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EACVI DOCUMENT

The role of multi-modality imaging in multiple valvular heart diseases: a clinical consensus statement of the European Association of Cardiovascular Imaging of the European Society of Cardiology

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With this document, the European Association of Cardiovascular Imaging provides an Expert Consensus on the role of multi-modality imaging (MMI) in the management of patients with multiple valvular heart disease (MVD). Emphasis is given to the use of MMI to unravel the diagnostic challenges that characterize these patients and to improve risk stratification. Complementing the last European Society of Cardiology and European Association of Cardio-Thoracic Surgery guidelines on valvular heart disease, this Expert Consensus document also outlines how MMI assessment should form an integral part of the multi-disciplinary heart team discussion for patients with MVD to help with complex decision-making regarding the choice and timing of treatment.

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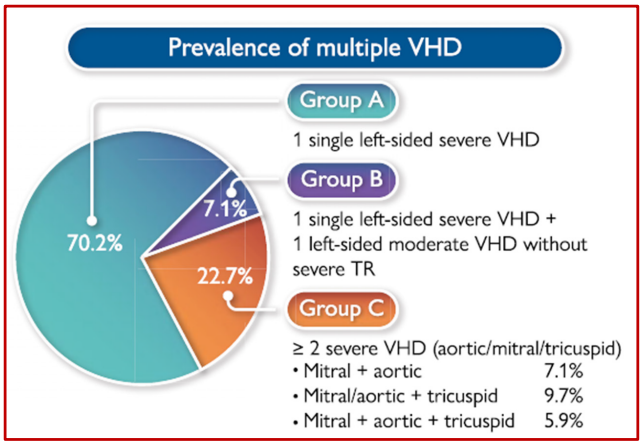
Graphical Abstract



- In presence of MVD use MMI to:
- Assess the severity of each valvular disease and identify the most severe ones (do not forget tricuspid regurgitation!)
- Define in details the mechanism of each valvular lesion.
- Assess the hemodynamic repercussions of MVD and particularly the extent of myocardial damage
- Plan treatment strategies and follow-up according to abovementioned points.

The prevalence of multiple valvular heart disease (according to the 2017 Valvular Heart Disease II Survey) is high and the management of these patients requires specific assessment, for which the role of multi-modality imaging is pivotal.

Keywords multi-modality imaging • multivalvular disease • heart team • myocardial damage

Introduction

Multiple valvular heart disease (MVD) is defined as the presence of a regurgitant and/or a stenotic lesion affecting at least two cardiac valves,[1] whereas mixed valvular heart disease (VHD) refers to the combination of stenotic and regurgitant lesions affecting the same valve. Although MVD is very common, data are scarce, and difficult to interpret due to non-standardized definitions and clinical heterogeneity. However, patients with severe MVD are characterized by a worse prognosis than single VHD[2] and should be timely referred to a Heart Valve Centre for consideration of treatment.

Management of patients with MVD presents several important challenges. In terms of diagnosis, although echocardiography remains the cornerstone investigation, the impact of MVD on cardiac flow and loading conditions can invalidate or reduce the accuracy of several echocardiographic parameters routinely used to assess isolated valve lesions (*Figure 1* and *Table 1*).[3,4] As examples, the continuity equation may be inaccurate when flow through different valves is unequal, and pressure half-time-derived methods cannot be applied when left ventricular (LV) diastolic properties are altered by the presence of MVD. For risk stratification, prognostic tools recommended for single VHD have not been substantially validated in MVD, and accepted cut-off values may not be applicable in these patients. Finally, in terms of therapeutic decision-making, the management of associated lesions that are less than severe in nature, as well as the timing (combined vs. sequential) and the type (surgical vs. percutaneous) of intervention, are challenging clinical choices.

The use of multi-modality imaging (MMI) can help solve some of the above challenges. In this setting, the European Association of Cardiovascular Imaging (EACVI) presents this Expert Consensus Document aiming at guiding the use of MMI in the management of patients with MVD. Of note, this document focuses on the assessment of moderate or greater MVD (in different combinations, but mild lesions are not considered); furthermore, it will not address the role of MMI in mixed VHD and in infective endocarditis (IE).

Methodology

This Expert Consensus document is based on a review of the literature performed by the members of the writing group. The clinical advice is based upon the evidence and/or consensus of the writing group and is classified into several categories, as shown in *Table 2*.

MVD: prevalence and evidence from registries

In a large nationwide hospital-based registry in Sweden, Andell *et al.*[5] reported an overall incidence of VHD of 63.9 cases per 100 000 persons years, and 10.4% of these cases had MVD or mixed VHD, with a higher incidence in men. In this study, the most frequent combination was aortic stenosis (AS) + aortic regurgitation (AR), followed by AS + mitral regurgitation (MR), and AR + MR. Patients with mitral stenosis (MS) also had AS or MR in 28.3% and 17.9% of cases, respectively. Overall, regurgitant valve lesions were more prone to be associated with other concomitant VHD.[6] Percentage may be even higher when performing screening rather than using registries.[7]

In this regard, specific attention should be given also to atrial secondary/functional MR (FMR), a recently proposed aetiology of MR due to annular dilatation in the absence of LV remodelling. Atrial FMR occurs in patients with atrial fibrillation or heart failure with preserved ejection fraction; these patients often present with concomitant significant atrial secondary/functional tricuspid regurgitation (TR) and may require customized management.[8,9]

In the EURObservational Research Programme Valvular Heart Disease II Survey,[2,10] among the 5219 patients with native VHD included in 222 centres from 28 countries, 24.9% had left-sided MVD[11] and 23% of patients had at least two severe VHDs (*Graphical Abstract*); interestingly, the combination of severe left-sided VHD + severe TR was frequent (16%). When looking at aetiology, MVD was most often an acquired condition, with degenerative valve disease as the leading cause.[2,10] Rheumatic heart disease (RHD) is still reported as a frequent cause of MVD but, as for single VHD, a shift in the

