Combined aortic stenosis and regurgitation: double the trouble

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INTRODUCTION

Mixed aortic valve disease (MAVD) refers to the coexistence of aortic stenosis (AS) and aortic regurgitation (AR). Despite the relatively high prevalence of MAVD, there are very few data on the outcome and management of this entity.[1–6] Nonetheless, a few recent studies have reported that the prognosis of patients with combined moderate AS and moderate AR is similar or worse than those with isolated severe AS or AR.[2 3] The therapeutic management of MAVD is complex and is currently based on the guideline recommendations for the predominant lesion, AS or AR.[1 7] The objective of this Education in Heart article is to provide an overview of the prevalence, pathophysiology, outcomes, diagnosis, severity grading and strategies for the therapeutic management of MAVD.

Learning objectives

- To be aware of the prevalence, pathophysiology and outcomes of mixed aortic valve disease (MAVD), which refers to combined aortic stenosis and aortic regurgitation.
- To assess the haemodynamic and clinical severity of MAVD using an echocardiographic multiparameter approach and, when necessary, other imaging modalities (dobutamine stress testing, multidetector computed tomography and cardiac magnetic resonance).
- To identify the triggers and optimal timing for aortic valve intervention in MAVD.

PREVALENCE, PATHOPHYSIOLOGY AND OUTCOMES OF MAVD

Prevalence of MAVD

In a nationwide epidemiology study conducted in Sweden,[8] the overall incidence rate of multiple valve disease was 6.4 per 100 000 person-years. This rate increased markedly with age and was higher in men (8.5 per 100 000 person-years) than in women (5.8 per 100 000 person-years).[8] MAVD was the most frequent multiple valve disease and 17.9% of patients with AR were diagnosed with concomitant AS.

Pathophysiology of MAVD

The pathophysiology and clinical impact of MAVD are complex and relate to the severity and chronicity of each aortic valve lesion and to the repercussions of these lesions on the remodelling and function of the left ventricle (LV) and other upstream cardiac chambers.[5] In patients with MAVD, AS indeed imposes a pressure overload that aggravates LV concentric hypertrophy, resulting in decreased LV compliance and thus in a disproportionate rise in LV diastolic pressure per unit of volume increase during diastole. The combination of modest LV dilation and marked LV wall thickening results in patients with MAVD having larger indexed LV mass than patients with either isolated AR or isolated AS.[3 6] Furthermore, the vast majority of patients with MAVD develop symptoms well before their LV end-systolic dimension reaches the cut-point value of 50 mm, that is, one of the triggers for intervention recommended in the guidelines[1 7] for patients with severe AR. These findings suggest that the LV hypertrophy resulting from AS may not allow the LV to dilate as a result of the volume overload associated with AR. However, the increase in stroke volume resulting from the aortic regurgitant volume may further contribute to increase the transvalvular pressure gradient and thus the severity of LV pressure overload associated with AS (figure 1). Patients with MAVD may therefore be at higher risk to develop subclinical myocardial fibrosis and dysfunction compared with patients with isolated AR, and these patients may progress to symptoms and heart failure even though neither the AS nor the AR has yet reached the severe stage.[9] They are also at higher risk to develop LV systolic dysfunction following valve intervention.[10]

Outcome of MAVD

There are limited data on the natural history of patients with MAVD, but the few studies available on this topic suggest similar or worse outcomes in patients with severe MAVD versus isolated severe AS or AR.[2–4 6 11] Furthermore, the progression rate of AS was faster in patients with moderate MAVD compared with those with isolated moderate AS.[4]

Asymptomatic patients with severe MAVD generally have worse outcomes, whereas those with moderate MAVD have similar outcomes compared with patients with severe isolated AS.[2 3 6] In asymptomatic patients with moderate AS, Sorajja *et al*[6] reported that the coexistence of a mild AR was associated with a significant negative impact on outcomes during follow-up. This finding may be related to the fact that patients with moderate AS primarily develop LV concentric hypertrophy and LV diastolic dysfunction, and they may thus not be able to tolerate an even mild aortic regurgitant volume. The main factors associated with higher risk of progression to symptoms and heart failure in MAVD are: older age, more severe AS and/or AR at baseline, larger LV mass index, more pronounced

