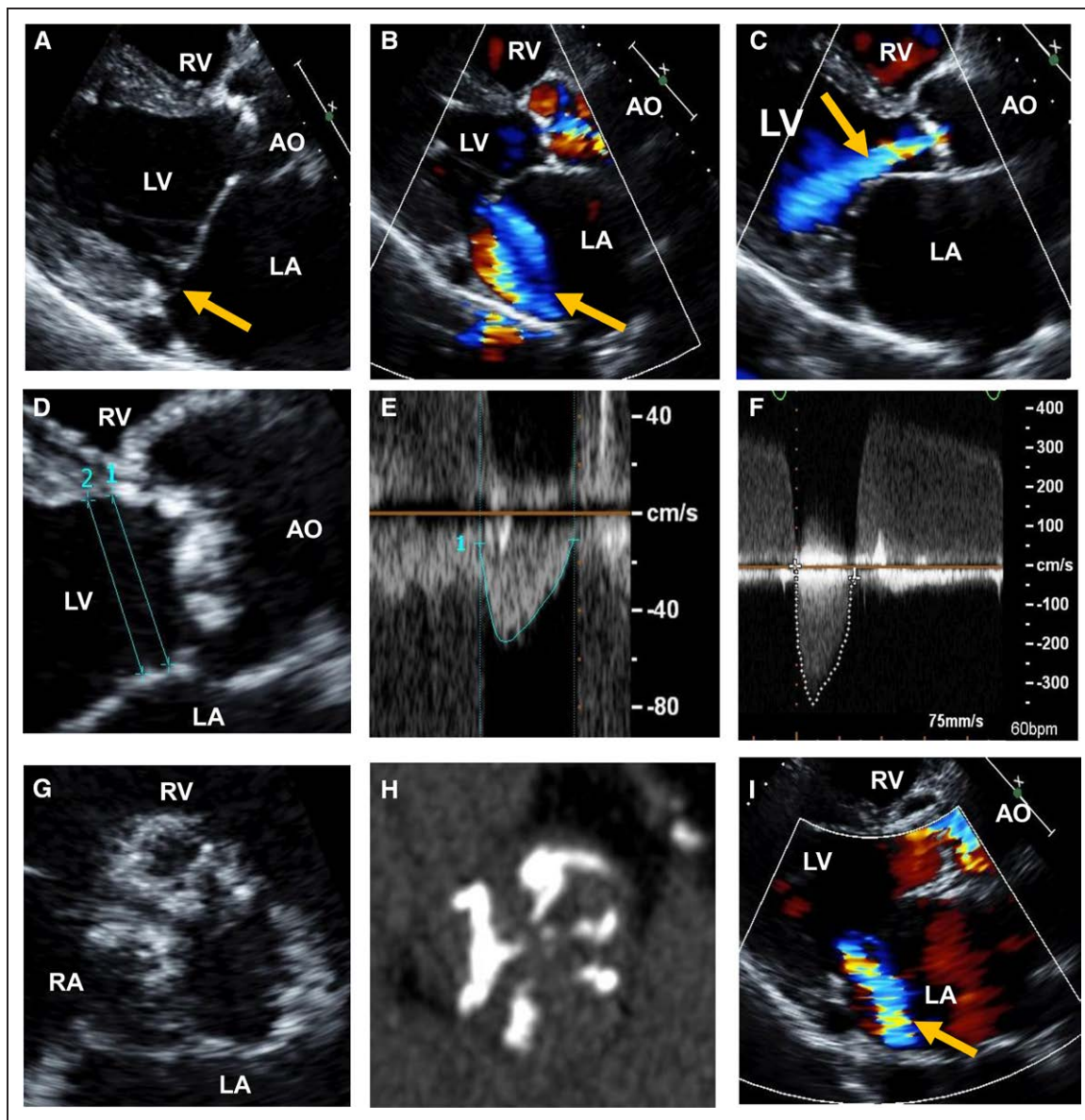
Whereas preload is increased by AR, it is decreased by MS. These opposing loading conditions may result in lower

**Table 2. Computed Tomographic Aortic Valve Calcium Scoring Thresholds (Agatston Unit) for Anatomically Severe Aortic Stenosis<sup>8,13,14</sup>**

	Source	Women			Men		
		Threshold	Sensitivity, %	Specificity, %	Threshold	Sensitivity, %	Specificity, %
Optimum	Pawade et al <sup>13</sup>	1377	87	84	2062	80	82
	ESC Guidelines 2017	1200			2000		
	Clavel et al <sup>14</sup>	1274	89	81	2065	80	82
Most specific	Pawade et al <sup>13</sup>	2646	51	96	3905	36	95
	ESC Guidelines 2017	1600			3000		
	Clavel et al <sup>14</sup>	1681	69	95	3381	59	95
Most sensitive	Pawade et al <sup>13</sup>	774	95	62	1196	95	58
	ESC Guidelines 2017	800			1600		
	Clavel et al <sup>14</sup>	791	95	63	1661	95	70

ESC indicates European Society of Cardiology.