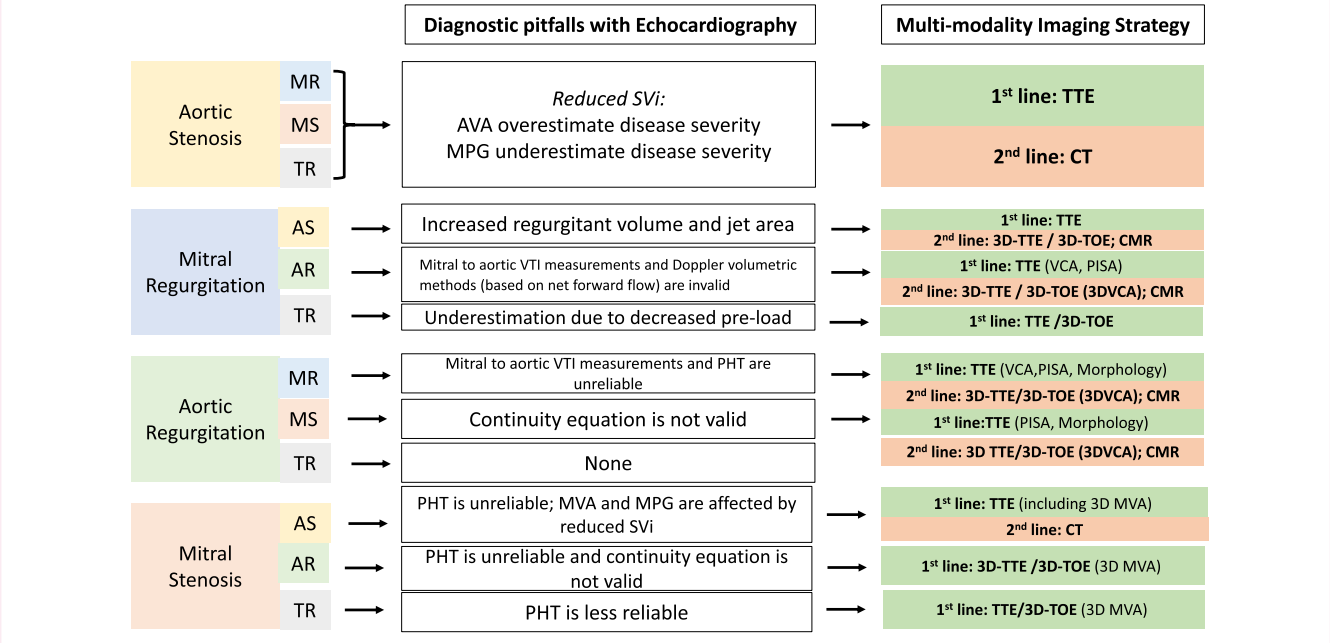


Figure 1 Echocardiographic pitfalls in the assessment of the severity of each VHD in the context of MVD (with different combinations). A step-approach multi-modality imaging strategy is proposed to solve the respective pitfalls.

predominant aetiology from rheumatic towards degenerative is currently being observed in industrialized countries.[2] The global increase in cardiometabolic risk factors and ageing of the population will contribute to increasing degenerative and calcific VHD. Nevertheless, rheumatic fever is an endemic disease not yet under control in low to middle-income countries, which is likely to lead to a doubling in VHD burden, with consequent increases in the incidence of MVD. Currently, in Western and Central Africa, 13% of patients with RHD and severe VHD showed combined lesions on more than one valve.[12]

Other acquired causes, including IE, radiation- and drug-induced VHD, inflammatory diseases, and congenital conditions, are much less frequent but require specific knowledge with respect to both their clinical care and imaging.[10] A recent analysis from a multi-centric study on 1340 consecutive patients has shown that MVD involvement is frequent in left-sided native valve IE, and is associated with more embolic events, congestive heart failure, and death than in single-valve IE.[11]

Combination of aortic stenosis with

Mitral regurgitation

The combination of AS and MR is the most common MVD, and up to 20% of patients with severe AS present some degree of MR. As demonstrated in the Partner C trial, the lower the risk profile of patients with AS, the lower the prevalence of MR.[13,14] The combination of severe AS and MR was 22% in the EURObservational Research Programme Valvular Heart Disease II Survey.[10,15] In a large cohort of echocardiographic studies of patients with AS, the prevalence of concomitant MR was 15.6%, being higher in women (21.4%) and in patients with low-flow low-gradient AS (18.2%).[16] Importantly, the prognosis of concomitant AS and MR has been shown to be worse than that of AS alone. Indeed, moderate-severe MR at baseline is associated with increased mortality after aortic valve replacement (AVR) for both surgical[17] and transcatheter (TAVR) procedures.[18]

The combination of AS and MR often results from a common aetiology (e.g. degenerative, rheumatic, post-radiotherapy). Of note, among the degenerative aetiologies, mitral annular calcification is an increasing cause of mitral valve disease particularly related to increased life-expectancy.[19,20] However, 80% of the MR cases in patients with severe AS are secondary to the cardiac damage (or remodelling) induced by the longstanding increase in afterload or by concomitant comorbidities including atrial fibrillation and ischaemic heart disease (*Figure 2*).[18] Assessment of LV and left atrium (LA) remodelling and their impact on mitral annulus dilatation and mitral valve leaflet tethering, is, therefore, of great importance to understand the mechanism of MR in patients with AS, and should always be performed.[21]

Echocardiographic assessment in patients with AS and MR should, therefore, provide a detailed report on the cause of MR in these patients, and might need to be complemented by *trans*-oesophageal echocardiography (TOE) or other imaging modalities (*Table 3*). Identification of the aetiology of MR may also help predict the likelihood of MR improvement following correction of AS. The PARTNER trial showed for example that FMR is more frequently reduced after TAVR (in ~70% of the cases) than organic (primary) MR.[15] Similarly, other studies suggested that the best likelihood of MR improvement after TAVR is observed in patients with atrial FMR, whereas baseline MR ≥ 3+ and primary MR aetiology are associated with the least MR improvement and worse outcomes (*Figure 3*).[22] Nevertheless, reduction of FMR after correction of AS remains relatively unpredictable, and follow-up imaging after aortic valve intervention is necessary.