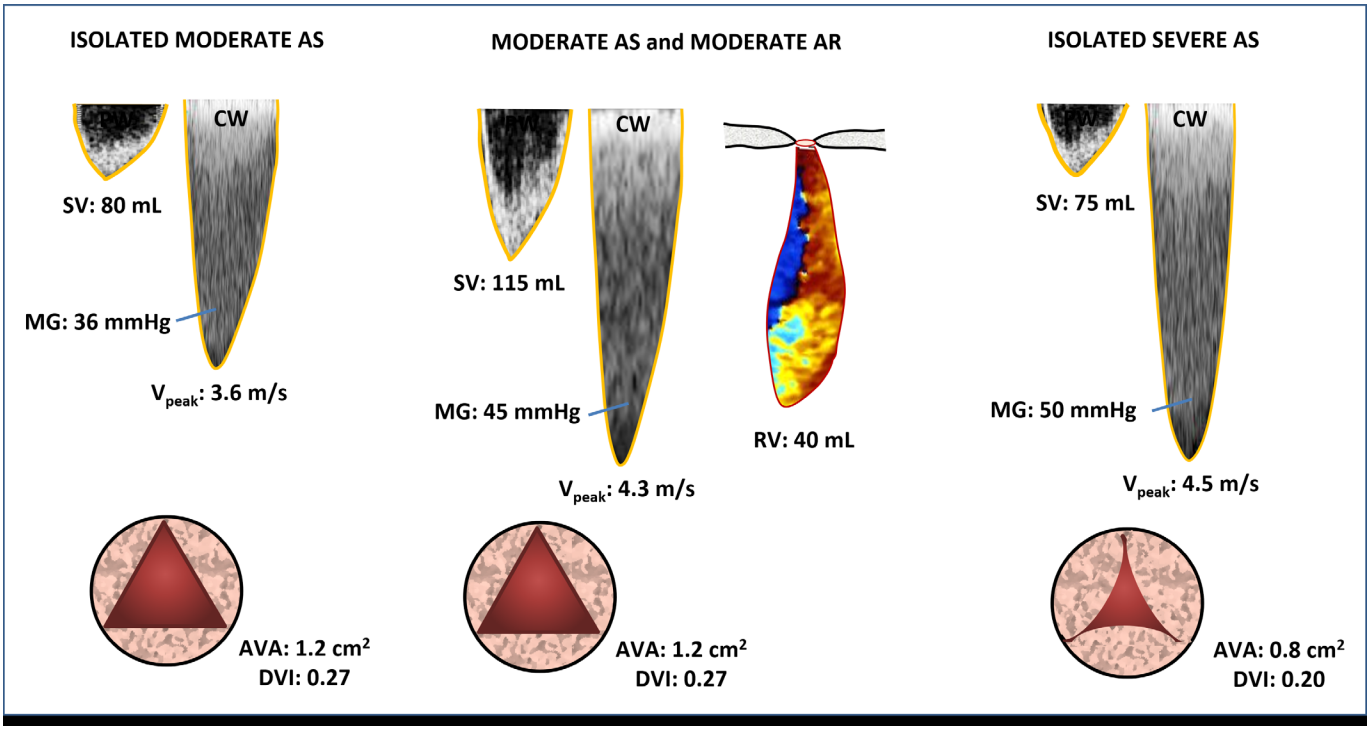

Figure 1 Haemodynamic interaction between AS and AR. This figure illustrates three scenarios: isolated moderate AS, isolated severe AS and concomitant moderate AS and moderate AR. In latter scenario, the regurgitant volume resulting from the moderate AR causes an increase in the LV stoke volume. In turn, this AR-related increase in forward stroke volume yields to an increase in the peak jet velocity and mean gradient for a given AVA. In this scenario, the peak aortic jet velocity and mean gradient overestimate the severity of the AS component but provide an adequate estimation of the overall haemodynamic severity of the combination of AS+AR. However, the AVA provides an adequate estimation of the severity of AS but underestimates the overall severity of AS+AR. AR, aortic regurgitation; AS, aortic stenosis; AVA, aortic valve area; CW, continuous-wave Doppler; MG, mean transvalvular pressure gradient; PW, pulsed-wave Doppler. DVI, Doppler velocity index; RV, aortic regurgitant volume; SV, stroke volume; V_{Peak}, peak aortic jet velocity. Figure artwork by Mia Pibarot.

LV concentric remodelling and advanced LV diastolic dysfunction.[3 4 10 12 13]

These findings emphasise that patients with MAVD need careful surveillance with close clinical and echocardiographic follow-up, especially if the patient harbours the risk factors mentioned above. The determination of the optimal timing for intervention in these patients is challenging and should account for the composite severity of both AS and AR and their combined haemodynamic effects on cardiac function (figure 2 and table 1).

DIAGNOSIS AND GRADING SEVERITY OF MAVD

Assessing the haemodynamic severity of MAVD

In patients with MAVD, one should assess the haemodynamic severity of each lesion: AS and AR and then the overall haemodynamic severity of the MAVD, that is, of the severity of the AS+AR combination (figure 2). Table 2 presents the caveats in the assessment of MAVD severity using Doppler echocardiography and other imaging modalities.

AS severity

The peak aortic jet velocity and mean transvalvular gradient, which are highly flow dependent, may overestimate the severity of AS in the context of MAVD because of the high transvalvular flow state associated with AR (table 2, figures 1 and 3). The effective aortic valve area (AVA) by the continuity equation method and Doppler velocity index (ie, ratio of the velocity time integrals in LV outflow tract versus aortic jet) are the best parameters to quantitate the AS severity in the context of MAVD (table 2, figures 1–3). The anatomic AVA measured by planimetry using transoesophageal echocardiography, contrast multidetector CT (MDCT) or cardiac magnetic resonance (CMR) imaging may help to corroborate AS severity.[14 15]

AR severity

Doppler echocardiography: the assessment of AR haemodynamic severity should rely on an integrative approach including structural, semiquantitative and quantitative parameters as recommended by the 2017 American Society guidelines for the non-invasive evaluation of native valvular regurgitation (table 2, figures 2 and 3).[16 17] Patients with MAVD generally have less LV dilation and thus smaller LV end-diastolic volume and stroke volume, compared with patients with isolated AR. Hence, a moderate AR on the basis of effective regurgitant orifice area, vena contracta width and regurgitant volume may, in fact, correspond to a moderate-to-severe or severe AR in terms of regurgitant fraction. In patients with MAVD, it is thus preferable to put more weight on the regurgitant fraction than on other parameters to grade AR severity (table 2).