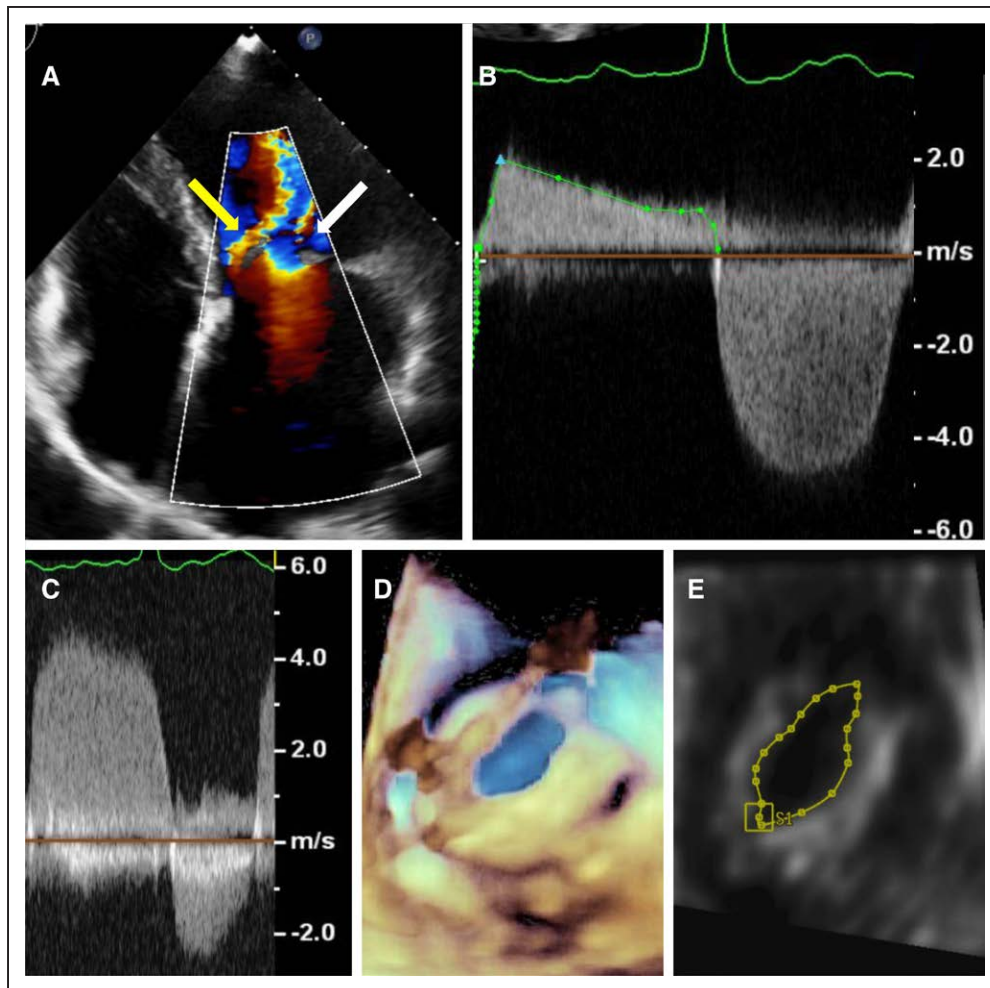


**Figure 1. Eighty-year-old symptomatic man with concomitant aortic stenosis, aortic regurgitation, and mitral regurgitation.**

**A**, Transthoracic echocardiographic parasternal long-axis view in midsystole. Left ventricular (LV) ejection fraction is 65%. The aortic valve is calcified, and there is a P2 mitral valve prolapse with a dilated left atrium (LA). **B**, Moderate mitral regurgitation with eccentric jet (orange arrow). **C**, Mild aortic regurgitation (orange arrow). **D**, Parasternal long-axis zoomed view of the LV outflow tract (LVOT) and aortic valve that appears severely calcified. The LVOT diameter is measured at 24.9 mm and aortic annulus diameter at 24.4 mm. **E**, LVOT flow velocity by pulsed wave Doppler. The LVOT velocity time integral is 11 cm, and the calculated forward stroke volume in the LVOT is 54 mL. The stroke volume index is thus 30 mL/m<sup>2</sup> (body surface area, 1.8 m<sup>2</sup>), consistent with a low-flow state. **F**, Continuous-wave Doppler of the aortic valve flow. The mean transaortic gradient is 28 mmHg, and the aortic valve area by continuity equation is 0.75 cm<sup>2</sup>. There is thus a discordant echocardiographic grading, with the concomitance of a small valve area and a low gradient. **G**, Parasternal short-axis view in midsystole showing a calcified aortic valve with restricted opening. **H**, Noncontrast multidetector computed tomography showing severe valve calcification (aortic valve calcium score, 2395 AU). On this basis, the patient was considered having true severe aortic stenosis and underwent transcatheter aortic valve replacement with a SAPIEN 3 valve. **I**, Mitral regurgitation (orange arrow) at 30 d post-valve replacement. The severity of the regurgitation was similar compared with baseline. The stroke volume increased to 60 mL but remained in the low-flow range (33 mL/m<sup>2</sup>). The aortic valve area was 1.97 cm<sup>2</sup>, and the mean gradient decreased to 7 mmHg. The patient who was in New York Heart Association class III before transcatheter valve replacement improved to class I to II 1 mo after intervention. In summary, this is a case of a patient with severe aortic stenosis who presented with a paradoxical (preserved LV ejection fraction) low-flow, low-gradient pattern. The low-flow state was, at least partly, related to the coexistence of moderate mitral regurgitation. The presence of severe aortic stenosis was confirmed by the quantification of aortic valve calcification by computed tomography. AO indicates aorta; RV, right ventricular.