The combination of AS and MR also poses important diagnostic challenges for the imager when grading VHD severity (*Figure 1* and *Table 1*). MR reduces forward flow across the aortic valve, both in cases of preserved and reduced LV function, resulting in potential underestimation of AS severity with higher aortic valve area and lower aortic valve peak velocities and mean pressure gradients.[23] In the presence of low-flow low-gradient AS [regardless of left ventricular ejection fraction (LVEF)] and MR, calcium scoring of the aortic valve by cardiac computed tomography (CT) provides a flow-independent anatomical and

Table 1 Main diagnostic challenges (and potential solutions) of echocardiography in the assessment of valvular disease severity and subsequent myocardial damage in MVD

	Diagnostic challenges in the assessment of myocardial damage	Diagnostic challenges in the quantification of valvular heart diseases severity
Combination of AS and MR	Over-estimation of LV Ejection due to significant MR. GLS (especially when discrepant from LV ejection fraction) might help but no cut-off is validated in this setting.	Mis-interpretation of AS severity by both paradoxical and classical low-flow, low-gradient AS. Increased *trans*-mitral systolic pressure gradient for which color-flow-mapping parameters becomes less reliable.
Combination of AS and TR	Severe myocardial damage of the right chambers might be more frequent but difficult to assess. RV–PA coupling and strain imaging of the RV and RA could be used in combination but need further validation.	Mis-interpretation of AS severity due to low LV pre-load related to the TR. (possible low-flow low-gradient AS). Difficult assessment of TR severity due to high load-dependency; anatomical characteristics (annulus dimension and leaflet tethering) could be used instead.
Combination of MR and AR	Severe LV remodelling due to the significant increase in pre-load (and afterload). GLS may be more sensitive than LV ejection fraction to depict LV dysfunction but no cut-off value is validated in this setting. Assessment of the aortic root and ascendens dimension is also important.	Pressure half-time method and mitral to aortic velocity time integral measurements are not reliable. Doppler volumetric methods using left-sided assessment of net forward flow are invalid. PISA and (3D) Vena contracta methods should be preferred.
Combination of MR and TR	Over-estimation of both LV and RV function by using ejection fraction. GLS might help but no cut-off value is validated in this setting, RV–PA coupling and strain imaging of the RV and RA could be used in combination but need further validation.	Under-estimation of the MR severity related to the decrease in pre-load.
Combination of MS and AS	Marked reduction in cardiac output, which is poorly tolerated. Risk for acute severe LV dysfunction related to the acute change in loading condition if the MS is treated alone.	Decrease in pressure gradients across both valves (low-flow low-gradient) and thus, risk of an under-estimation of both valvular heart diseases. MS pressure half-time method becomes unreliable.
Combination of MS and AR	Presence of severe MS may delay the AR-related LV dilatation (used for timing the intervention).	MS severity should not be evaluated using the continuity equation with the aortic valve flow as reference; pulmonic flow could be eventually used. Pressure half-time across the mitral valve may be shortened, leading to mitral valve area over-estimation. Mitral valve area could be assessed by direct planimetry (3D preferred).

prognostic assessment of AS severity that is currently recommended in clinical guidelines for the assessment of patients with discordant echocardiographic measurements (*Table 3* and *Figure 4*).[24] Of note in this setting, dobutamine stress echocardiography is often unable to induce a significant increase in LV forward stroke volume and is, therefore, not of help for the confirmation of AS severity.

With respect to the assessment of MR severity, most standard 2D echocardiographic approaches should be interpreted in the knowledge that the *trans*-mitral systolic pressure gradient is increased in the presence of AS. Thus, for example, the MR jet area using colour-flow mapping will appear bigger, and for any given mitral effective regurgitant orifice, a higher regurgitant volume will be measured. Exercise stress echocardiography could be considered to better assess the dynamic nature of the MR in this setting: a low level of exercise is in most cases sufficient to increase MR to significant AS.[24] In addition, assessment of MR severity in this setting might be improved by using 3D echocardiography and cardiovascular magnetic resonance (CMR) imaging (*Table 3*). Particularly, the difference between the forward flow in the proximal ascending aorta derived from velocity-encoded CMR imaging and the LV stroke volume derived from a cine stack is recommended for this assessment.

Table 2 Categories of clinical advice

	Definition	Symbol
Strength of advice	Clinical advice, based on robust published evidence	
	Clinical advice, based on the uniform consensus of the writing group	
	May be appropriate, based on published evidence	
	May be appropriate, based on consensus within the writing group	
	Area of uncertainty	