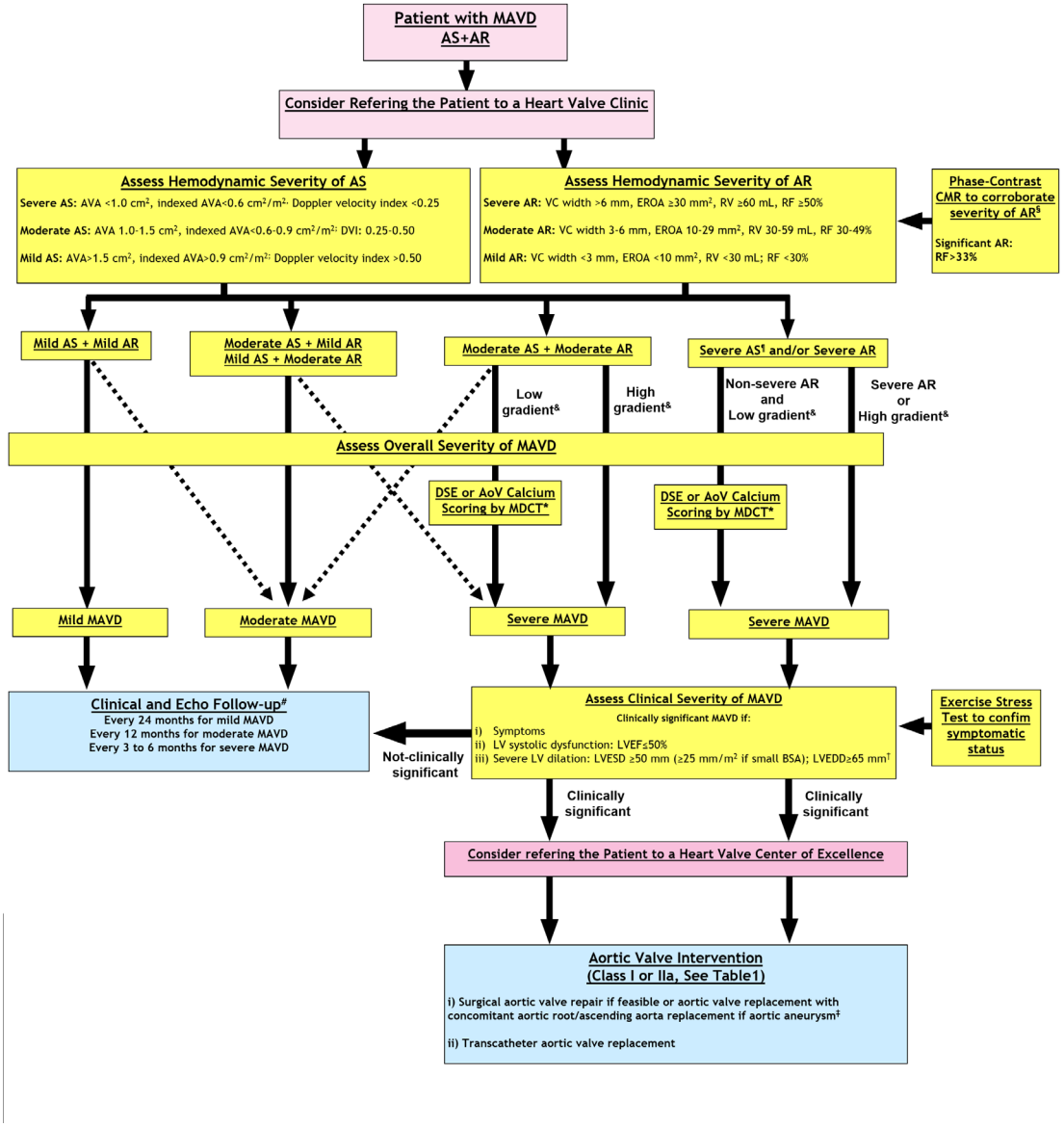

Figure 2 Proposed algorithm for the diagnosis and management of MAVD. §: phase-contrast CMR may be used when Doppler echocardiographic quantitation of AR is not feasible or potentially inaccurate. However, the cut-off values of regurgitant fraction to define moderate and severe AR are not well validated. One study[18] reported that an RF >33% defined as 'significant' AR is associated with worse clinical outcomes in chronic isolated AR. ¶: severe AS on the basis of AVA (<1.0 cm^2) and Doppler velocity index (<0.25) measured on resting echocardiogram. &: low gradient is defined as mean gradient <40 mm Hg and peak aortic jet velocity <4 m/s; high gradient: mean gradient ≥40 mm Hg or peak velocity ≥4 m/s. *: low dose dobutamine stress echocardiography (DSE) or aortic valve scoring by MDCT may be used to confirm the overall severity of MAVD in the case of: (1) combined moderate AS and moderate AR associated with low gradient (not specifically recommended in the guidelines) or (2) non-severe AR combined with severe AS (on the basis of AVA, indexed AVA and Doppler velocity index) associated with low gradient (recommended in the guidelines for AS).[7] The criteria for severe AS or severe MAVD are: (1) for DSE: peak stress mean gradient ≥40 mm Hg and (2) for non-contrast MDCT: aortic valve calcium score≥ 1200 AU in women and≥ 2000 AU in men.[7] The dotted arrows indicate that, based on assessment of overall severity of MAVD using DSE or MDCT, the combination of mild AS plus mild AR may be classified into moderate MAVD or moderate AS plus mild AR classified into severe MAVD and so on. †: some emergent parameters of severity previously proposed to enhance risk stratification in patients with isolated AS or AR may also be considered in those with MAVD but have not been yet been included in the guidelines and will thus need to be validated in this context: that is, LVEF <60% (instead of 50%), global LV longitudinal strain <−16%, resting systolic pulmonary arterial pressure ≥50 mm Hg, exercise systolic pulmonary arterial pressure ≥60 mm Hg; exercise-induced increase in mean transaortic gradient ≥20 mm Hg; cardiac damage stage ≥1.[27] Other parameters have also been associated with worse prognosis in patients with MAVD and may also be considered to trigger intervention in these patients: relative wall thickness ratio >0.46 or LV mass index/LV end-diastolic diameter ratio >3.1, E/e' ratio >14. ‡: concomitant replacement of the aortic root or tubular ascending aorta should be considered when aorta diameter is ≥45 mm, particularly