LV volumes compared with isolated AR.<sup>20</sup> In the presence of MS, the typical signs of AR, including increased pulse pressure, may be absent.<sup>21</sup> Figure 2 shows a patient with rheumatic heart disease and concomitant AR and MS. In such cases, both the continuity equation and pressure half-

time methods are invalid to calculate mitral valve effective orifice area, because of the presence of concomitant significant ( $\geq$ moderate) AR (Table 1). Transthoracic 3-dimensional echocardiography may be used to assess mitral valve anatomic orifice area and confirm MS severity (Figure 2).



**Figure 2.** Patient with multiple mitral and aortic valve diseases.

Fifty-six-year-old woman with concomitant rheumatic mitral and aortic valve disease. **A**, Transthoracic echocardiographic color Doppler apical 4-chamber view during diastole showing aortic regurgitation jet (yellow arrow) and accelerated transmitral flow velocities consistent with mitral stenosis (white arrow). **B**, Continuous wave Doppler signal and tracing across the mitral valve, with an 8-mmHg mean diastolic pressure gradient, a 1.5 cm<sup>2</sup> mitral valve area using the pressure half-time method. **C**, Continuous wave Doppler tracing across the aortic valve; mean pressure gradient was 16 mmHg, aortic valve area was 1.5 cm<sup>2</sup> by continuity equation method, and the effective regurgitant orifice was 0.20 cm<sup>2</sup> by the proximal isovelocity surface area method (not shown). **D**, Three-dimensional (3D) view of the mitral valve orifice, with a 1.1-cm<sup>2</sup> mitral valve area using 3D reconstruction of the mitral valve orifice (**E**). This case highlights the overestimation of mitral valve area using the pressure half-time method in the presence of concomitant aortic valve disease. Furthermore, the continuity equation method cannot be used to calculate the mitral valve area because of the coexistence of moderate aortic regurgitation. In such situation, 3D echocardiography and planimetry of the mitral valve anatomic orifice area can be used to corroborate mitral stenosis severity. In summary, this patient had concomitant severe mitral stenosis, moderate aortic regurgitation, and mild-to-moderate aortic stenosis.

### AR and MR

MR associated with AR may be primary or secondary to LV remodeling as a consequence of AR. LV relaxation and compliance have been shown to influence AR pressure half-time.<sup>22</sup> In turn, chronic MR may lead to LV dilation and increase in LV compliance.<sup>23</sup> Hence, pressure half-time to assess AR severity should be interpreted cautiously in the presence of MR or in the presence of any condition altering LV relaxation/compliance. In the presence of severe MR, mild-to-moderate AR is usually well tolerated.<sup>24</sup> However, when AR is severe, any degree of MR may substantially worsen the LV dilation and dysfunction. AR and MR both contribute to increase preload, which may result in accelerated LV dilatation and dysfunction. Furthermore, mitral valve competency normally protects the left atrium and the pulmonary veins from the deleterious effects of the increased LV pressure related to AR.