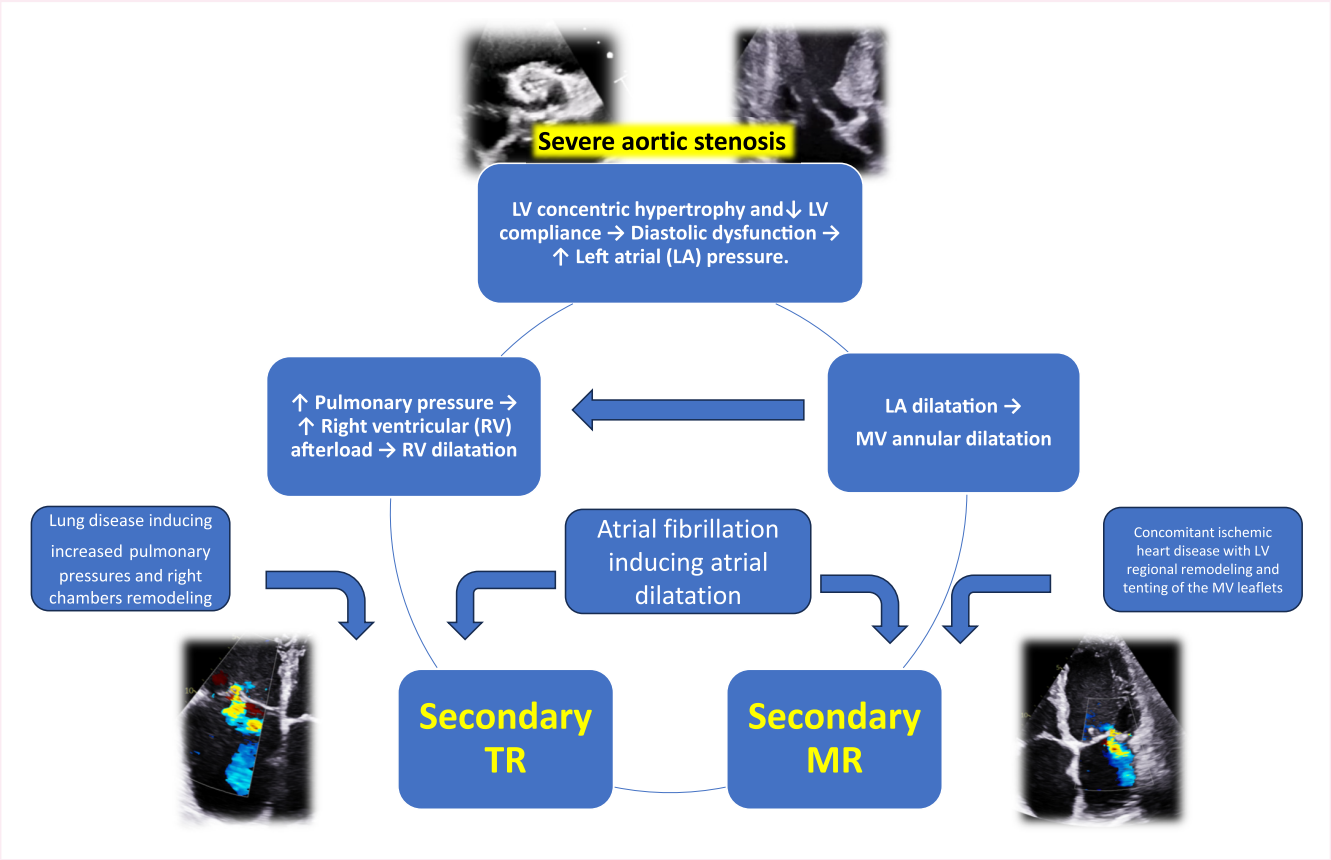


Figure 2 Contributing factors and physiopathology underlying the presence of concomitant secondary mitral and/or tricuspid valve regurgitation in patients with severe aortic stenosis.

The myocardial damage (or remodelling) that occurs secondary to the combined effects of significant AS together with MR is frequently greater than with single lesions, combining both pressure and volume overload of the LV.[6] However, LV contractility might be overestimated in the presence of MR, so that a careful assessment of LV size and function should always be performed (*Tables 1* and *3*). Advanced echocardiographic tools such as global longitudinal strain (GLS) may help better estimating myocardial contractility in this setting and should be combined with the standard assessment. In addition, CMR can be used to detect and quantify the extent of both replacement (using late gadolinium enhancement) and interstitial [by T1 mapping with extra-cellular volume (ECV) calculation] myocardial fibrosis.[25] This provides an objective assessment of the severity of myocardial damage in response to both AS and MR. Fibrosis assessment by CMR has also been shown to be valuable for risk stratification in AS (*Table 3*).[25,26]

The association between low-flow low-gradient AS and amyloidosis has been demonstrated, as this disease can also result in the thickening of valvular leaflets; more recently, the association of amyloidosis and MR has also been described.[27] In this specific scenario, bone scintigraphy and CMR with T1 mapping and late gadolinium enhancement are crucial for the diagnosis of cardiac amyloidosis and to assess the extent of myocardial damage.[28]

Finally, the management of concomitant AS and MR remains a clinical challenge. MMI can provide important information for the decision-making process (*Table 3*), but local resources, cost, expertise, and the individual patient's wishes, are also to be considered by the Heart team. Accurate assessment of the severity of each valvular lesion and the impact on the myocardium and pulmonary vasculature is crucial for the indication and timing of intervention, and as above mentioned should include a multi-parametric and imaging approach. The difficulty to predict the course of MR after aortic valve intervention represents a major issue in decisions regarding the optimal treatment strategy.[29] Reduced afterload after aortic valve intervention may initially reduce MR, but whether this reduction is sufficient over both the short and long-terms depends on several factors, including the mechanism of MR and the chance of progressive cardiac reverse remodelling after intervention.[30] Currently, both American and European Guidelines recommend concomitant mitral valve surgery in patients with severe MR undergoing aortic valve surgery,[1,31] as surgery is typically intended as 'one-stop-shop' procedure. However, in case of moderate MR, due to lack of evidence, no clear indication is given. In patients considered at 'high-risk' for surgery and therefore undergoing TAVR, treatment of concomitant severe MR should be considered depending on the mechanism of MR. In case of primary MR, transcatheter edge-to-edge repair (TEER) or mitral valve replacement can be performed simultaneously with TAVR or most commonly shortly after, as the probability of MR improvement after TAVR is very low. TOE and CT are of great value, not only for the planning of TAVR (*Figure 4*) but also to evaluate the suitability of the mitral valve for these specific interventions, providing anatomical detail of the leaflet lesion, the distribution of calcification and size of the neo-left ventricular outflow tract (*Figure 5*).[32] In cases of FMR, a 'two-step-shop' approach, with a relatively longer watchful waiting time after TAVR is usually preferred to assess the potential spontaneous reduction of MR after TAVR, as also suggested by current guidelines.[1] The extent of myocardial damage with CMR might help

Table 3 Value of each imaging modality in the assessment of both valve disease severity and subsequent myocardial damage according to the different combinations of valvular heart diseases