in the presence of a bicuspid valve. #: the timing of follow-up in MAVD is not described in the guidelines. However, given that patients with MAVD are at higher risk for faster disease progression, it appears reasonable to perform a closer and more frequent follow-up than what is generally recommended for isolated AS or AR. AR, aortic regurgitation; AS, aortic stenosis; AVA, aortic valve area; CMR, cardiac magnetic resonance; DSE,dobutamine-stress echocardiography; DVI, Doppler velocity index; LV, left ventricle; LVEF, LV ejection fraction; MAVD, mixed aortic valve disease; MDCT, multidetector CT; RF, regurgitant fraction.

Table 1 Indications for aortic valve intervention in MAVD according to European guidelines

	Mild AR	Moderate AR	Severe AR
Mild AS	**Mild/moderate MAVD** **No indication for AV Intervention**	**Moderate MAVD** **No indication for AV Intervention**	**Severe MAVD** **AV Intervention (class I) if:** ► Symptoms, LVEF ≤50%, and/or undergoing other cardiac surgery. **AV Intervention (Class IIa) if:** ► Asymptomatic, LVEF >50% and LVESD ≥50 mm.
Moderate AS	**Moderate MAVD** **No indication for AV Intervention**	**Likely severe MAVD*** **AV intervention (Class I) if:** ► High gradient. ► Symptoms, LVEF ≤50%, and/or undergoing other cardiac surgery. **AV intervention (class IIa) if:** ► Low gradient. ► Symptoms, LVEF ≤50%, and/or LVESD ≥50 mm. ► Confirmation of AV disease severity by DSE or MDCT.	**Severe MAVD** **AV intervention (class I) if:** ► Symptoms, LVEF ≤50%, and/or undergoing other cardiac surgery. **AV intervention (class IIa) if:** ► Asymptomatic, LVEF >50% and LVESD ≥50 mm.
Severe AS	**Severe MAVD** **AV intervention (class I) if:** ► High gradient. ► Symptoms, LVEF <50% and/or undergoing other cardiac surgery. **AV intervention (class IIa) if:** ► Low flow, low gradient. ► Symptoms and/or LVEF <50%. ► Confirmation of severe AS by DSE or MDCT. **AV intervention (class IIa) if:** ► High gradient. ► Asymptomatic and LVEF ≥50%. ► Low surgical risk.	**Severe MAVD** **AV intervention (class I) if:** ► High gradient. ► Symptoms, LVEF <50% and/or undergoing other cardiac surgery. **AV intervention (class IIa) if:** ► Low flow, low gradient. ► Symptoms and/or LVEF <50%. ► Confirmation of severe AS by DSE or MDCT. **AV intervention (class IIa) if:** ► High gradient. ► Asymptomatic and LVEF ≥50%. ► Low surgical risk.	**Severe MAVD** **AV intervention (class I) if:** ► Symptoms, LVEF ≤50% and/or undergoing other cardiac surgery. **AV intervention (class IIa) if:** ► Asymptomatic, LVEF >50% and LVESD ≥50 mm. ► Low surgical risk.