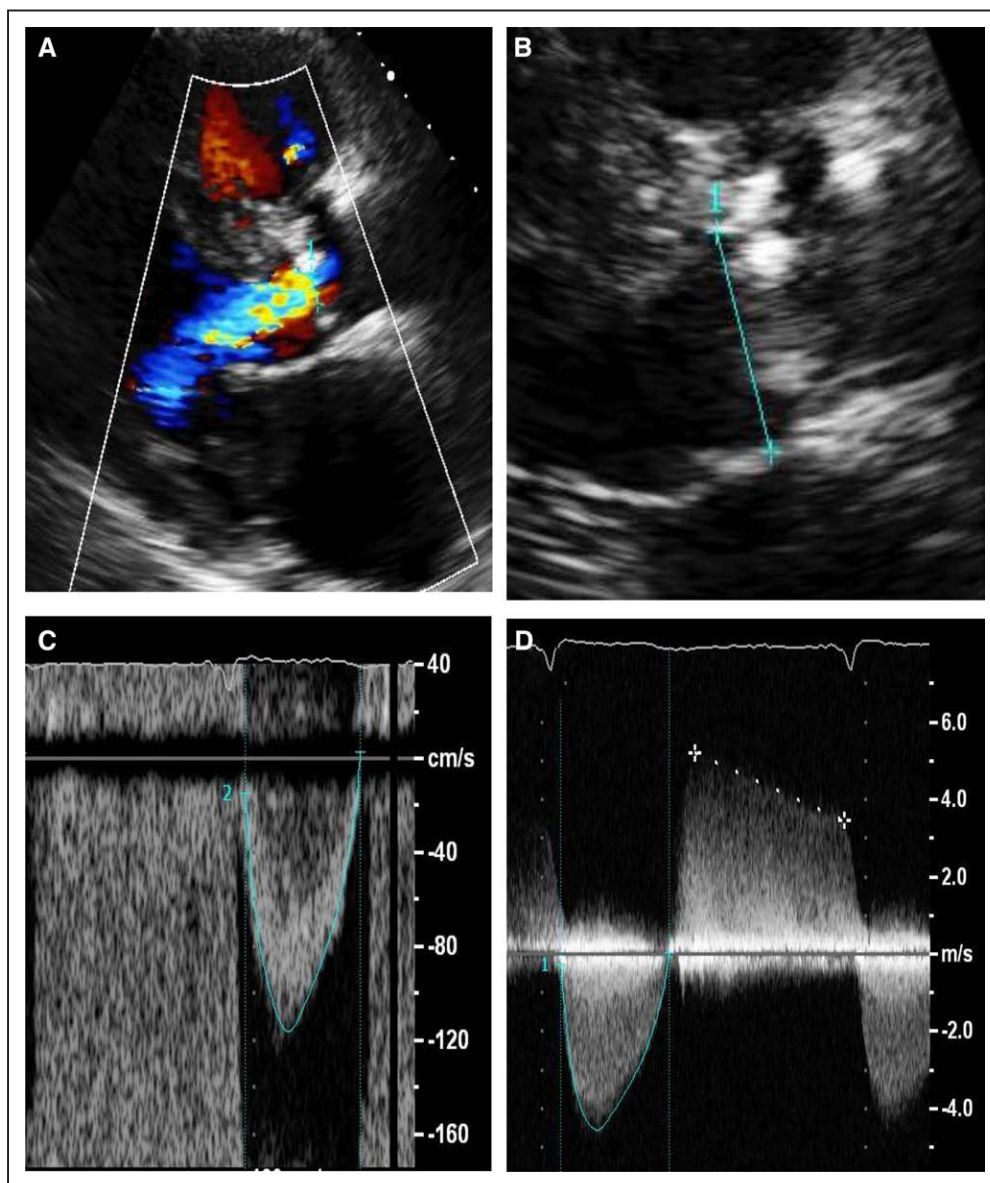
However, the coexistence of AR and MR exacerbates the impact of LV volume and pressure overload on the left atrium, pulmonary circulation, and right chambers. Hence, this combination is poorly tolerated, and postoperative LV dysfunction is more likely to occur than in isolated valve regurgitation.<sup>25</sup> In the long-term, LV function may eventually improve after double-valve surgery,<sup>26</sup> but, in a small series, persisting symptoms were more frequent than in patients undergoing valve replacement for isolated AR, and survival rates were lower compared with patients with symptomatic MR who had been operated on.<sup>27</sup>

### TR and Left-Sided VHD

The prevalence of secondary TR is high among patients presenting with left-sided VHD. Although it

was initially mainly studied for mitral VHD,<sup>28</sup> there is now evidence that it may also occur as a result of aortic VHD. TR is associated with reduced long-term functional capacity and survival after treatment of the left-sided VHD.<sup>29</sup> A complex interplay of many factors may contribute to the occurrence and severity of secondary TR in the setting of downstream VHD, including pulmonary hypertension, atrial fibrillation, right ventricular dilatation and dysfunction, leaflet tethering, annular dilatation toward the right ventricular

free wall, or right atrial enlargement. Because TR is highly sensitive to changes in loading conditions, it has been proposed that annular dilatation and leaflet coaptation, rather than TR severity itself, would be a predictor for the future development of TR and would serve as a therapeutic guide.<sup>30</sup> Thermodilution-derived cardiac output may be erroneously low in patients with severe TR, which may lead to underestimation of aortic valve area by the Gorlin equation and thus overestimation of AS severity.<sup>31</sup>



**Figure 3. Patient with mixed aortic stenosis and regurgitation.**

Transthoracic echocardiographic images in a symptomatic (New York Heart Association class II and III) man with a body surface area of 1.85 m<sup>2</sup>. **A**, Parasternal long-axis color Doppler view showing a moderate aortic regurgitation. The vena contracta width is 5.8 mm. **B** and **C**, Left ventricular outflow tract diameter is 26.5 mm, and velocity-time integral by pulsed wave Doppler is 25 cm with a calculated stroke volume of 138 mL. The aortic flow velocity time integral by continuous wave Doppler valve effective orifice area by continuity equation is 1.34 cm<sup>2</sup> (indexed, 0.72 cm<sup>2</sup>/m<sup>2</sup>). Hence, the echocardiographic findings suggest the concomitance of a moderate aortic regurgitation with a moderate aortic stenosis. In this case, it is challenging to establish whether or not aortic valve intervention is indicated. Neither the aortic regurgitation nor the aortic stenosis is severe and mandate intervention according to the guidelines. However, **(D)** shows a peak velocity of 4.5 m/s and a mean gradient of 44 mmHg. These parameters provide an assessment of the severity of the overall aortic valve disease, that is, regurgitation plus stenosis. Indeed, the peak aortic jet velocity and mean gradient increase with both aortic stenosis and aortic regurgitation (because of increase in transvalvular flow). The patient was thus referred to aortic valve replacement.