	TTE	TOE	Cardiac CT	Cardiac MR	Exercise stress echocardiography	Dobutamine stress echocardiography
Combination of AS and MR	+++ Severity of valve disease. Mechanism of MR. Myocardial damage.	++ Mechanism of the MR. Feasibility/planning and guidance of surgical or transcatheter interventions mainly for MR.	++ Severity of AS (calcium scoring). Planning for transcatheter procedures for both AS and MR (replacement).	+ Myocardial damage including assessment of myocardial fibrosis. Severity of MR.	+ Severity of MR in selected cases.	+ Severity of AS in case of low-flow (stroke volume <35 mL/m^2) low-gradient (mean pressure gradient <40 mmHg) And depressed LVEF.
Combination of AS and TR	+++ Severity of valve disease. Myocardial damage, with special focus on the right chambers.	+ Feasibility/planning and guidance of transcatheter intervention of the TR	++ Planning for transcatheter procedures for the AS and for some of the TR (annuloplasty or replacement)	+ Myocardial damage including assessment of myocardial fibrosis. Severity of TR.		+ Severity of AS in case of low-flow (stroke volume <35 mL/m^2) low-gradient (mean pressure gradient < 40 mmHg)and depressed LVEF
Combination of MR and AR	+++ Severity of the valve diseases and mechanism. Myocardial damage. Aorta dimension assessment.	++ Mechanism and severity of AR and MR. Feasibility/planning and guidance of transcatheter procedures mainly for MR.	+ Planning for transcatheter valve replacement.	++ Severity of valve disease. Myocardial damage including myocardial fibrosis assessment. Aortic dimensions.	+ Severity of MR in selected cases.	Combination of MR and AR
Combination of MR and TR	+++ Severity of valve disease. Mechanism of MR and TR. Myocardial damage.	++ Mechanism of the MR and TR. Feasibility/planning and guidance of surgical or transcatheter interventions both for TR and MR.	+ Planning for transcatheter tricuspid valve annuloplasty or replacement or mitral valve replacement.	++ Severity of TR and MR. Myocardial damage including assessment of myocardial fibrosis.	+ Severity of MR in selected cases	
Combination of MS and AS	+++ Quantification of valve diseases and myocardial damage. Determine the aetiology of MS and suitability of the mitral valve for PBMV.	++ Determine the aetiology of MS and suitability of the mitral valve for PBMV. Ensure the absence of left atrial appendage thrombus.	++ Severity of AS (calcium scoring). Assessing the calcifications of the mitral valve.		+ Possibly to assess the severity of MS by exercise (valve area and pulmonary pressures).	

Continued

Table 3 Continued

	TTE	TOE	Cardiac CT	Cardiac MR	Exercise stress echocardiography	Dobutamine stress echocardiography
Combination of MS and AR	+++ Quantification of valve diseases (direct planimetry and vena contracta width preferred) and myocardial damage. Determine the aetiology of MS and suitability of the mitral valve for PBMV.	+++ More accurate assessment of valve disease severity. Determine the aetiology of MS and suitability of the mitral valve for PBMV.	++ Assessing the calcifications of the mitral valve	++ Quantification of AR severity. Myocardial damage.	+ Possibly to assess the severity of MS by exercise (valve area and pulmonary pressures).	

The role of each imaging modality for the assessment of the feasibility and the planning of surgical and transcatheter interventions is also highlighted.

predicting LV reverse remodelling after TAVR but the evidence is still lacking and the intervention cannot be based on the extent of late gadolinium enhancement.[33] A proposal for the management of patients with severe AS and severe MR is depicted in *Figure 3*.

Key messages

- The prognosis of concomitant AS and MR is worse than that of severe AS alone
- Combination of AS and MR can make the assessment of the severity of both valve lesions challenging. Echocardiography is the first-line imaging technique but CT calcium scoring can help adjudicate aortic stenosis severity in challenging situations. In selected cases, CMR can be performed to aid MR quantification
- The aetiology of the MR in patients with severe AS should be precisely defined by imaging, since it will impact the management of these patients and particularly the choice of timing (and type) for intervention
- The extent of myocardial damage, resulting from both heart valve diseases, should be reported precisely, using echocardiography and CMR as required

Tricuspid regurgitation

The combination of AS and TR is relatively common, as up to 40% of patients with severe AS show also significant TR.[34,35] Moderate to severe TR can represent a downstream consequence of the AS mostly at an advanced stage, when a significant increase in LV end-diastolic pressure and pulmonary pressures occur, often also with right ventricular (RV) and right atrial (RA) remodelling (ventricular TR) (*Figure 2*). As the primary pathophysiological mechanism is an increase in LV end-diastolic pressure, secondary TR in patients with severe aortic stenosis is frequently associated also with FMR, complicating further the diagnosis and management of these patients.

However, significant TR can also be present as concomitant valve disease, without direct association with AS but related instead to the complex interplay of different factors, including significant lung disease or, importantly, atrial fibrillation with bi-atrial dilatation (*Figure 2*).[36] The presence of significant TR in patients with AS has been associated with worse outcome[37] although with a strong relationship with the presence of MR and RV dilatation. In addition, the course of TR after surgical or transcatheter treatment of AS is difficult to predict as both improvement and worsening have been described.[36,38]

Imagers are, therefore, required to systematically assess the presence and severity of TR in patients with significant AS and consider the potential implications for diagnosis and decision-making. Akin to MR, co-existent TR and AS may lead to a reduced pre-load of the LV and therefore a low-flow state with low *trans*-aortic valve gradient and erroneous AS severity evaluation (*Figure 1* and *Table 1*). MMI and CT calcium scoring of the aortic valve can be helpful in providing an anatomical assessment of AS severity (*Figure 4*).[34,38,39] Assessment of TR severity is also challenging as it is highly sensitive to changes in loading conditions and the regurgitant orifice is mostly non-circular and of irregular shape. As the mechanism of TR is in most of the cases secondary, anatomical characteristics such as tricuspid valve annular dilatation, degree of leaflet tethering, and both RV and RA remodelling, have been proposed to better guide therapeutic management of these patients rather than TR severity itself (*Table 3* and