*There is little detail in the guidelines for the MAVD category of moderate AS+moderate AR. However, the ESC guidelines suggest to consider these patients as having severe MAVD and assess the repercussions of the disease on symptomatic status and LV function. AV intervention refers to surgical aortic valve replacement, surgical aortic valve repair or transcatheter aortic valve replacement.

AR, aortic regurgitation; AS, aortic stenosis; AV, aortic valve; DSE, dobutamine-stress echocardiography; LV, left ventricle; LVESD, LV end-systolic diameter; LVEF, LV ejection fraction; MAVD, mixed aortic valve disease; MDCT, multidetector CT.

CMR: given that the feasibility and validity of several Doppler echocardiographic parameters of AR severity is compromised by the coexistence of AS, CMR imaging with phase-contrast performed at 10 mm above the aortic annulus may be helpful to confirm the AR volume and fraction in patients with MAVD (table 2; figure 4).[18] In patients with MAVD, the regurgitant fraction appears to be the best parameter to corroborate AR severity; a fraction >33% has been associated with worse clinical outcomes in chronic isolated AR.[18] CMR should be considered when the quantitative assessment of AR by Doppler echocardiography is not feasible or uncertain, which is more likely to occur in patients with MAVD (figures 2 and 4).[17]

Overall severity of MAVD

The peak aortic jet velocity and mean transvalvular gradient may be superior to other severity parameters of AS or AR to reflect the overall haemodynamic severity of MAVD (table 2, figures 1 and 3).[5] The AVA and Doppler velocity index indeed reflect the severity of AS, whereas the effective regurgitant orifice area, vena contracta width of the AR jet, regurgitant volume and regurgitant fraction reflect the severity of AR but none of these parameters adequately assess the overall haemodynamic burden resulting from the combination of AS and AR. However, the peak aortic jet velocity and mean gradient increase with the severity of AS but also with that of AR due to the increase in transvalvular flow. Hence, these parameters may be useful to assess the overall haemodynamic severity of MAVD (table 2, figures 1 and 3) and have been shown to correlate with outcomes in these patients.[2 4] Hence, a patient with moderate AS (according to AVA, indexed AVA and Doppler velocity index) and moderate AR (according to effective regurgitant orifice area, vena contracta width and regurgitant volume and fraction) should be considered having severe MAVD if they harbour a peak jet velocity ≥4 m/s and/or a mean gradient ≥40 mm Hg (figures 2 and 3). The coexistence of moderate AS and mild AR or vice versa moderate AR and mild AS generally corresponds to moderate MAVD (table 1 and figure 2). However, the overall haemodynamic severity of MAVD is more difficult to determine in patients with moderate AS (on the basis of AVA) and moderate AR harbouring a peak velocity <4 m/s and mean gradient <40 mm Hg (figure 4). The European Society of Cardiology guidelines suggest that, in such patients, the MAVD is likely severe (table 1). However, additional tests such as stress echocardiography or quantitation of aortic valve calcification by non-contrast MDCT, and quantitation of AR by phase-contrast CMR may be useful to differentiate a true severe versus a moderate

Table 2 Caveats in the assessment of MAVD by multimodality imaging

	TTE/TOE	CMR	MDCT	Cardiac catheterisation
AS severity	► Simplified Bernoulli formula may not be applicable for the measurement of transvalvular gradients if LV outflow tract velocity is elevated. ► Peak aortic jet velocity and mean gradient may: (1) overestimate AS severity in presence of significant AR due high transvalvular flow; and (2) underestimate AS severity in presence of depressed LVEF and low flow state. ► Continuity equation is valid for the calculation of effective AVA in the context of MAVD. ► Anatomic AVA measured by planimetry is often smaller than effective AVA due to flow contraction phenomenon. Anatomic AVA may thus underestimate AS haemodynamic severity. ► AVA and DVI are the best parameters to assess the severity of AS in the context of MAVD. These parameters may overestimate AS severity in presence of low flow state.	► Not recommended in clinical practice.	► Anatomic AVA measured by planimetry using contrast MDCT is often smaller than the effective AVA due to flow contraction phenomenon. Anatomic AVA may thus underestimate AS severity. This technique is associated with a high radiation dose. Non-contrast CT for assessment of AVC score can be achieved with a lower radiation dose. ► Effective AVA cannot be measured by MDCT.	► AVA by Gorlin formula using thermodilution or Fick methods is not valid in the presence of MAVD.
AR severity	► AR pressure half time may overestimate AR severity in patients with MAVD due to frequent concomitant LV diastolic dysfunction. ► Timing and end-diastolic velocity of the flow reversal in the descending aorta may overestimate AR severity in patients with MAVD due to frequent concomitant reduced aortic compliance. ► VC width, EROA and RV may underestimate AR severity in the context of MAVD. RF may be preferable to assess AR severity in MAVD.	► CMR may be used to corroborate RV and RF. ► RV may underestimate AR severity in the context of MAVD. RF may be preferable to assess AR severity in MAVD.		► Aorta angiography may be used to assess AR severity but is dependent on technique, operator and amount of injected contrast.
MAVD severity	► Peak aortic jet velocity and mean gradient are the best parameters to assess the overall haemodynamic severity of MAVD. ► Peak aortic jet velocity and mean gradient may underestimate MAVD severity in presence of low flow state.		► AVC score by non-contrast MDCT may be used to assess the overall severity of MAVD. ► AVC should be interpreted with caution in younger patients, especially women, with a bicuspid aortic valve, as this parameter is associated with high rate of false-negative cases.	