**AS and AR**

Mixed aortic VHD is characterized by a combination of pressure and volume load that imposes a greater stress on the LV than that induced by isolated AS or AR. The stenotic component imposes a pressure overload that aggravates LV hypertrophy, resulting in decreased LV compliance and thus in a disproportionate increase in LV diastolic pressure per unit of volume increase during diastole.<sup>32,33</sup> Symptomatic patients rarely achieve a LV end-systolic dimension of 50 mm, which suggests that LV hypertrophy may not allow the LV to dilate as a result of the volume overload.<sup>33-35</sup> Moreover, the increase in stroke volume resulting from the regurgitant flow may further contribute to severe pressure overload even when the aortic valve area is >1.0 cm<sup>2</sup>. The aortic valve area reflects the severity of AS, whereas the effective regurgitant orifice area or regurgitant volume reflects the severity of AR. However, none of these parameters adequately reflects the overall hemodynamic burden associated with the summation of AS and AR. However, the peak aortic jet velocity and mean gradient increase with

AS but also with AR because of increase in transvalvular flow. Hence, these parameters may be useful to assess the overall severity of the aortic valve disease (AS+AR)<sup>34</sup> and have been shown to correlate with the outcomes.<sup>32-34</sup> Hence, a symptomatic patient with moderate AS and moderate AR having a peak jet velocity ≥4 m/s and a mean gradient ≥40 mm Hg should be referred to intervention. The example of a patient presenting moderate AS combined with moderate AR resulting in a markedly increase in transaortic velocity is depicted in Figure 3.

**MS and MR**

MR increases the flow rate across the mitral valve. Because transvalvular pressure gradient is a function of the square of the transvalvular flow rate, left atrial pressure may be markedly increased in patients with mixed mitral VHD, resulting in severe exercise intolerance through an increase in pulmonary venous and capillary pressure. Because of the volume overload, LV size is usually larger than in isolated MS. Similar to aortic VHD, the association of moderate MS and moderate

**Table 3. Indications for Valve Surgery in Patients Undergoing Surgery on Another Valve When the 2 Valve Lesions Are Severe, According to the AHA/ACC and ESC/EACTS Guidelines<sup>8,10,11</sup>**

Valve Lesion	2014–2017 AHA/ACC Guidelines	2017 ESC/EACTS Guidelines
AS	AVR is indicated for patients with severe AS when undergoing other cardiac surgery (class I, LOE B)	Surgical AVR is indicated in patients with severe AS undergoing surgery of the ascending aorta or on another valve (class I, LOE C)
AR	AVR is indicated for patients with severe AR (stage C or D) while undergoing cardiac surgery for other indications (class I, LOE C)	Surgical aortic valve replacement or repair is indicated in patients with severe AR undergoing surgery of the ascending aorta or on another valve (class I, LOE C)
MS	Concomitant mitral valve surgery is indicated for patients with severe MS undergoing other cardiac surgery (class I, LOE C)	Severe concomitant aortic VHD or severe combined tricuspid stenosis and regurgitation requiring surgery is a contraindication to PMC
		In patients with severe MS combined with severe aortic VHD, mitral valve surgery is preferable when it is not contraindicated
		In patients with severe TR, PMC may be considered in selected patients with sinus rhythm, moderate left atrial enlargement, and functional TR secondary to pulmonary hypertension. In other cases, surgery of both valves is preferred
MR	Concomitant mitral valve repair or replacement is indicated in patients with chronic severe primary MR undergoing cardiac surgery for other indications (class I, LOE B)	Severe primary MR: not specifically mentioned
	Mitral valve surgery is reasonable for patients with chronic severe secondary MR (stages C and D) who are undergoing AVR (class IIa, LOE C)	Mitral valve surgery is indicated in patients with severe secondary MR undergoing CABG and LVEF >30% (class I, LOE C). No recommendation is made in case of concomitant other valvular surgery
TR	Tricuspid valve surgery is recommended for patients with severe TR (stages C and D) undergoing left-sided valve surgery (class I, LOE C)	Tricuspid valve surgery is indicated in patients with severe primary or secondary TR undergoing left-sided valve surgery (class I, LOE C)
TS	Tricuspid valve surgery is recommended for patients with severe TS at the time of operation for left-sided VHD (class I, LOE C)	Intervention on the tricuspid valve is usually performed at the time of intervention on the other valves in patients who are symptomatic, despite medical therapy
		Balloon commissurotomy can be considered in the rare cases with anatomically suitable valves when additional MS can also be treated interventionaly

ACC indicates American College of Cardiology; AHA, American Heart Association; AR, aortic regurgitation; AS, aortic stenosis; AVR, aortic valve replacement; CABG, coronary artery bypass grafting; EACTS, European Association for Cardio-Thoracic Surgery; ESC, European Society of Cardiology; LOE, level of evidence; LVEF, left ventricular ejection fraction; MR, mitral regurgitation; MS, mitral stenosis; PMC, percutaneous mitral commissurotomy; TR, tricuspid regurgitation; TS, tricuspid stenosis; and VHD, valvular heart disease.