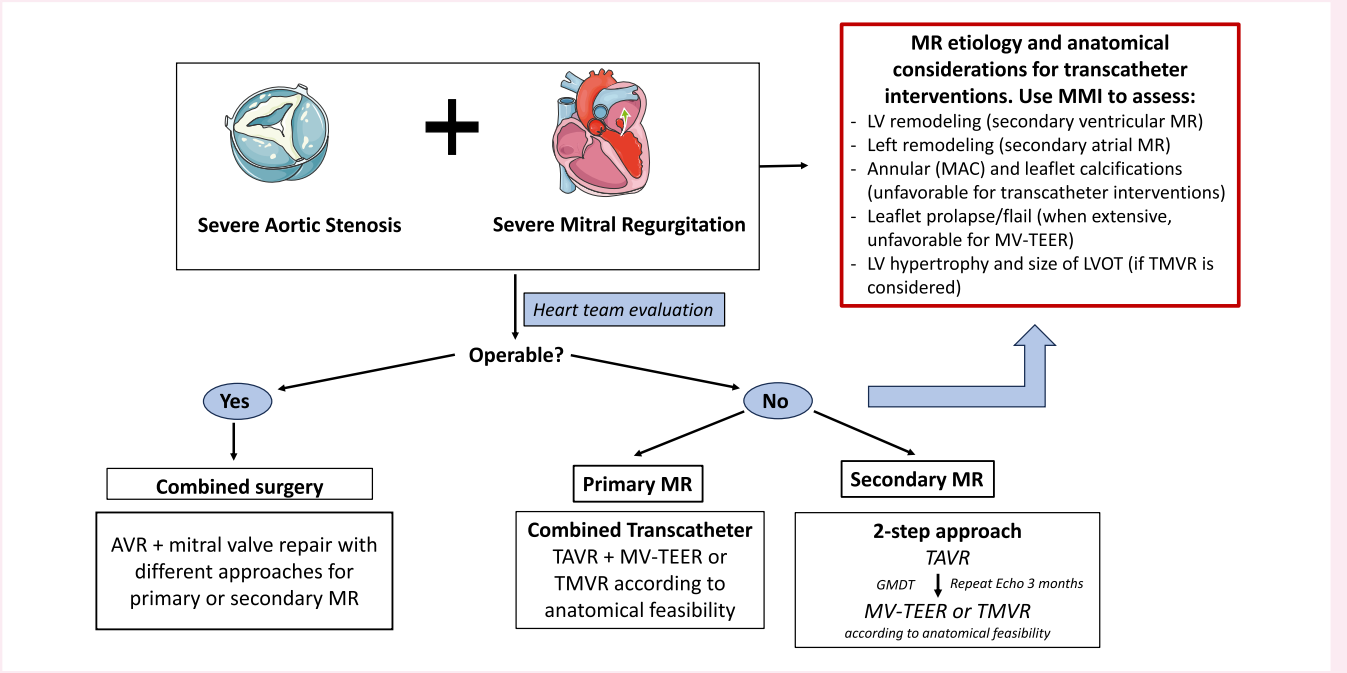


Figure 3 Proposed algorithm for the management of patients with severe aortic stenosis combined with severe MR. MMI plays a crucial role in identifying the aetiology and mechanism of MR, and the anatomical details to be considered (favourable or unfavourable) when referring patients for surgical or transcatheter interventions.

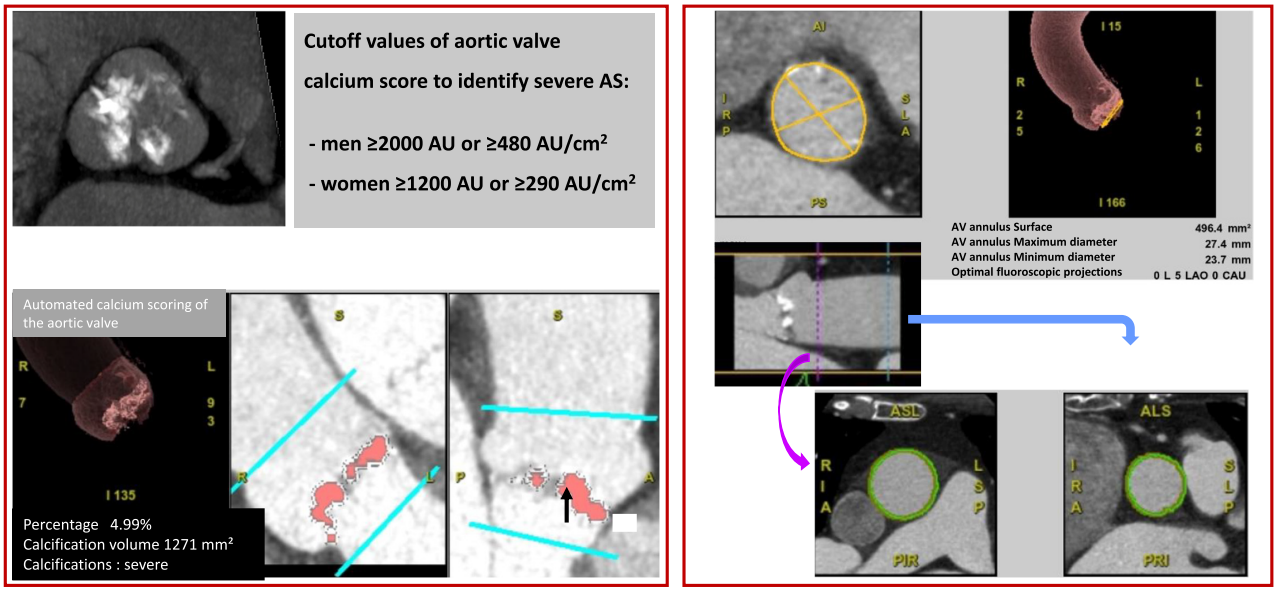


Figure 4 Value of CT for the measurements of aortic valve calcium scoring (left panel) in the assessment of aortic stenosis severity, and of the aortic valve and aorta dimensions (right panel) for the correct planning of surgical and transcatheter interventions.