AR, aortic regurgitation; AS, aortic stenosis; AVA, aortic valve area; AVC, aortic valve calcification; CMR, cardiac magnetic resonance; DVI, Doppler velocity index; EROA, effective regurgitant orifice area; LV, left ventricle; LVEF, LV ejection fraction; MAVD, mixed aortic valve disease; MDCT, multidetector CT; RF, regurgitant fraction; RV, regurgitant volume; TOE, transoesophageal echocardiography; TTE, transthoracic echocardiography; VC, vena contracta.

MAVD in patients with low transvalvular gradient (figures 2 and 4).

MAVD with low flow, low gradient

Some patients with MAVD may have a decline in LV systolic dysfunction (LVEF <50%) and thus in stroke volume due to the haemodynamic burden related to the combination of AS and AR and/or to other cardiomyopathies, the most frequent being an ischaemic cardiomyopathy. In presence of low-flow state (stroke volume index <35 mL/m^2, mean transvalvular flow rate <200 mL/s), the peak aortic velocity and mean gradient may underestimate the severity of the AS component as well as that of the MAVD (table 2). However, the AVA and Doppler velocity index may overestimate the severity of AS, and there is thus often a discordant grading pattern with AVA being in the severe range but with peak velocity and mean gradient being in the non-severe range.

Dobutamine stress echocardiography: in these patients, a low-dose dobutamine stress echocardiography may theoretically be helpful to assess the presence of LV contractile/flow reserve and to confirm the overall haemodynamic severity of MAVD (figures 2 and 4). There are currently no published data on the utilisation of dobutamine stress echocardiography in patients with MAVD. Nonetheless, by analogy with low-flow, low-gradient isolated AS, the MAVD could be considered severe if the peak jet velocity increases to ≥4 m/s and/or mean gradient to ≥40 mm Hg with dobutamine stress (figure 2). Stress echocardiography could also be applied to patients with moderate AS and moderate AR and low velocity/gradient to corroborate the overall severity of MAVD (figure 4).

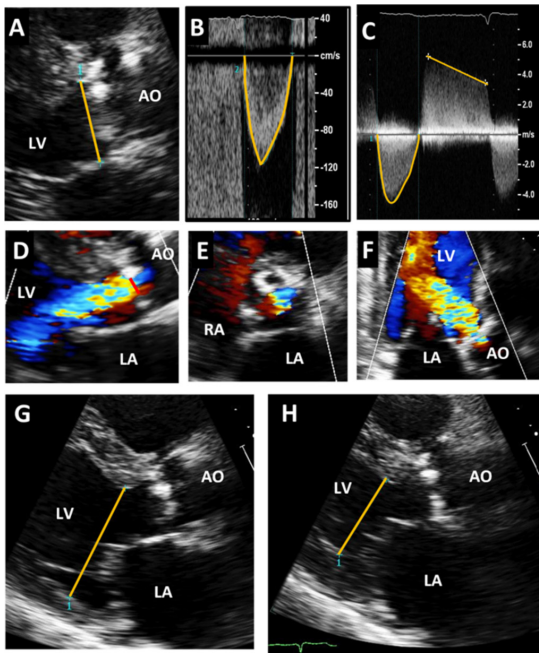

Figure 3 Case of moderate aortic stenosis (AS) and moderate aortic regurgitation (AR) resulting in severe MAVD. Transthoracic echocardiographic images in a symptomatic (NYHA Class II-III) 80-year-old man with a body surface area of 1.85 m². (A and B) LV outflow tract diameter is 26.5 mm and velocity-time integral by pulsed-wave Doppler is 25 cm with a calculated stroke volume at 138 mL. (C) The aortic valve area (AVA) by continuity equation is 1.34 cm^2 (indexed: 0.72 cm^2/m^2), and the Doppler velocity index is 0.26, suggesting a moderate AS. (D–F) Parasternal long axis, parasternal short axis and apical three-chamber colour Doppler views showing a moderate AR. The vena contracta width (**D**) is 5.8 mm. The images of the proximal acceleration surface area were suboptimal but suggests an effective regurgitant orifice area of 26 mm^2 and regurgitant volume of 55 mL. (G and H) These show the left ventricular dimensions (LV end-diastolic diameter: 61 mm, LV end-systolic diameter: 42 mm) and the presence of significant LV hypertrophy. The LV ejection fraction by biplane Simpson was 65%. Hence, this patient has a combination of moderate AS and moderate AR. In this case, neither the AR nor the AS is severe and mandate intervention according to the guidelines for each isolated lesion. However, figure part C shows a peak velocity of 4.5 m/s and a mean gradient of 44 mm Hg. These parameters overestimate the severity of the AS component of the disease because of the high transvalvular flow rate associated with AR. Nonetheless, these parameters provide a valid assessment of the overall severity of the MAVD (AS+AR). Indeed, the peak aortic jet velocity and mean gradient increase with both AS and AR (due to increase in transvalvular flow). The patient was treated by transcatheter aortic valve replacement. AO, aorta; LA, left atrium; LV, left ventricle; MAVD, mixed aortic valve disease; NYHA, New York Heart Association; RA, right atrium.