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MR may be hemodynamically and clinically significant, and some patients with seemingly nonsevere mixed mitral valve disease may complain of exertional dyspnea or fatigue, which has been, at least partly, attributed to flow-dependent increases in the transmitral pressure gradient.<sup>36</sup> Because LV and left atrial compliances may be altered in the presence of significant MR<sup>37</sup> and pressure half-time is highly influenced by LV or left atrial compliance, mitral valve area derived from pressure half-time may not be reliable to assess the severity of concomitant MS.<sup>38</sup>

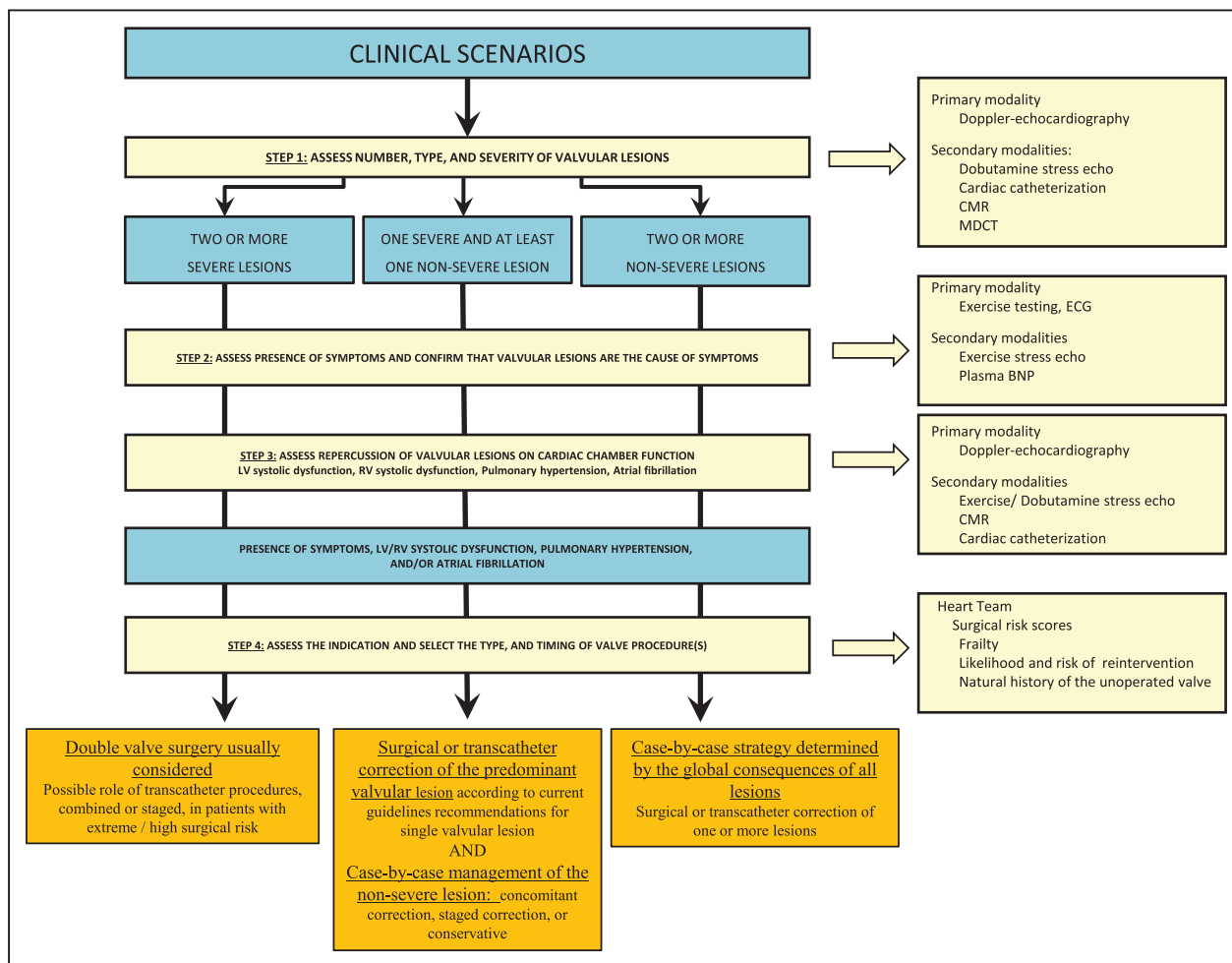
The mitral valve effective orifice area measured by the continuity equation (stroke volume measured in the LV outflow tract) may overestimate the severity of MS in the presence of concomitant MR (Table 1). The mitral valve anatomic orifice area measured by 3-dimensional transthoracic or transesophageal echocardiography may be used to corroborate MS severity in this context. As in patients with mixed aortic VHD, the peak transmitral velocity, mean gradient, or mitral velocity-time integral may provide an assessment of the overall severity of the mixed mitral VHD.