Figure 6).[9] However, the measurements of the tricuspid valve apparatus and right chambers should be preferably performed with 3D echocardiography considering the complex geometry of these structures which is not adequately assessed from a 2D (RV focused) four-chamber view (*Figure 6*).[9,40]

In addition, the details of the accompanying myocardial and pulmonary vasculature damage, including RV and RA function and pulmonary pressures, should be provided considering their demonstrated prognostic value,[34,41] but also the implications for the choice of intervention. In this regard, the use of RV–arterial coupling

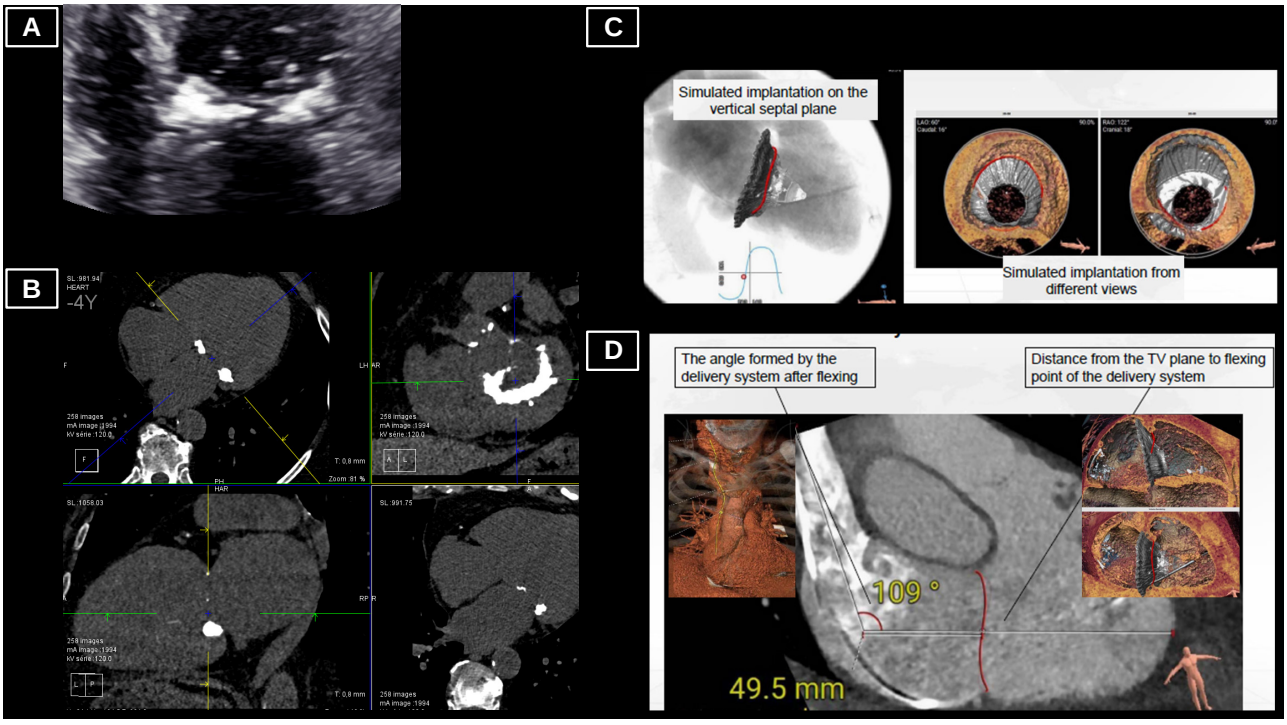


Figure 5 Example of the value of cardiac CT for assessing mitral valve calcifications. (*A*, *B*) Echocardiographic vs. cardiac CT assessment. (*C*, *D*) Example of the fundamental role of cardiac CT for the planning of transcatheter atrio-ventricular valve prosthesis implantation, in this case of a Lux valve in tricuspid valve position.

[tricuspid annulus plan excursion (TAPSE)/systolic pulmonary artery pressure (sPAP)] and of echocardiographic strain imaging of the RV and of the RA might help in assessing right heart function.[42,43] In addition, CMR can provide important additional information on TR severity and its consequences on right heart remodelling, while right heart catheterization should be used to assess pulmonary pressures and supplement the evaluation of RV function (*Table 3*).[44]

The vicious circle of 'TR begets TR' should not be overlooked by the Heart team when discussing the management of AS. Current European guidelines recommend repairing the tricuspid valve during left-sided surgery in patients with severe secondary TR (Class I-B) and in those with mild or moderate secondary TR and either a tricuspid annulus diameter >40 mm (21 mm/m^2) or prior signs of right-sided heart failure (Class IIa-B)[1] (measuring the diameter at end-diastole allows for assessing the maximum size of the annulus and provides a more accurate evaluation of its dilation). Noteworthy, the literature supporting this recommendation was largely based on MR surgery studies, with additional data on TR surgery provided by more recent clinical trials (see chapter on concomitant MR and TR). However, the same considerations could be extrapolated for patients undergoing aortic valve surgery. In cases where patients are referred for TAVR, data are also scarce on the effect of this intervention on TR progression, but so far, a two-step-shop approach is normally applied, with a second echocardiographic assessment repeated at least 3 months after the procedure. In case of persistent severe TR (and symptoms), the feasibility of a tricuspid valve TEER or transcatheter annuloplasty or valve replacement can be carefully evaluated by using 3D *trans*-thoracic and TOE for the assessment of tricuspid valve annulus and leaflet geometry, and of the size and function of the RV and RA (*Table 3* and *Figure 6*).[40] CT and CMR may provide important additional information regarding tricuspid annulus shape and dimension, the proximity to the right coronary artery, and of RV/RA remodelling respectively.[45] On top of these imaging techniques, a right heart catheterization is most of the time needed to insure complete haemodynamic measurements measurement and if possible, the calculation of pulmonary vascular