Non-contrast MDCT: the quantitation of aortic valve calcium score by non-contrast MDCT and the modified Agatston method may also be used in patients with MAVD and low gradient to confirm the overall aortic valve disease severity (table 2, figures 2 and 4). A calcium score ≥2000 AU in men and ≥1200 AU in women would suggest severe MAVD.[7 19 20]

Assessing the clinical severity of MAVD

A haemodynamically severe MAVD may be well tolerated in some patients, whereas a moderate MAVD may have a detrimental impact on LV function and symptomatic status in others.[21] This is why, besides the grading of the haemodynamic severity of MAVD, it is essential to assess the clinical severity, which reflects the repercussion of the haemodynamic burden associated with the AS+AR combination on cardiac chamber geometry and function and patient's clinical status (figure 2).

One of the key aspects in the assessment of the clinical severity of MAVD and the indication for intervention is the presence of symptoms. As for isolated AS or AR, a treadmill exercise testing using a Bruce or modified Bruce protocol may be useful to unmask symptoms in apparently asymptomatic patients (figure 2).

Patients with MAVD and a preoperative LVEF <50% are also at higher risk of adverse clinical outcomes following AVR.[10] Given that patients with MAVD may have a greater susceptibility to develop LV systolic dysfunction, the consideration of a higher cut-point of LVEF (ie, 60% vs 50%) for intervention, as recently suggested for patients with isolated AS,[22–24] might also be relevant in these patients with MAVD. Global longitudinal strain has been shown to be useful to identify subclinical LV dysfunction and enhance risk stratification in patients with isolated AS or isolated AR,[25 26] and this parameter may thus also be potentially helpful in those with MAVD. The onset of atrial fibrillation, pulmonary arterial hypertension and/or right ventricular dysfunction, which mark an impact on upstream cardiac chambers have also been associated with higher risk of adverse cardiac events both prior or after valve intervention in patients with aortic valve disease.[27] Figure 2 presents the parameters and criteria that can be used to assess the haemodynamic and clinical severity of MAVD and therefore eventually trigger intervention. Some of these parameters and criteria are those proposed in the guidelines for isolated AS or AR and other emerging parameters and staging approach will need to be validated in the context of MAVD.

THERAPEUTIC MANAGEMENT OF MAVD

The management of MAVD ideally requires the expertise and resources of multidisciplinary dedicated heart valve clinics in order to better address the numerous pitfalls and challenges in the grading of haemodynamic and clinical severity of MAVD and in the determination of the optimal timing for intervention (figure 2).[28–30]

Indication and type of intervention

According to current guidelines,[1 7] the general principles for the management of MAVD are as follows: (1) when either AS or AR is predominant, management follows the recommendations related to the predominant lesion (table 1). (2) When the haemodynamic severity of both AS and AR is balanced (eg, moderate AS and moderate AR), indications for intervention should be based on symptoms and objective consequences on the LV (presence of LV dilatation or dysfunction), that is, clinical severity, rather than on the haemodynamic severity indices of AS or AR (figure 2 and table 1). The combination of moderate AS and moderate AR associated with high peak aortic jet