## MANAGEMENT STRATEGY

### General Principles

The limited evidence on medical, surgical, and interventional management is emphasized by the C level of evidence given in most recommendations made by the American Heart Association/American College of Cardiology and European Society of Cardiology/European Association for Cardio-Thoracic Surgery guidelines (Tables 3 and 4).<sup>8,10,11</sup> Because of the large number of possible combinations of valve lesions, a standardized approach cannot be proposed. Nevertheless, the clinician may face one of the following 3 clinical scenarios (Figure 4)<sup>39</sup>:

1. Two or more severe lesions are present. In this situation, the likelihood of severe functional intolerance is high if one of the lesions is left untreated. Therefore, addressing the 2 (or more) lesions during the intervention has been given a class I recommendation in current European and American guidelines (Table 3).
2. One severe lesion is associated with  $\geq 1$  non-severe lesion(s). In this common scenario, the



**Figure 4. Clinical scenarios and proposed decision-making process in the management of patients with multiple valvular heart disease.**

BNP indicates brain natriuretic peptide; CMR, cardiac magnetic resonance; LV, left ventricular; MDCT, multidetector computed tomography; and RV, right ventricular.

management of the most severely diseased valve is defined by current guidelines. The management of the less-than-severe lesion(s) is less straightforward, and, in most situations, a class II recommendation has been given for intervention (Table 4).

3. If  $\geq 2$  moderate lesions are present and if the overall hemodynamic burden imposed by these lesions is believed to be the main cause of the symptoms or LV systolic dysfunction, a surgical or transcatheter valve intervention could be considered. The latter scenario, whose exact prevalence is unknown, is not covered by current guidelines. In this setting, it is of particular importance to determine the global consequences of the lesions. This includes careful assessment of ventricular volumes and pulmonary pressure, natriuretic peptides measurements, and, in selected cases, the assessment of functional capacity, maximal oxygen consumption, and pulmonary pressure during exercise, although there is only limited literature in the specific setting of multiple valve disease.

Similarly, mixed VHD may present as (1) the combination of severe stenosis and regurgitation, (2) the

combination of severe stenosis (or regurgitation) and nonsevere regurgitation (or stenosis), and (3) the combination of moderate stenosis and moderate regurgitation. The first 2 scenarios should be managed following the current guideline recommendations applicable to the most severe lesion. Although the combination of aortic or mitral moderate stenosis and regurgitation is not a classical indication for intervention, this scenario may be associated with symptoms, reduced exercise tolerance, LV repercussions, and pulmonary hypertension and, thereby, intervention may be considered (Figure 4).

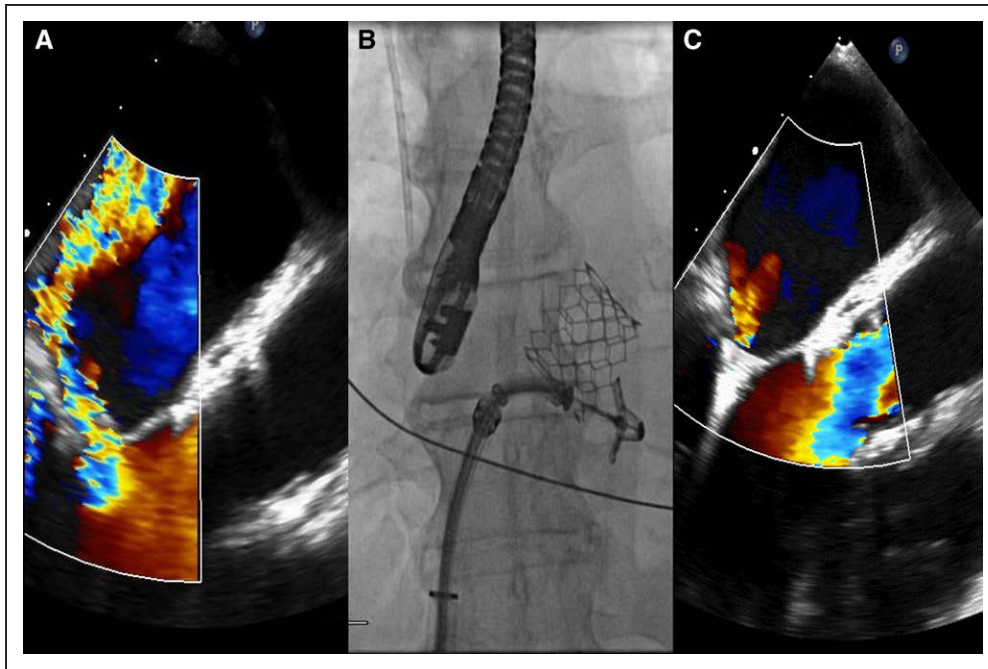
### Heart Team Approach and How to Follow the Patients

A collaborative approach between cardiologists and cardiac surgeons is critical in the management of patients with multiple and mixed VHD. The situation is further complicated by the high prevalence of coronary artery disease. The Heart Team-based management strategy is now recommended by current guidelines.<sup>8,10,11</sup> The decision-making in patients with multiple and mixed VHD should be individually tai-

**Table 4. Indications for Concomitant Valve Surgery on Less-Than-Severe Valve Lesions in Patients Undergoing Surgery on Another Valve, According to the AHA/ACC and ESC/EACTS Guidelines<sup>8,10,11</sup>**

Valve Lesion	2014–2017 AHA/ACC Guidelines	2017 ESC/EACTS Guidelines
AS	AVR is reasonable for patients with moderate AS who are undergoing other cardiac surgery (class IIa, LOE C)	Surgical AVR should be considered in patients with moderate AS undergoing surgery of the ascending aorta or another valve, after Heart Team decision (class IIa, LOE C) In cases with severe MS with moderate aortic VHD, PMC can be performed to postpone the surgical treatment of both valves
AR	AVR is reasonable in patients with moderate AR who are undergoing other cardiac surgery (class IIa, LOE C)	Not mentioned
MS	Concomitant mitral valve surgery may be considered for patients with moderate MS (MV area, 1.6–2.0 cm <sup>2</sup> ) undergoing other cardiac surgery (class IIb, LOE C)	Not mentioned
MR	Concomitant mitral valve repair is reasonable in patients with chronic moderate primary MR (stage B) undergoing cardiac surgery for other indications (class IIa, LOE C)	Primary MR: not mentioned
	Mitral valve repair may be considered for patients with chronic moderate secondary MR (stage B) who are undergoing other cardiac surgery (class IIb, LOE C)	The potential impact of mitral valve intervention (surgery and catheter intervention) on survival in patients with secondary MR needs to be evaluated
TR	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 dilation or (2) prior evidence of right heart failure (class IIa, LOE B)	Tricuspid valve surgery should be considered in patients with moderate primary TR undergoing left-sided valve surgery (class IIa, LOE 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 (class IIb, LOE 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 <sup>2</sup> ) undergoing left-sided valve surgery (class IIa, LOE 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 (class IIb, LOE C)
TS	Not mentioned	Not mentioned

ACC indicates American College of Cardiology; AHA, American Heart Association; AR, aortic regurgitation; AS, aortic stenosis; AVR, aortic valve replacement; EACTS, European Association for Cardio-Thoracic Surgery; ESC, European Society of Cardiology; LOE, level of evidence; MR, mitral regurgitation; MS, mitral stenosis; PMC, percutaneous mitral commissurotomy; TR, tricuspid regurgitation; TS, tricuspid stenosis; and VHD, valvular heart disease.



**Figure 5.** Eighty-five-year-old patient presenting severe aortic stenosis and degenerative mitral regurgitation (MR).

This 85-y-old patient presenting severe aortic stenosis and degenerative mitral regurgitation because of prolapsed A2 segment underwent transcatheter aortic valve replacement as initial procedure. Severe MR persisted after aortic valve replacement, as shown by the long-axis transesophageal view (A), and the patient remained symptomatic. A MitraClip procedure was thus performed (B), with only minimal residual MR (C).

lored, including imaging and clinical factors discussed here above.

Because of the paucity of data on its natural history, the appropriate timing for the follow-up visits of patients with multiple and mixed VHD is unclear. When one lesion is clearly predominant, the follow-up should be made in accordance to current guidelines. However, when severity of lesions is balanced, the combination may have detrimental consequences, and interval between follow-up visits should be shorter than in single-valve/single-lesion disease. Similarly, high event rates may be expected in patients with the combination of moderate AS and moderate AR, and more frequent serial evaluations are thus warranted. The follow-up of patients with multiple VHD should be performed in dedicated and structured outpatient heart valve clinics,<sup>40</sup> linked to comprehensive multidisciplinary inpatient teams, in the setting of Heart Valve Centers.<sup>41</sup>

Whether or not leaving unoperated a less-than-severe valve lesion requires the integration of numerous factors, including the natural history of the unoperated valve and the possible changes in MR or TR severity after treatment of a downstream valvular lesion, the life expectancy and comorbidities, the individual surgical risk profile, the possibility of repair, the increased risk of redo surgery, and the feasibility of transcatheter approaches (Figures 4 and 5). All these factors should be integrated by the multidisciplinary heart valve team. Future studies are needed to determine whether simultaneous or staged transcatheter

aortic, mitral, or tricuspid valve interventions will improve outcomes in patients with multiple VHD.

## CONCLUSIONS

Multiple and mixed VHDs are highly prevalent. Whereas rheumatic heart disease remains the most prevalent pathogenesis in developing countries, degenerative pathogenesis are more prevalent in industrialized regions. Hemodynamic interactions may alter the clinical expression of each singular lesion, and the clinician should be aware of these interactions that may impact the diagnosis. Patients with multiple or mixed VHD should be followed in heart valve clinics. A case-by-case therapeutic management strategy should be made by a Heart Valve team, taking into account multiple factors, including the severity of each single valvular lesion, the individual risk profile, the increased long-term morbidity of multiple prostheses, and the natural history of each valvular lesion if left untreated (Figure 4). Current and future advances in transcatheter valve therapies are likely to change the therapeutic approach of multiple VHD, but there is currently no evidence-based management strategy in this setting.

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