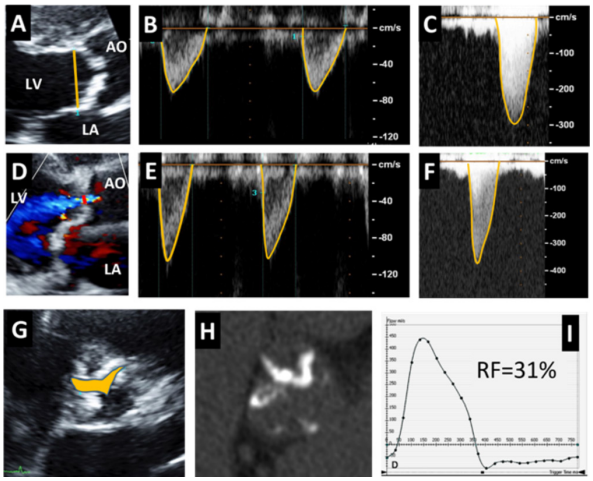

Figure 4 Case example of a patient with MAVD and low LVEF, low flow, low gradient. Transthoracic echocardiographic images in a mildly symptomatic (NYHA Class II) man with a body surface area of 1.90 m². (A and B) The stroke volume measured in the LV outflow tract is 62 mL; the patient is thus in low flow state (indexed stroke volume: 32 mL/m^2). LV ejection fraction by biplane Simpson is 30%. (C and G) The mean gradient is 25 mm Hg, effective AVA by continuity equation is 1.02 cm^2, indexed AVA is 0.54 cm^2/m^2 and anatomic AVA by 2D planimetry is 1.21 cm^2. These findings suggest moderate-to-severe AS (according to AVA) but with low (moderate) gradient. (D) Colour Doppler view suggests a mild-to-moderate aortic regurgitation (AR) on the basis of a vena contracta width of 3.5 mm. The quantitative methods were not feasible in this patient. On Doppler echocardiography exam, this patient thus has borderline severity of AS (moderate/severe) and AR (mild/moderate) and uncertain overall severity of MAVD. (I) A phase-contrast CMR was performed to corroborate the severity of AR and revealed a regurgitant fraction of 31%, thus confirming the presence of a moderate AR. (E and F) A low-dose dobutamine stress echocardiography was performed to confirm severity of AS and MAVD. LVEF increased to 42% and stroke volume to 75 mL (39.5 mL/m^2). The AR vena contracta width remained stable at 3.7 mm (not shown), whereas the AVA increased to 1.28 cm^2 (0.67 cm^2/m^2) and mean gradient increased to 33 mm Hg but remained in the moderate range. (H) Aortic valve calcium score was also measured by non-contrast MDCT at 1302 AU, which is considered moderate for a man. Hence, the severity of AS was confirmed to be moderate, and the overall severity of the MAVD was graded moderate; the patient was managed conservatively. Abbreviations as in figure 3.

velocity or mean gradient should be considered as severe MAVD (figures 1 and 3) and managed according to the guidelines recommendations for severe AS or severe AR. In patients with moderate AS and moderate AR associated with peak velocity <4 m/s and mean gradient <40 mm Hg (figure 4 and table 1), AVR may be considered if there is evidence that the overall severity of the MAVD is severe and if the MAVD is clinically significant: that is, the patient presents with symptoms, LV systolic dysfunction (LVEF ≤50%) or severe LV dilation (LV end-systolic diameter ≥50 mm). Although this is not mentioned in the guidelines, low-dose dobutamine stress echocardiography and/or aortic valve calcium scoring by MDCT may be useful to confirm the haemodynamic/anatomic severity of MAVD, especially if the patient is in low flow state (table 2). Once the indication of AVR is confirmed, the next step is to select the type of AVR (figure 2). Surgical aortic valve repair may be considered in patients with MAVD but is rarely feasible in these patients because of often extensive aortic valve calcification and fibrosis.[7] Surgical AVR is thus the standard of care for patients with MAVD and low to intermediate surgical risk. Concomitant replacement of the aortic root and of the tubular ascending aorta should be performed at the time of AVR in patients with dilated aorta (≥45 mm, especially if the valve is bicuspid). Transcatheter AVR may be considered in patients with ≥intermediate surgical risk if the anatomy and size of the aortic root is suitable. This procedure may not be feasible in patients with large aortic annulus and dilated aortic root. Several studies reported that patients with MAVD have favourable outcomes (in terms of mortality, stroke, residual AR, LV mass regression and functional improvement) following surgical or transcatheter AVR and that these outcomes are comparable with patients with isolated AS.[10 31]

Asymptomatic patients with severe MAVD are at high risk for cardiac events in the short term, particularly if they have high gradient and significant LV hypertrophy. These patients may thus benefit from earlier intervention. However, this approach has not yet been validated and is not supported by the guidelines.

KNOWLEDGE GAPS AND FUTURE PERSPECTIVES

As highlighted in this article, there is a considerable knowledge gap in the field of MAVD. More data are required on the natural history and the impact of intervention on outcomes in order to better define the indications for intervention. One of the priorities in the future would be to develop and validate a comprehensive algorithm including Doppler echocardiography, multimodality imaging and stress testing for an accurate and standardised evaluation of the haemodynamic and clinical severity of MAVD and for the determination of the optimal timing of valve intervention in this population. In particular, the staging scheme proposed by Généreux *et al*[27] in the context of isolated AS to assess the extent of associated cardiac damage will have to be tested and validated in the context of MAVD.

There are, to date, no data regarding the best timing of intervention to optimise outcomes in asymptomatic MAVD. Ongoing randomised trials such as the EARLY-TAVR trial or the EvoLVeD trial are comparing early AVR versus clinical surveillance with AVR performed when the patient develops symptoms or LV dysfunction. However, the vast majority of patients with moderate AS and concomitant AR are not eligible for the EARLY-TAVR trial, which requires a peak jet velocity ≥4 m/s and an AVA <1.0 cm^2 for inclusion. There is thus a need for randomised trials specifically dedicated to asymptomatic patients with MAVD.

CONCLUSION

The diagnosis, severity grading and therapeutic management of MAVD are complex and challenging. The decision to intervene is based on an integrative evaluation of the overall haemodynamic severity, the AS+AR combination and the repercussions of the haemodynamic burden related to the

MAVD on the function of the LV and other cardiac chambers and the patient's clinical status.

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