Key messages

- When evaluating a patient with significant AS, a precise assessment of the right heart should always be performed, including the presence and severity of TR, quantification of RV size and function, RA size, and pulmonary pressures, as they portend prognostic and management implications
- The combination of significant AS and TR can challenge severity assessments of the individual valve lesions. A MMI approach should be used, starting with echocardiography, and incorporating CT calcium scoring (for AS) or CMR (for TR) as required to improve assessment
- MMI and the combination of 3D echocardiography and CMR, should also be used to assess myocardial damage in terms of RV and RA remodelling. In addition, right heart catheterization might be valuable for the assessment of pulmonary pressures and estimation of RV function
- In case of transcatheter intervention, a sequential approach is normally applied to treat both valve diseases and MMI, including 3D echocardiography and CT, is crucial to assess the feasibility of each procedure

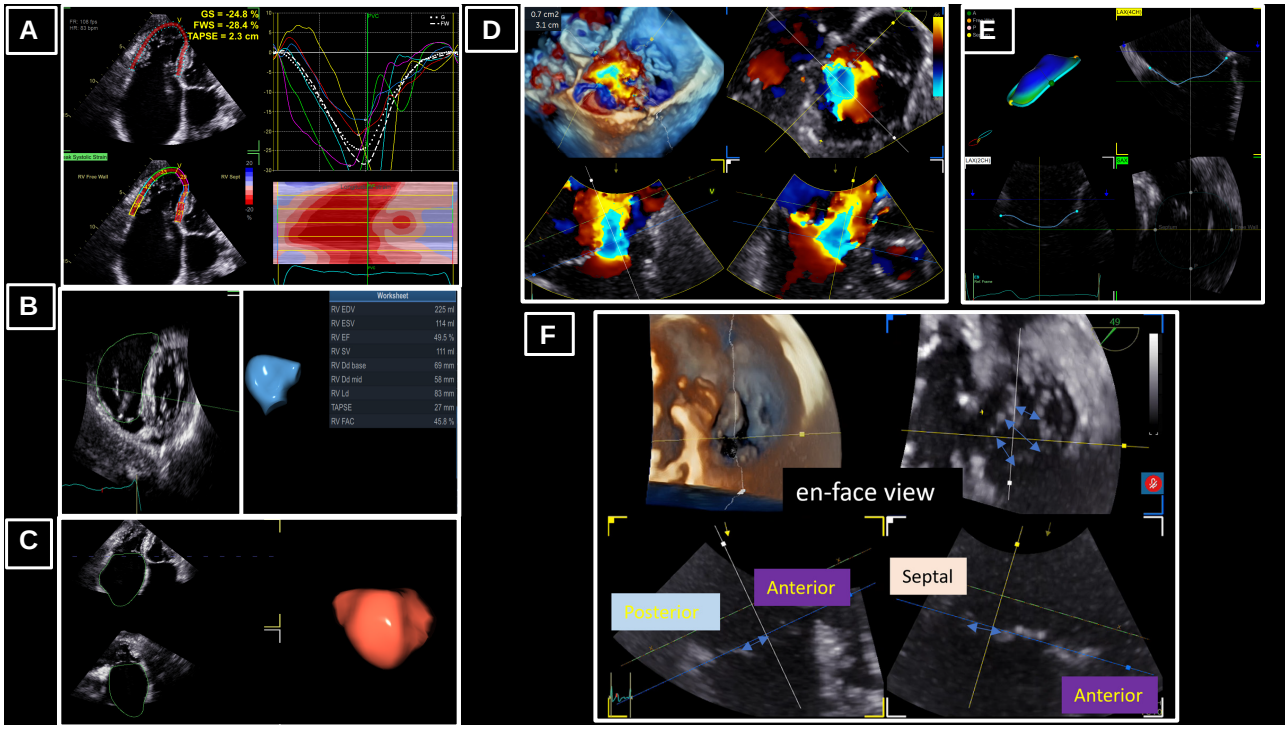


Figure 6 Comprehensive *trans*-thoracic and *trans*-esophageal echocardiographic assessment of a patient with severe tricuspid regurgitation associated with left-sided VHD. (*A–C*) Quantification of RV function by global strain (GS) and free wall strain (FWS) analysis (*A*) and 3D volumetric measure of the RV (*B*), and of the RA (*C*), which provide crucial information for decision-making; In addition, the assessment of TR severity can be improved by measuring the 3D vena contracta area (*D*) using multi-planar reformatting planes, 3D evaluation of valve geometry including the quantification of annulus dimension and leaflet tenting (*E*), but also the measure of the coaptation gap (*F*).

resistance (with the limit of the thermodilution in patients with TR for the measurement of the cardiac output).

Ascending aorta, aortic root involvement, and aortic regurgitation

AS is commonly associated with ascending aorta and/or aortic root disease, particularly in patients with congenital heart disease, such as bicuspid aortic valve (BAV), or in those with connective tissue disease.[46,47] For example, at the time of aortic valve intervention for severe AS, ~30% of patients with BAV have been reported to require concomitant aortic root replacement.[48] In case of significant AS, measurements of the proximal aorta should be reported and typically require MMI, as outlined by the recent dedicated EACVI document on imaging in thoracic aortic disease.[49] Cross-sectional imaging with CT or CMR should always be used when there is evidence of dilatation by echocardiography or in patients with BAV, especially for the assessment of the ascending aorta which may not be fully visualized with echocardiography (*Figure 4*). The 'root phenotype' or 'ascending phenotype' can be, therefore, also identified as it has an impact on the chosen cut-off value of aortic dilatation for surgery indication. In any case, current European Society of Cardiology (ESC) guidelines recommend surgery for aortic dilatation in patients undergoing aortic valve surgery at a root or ascending aorta diameter ≥45 mm.[50,51]

Key message

- CT or CMR must be used to confirm echocardiographic measurements in patients with aortic root or ascending aorta dilatation associated with aortic valve disease
- CT or CMR should be used to assess the entire thoracic aorta in patients with BAV disease being considered for valve intervention

Combination of mitral regurgitation with

Aortic regurgitation

The combination of MR and AR is common. In the European Valvular Heart Disease II Survey, 183 of the 1516 patients (12.1%) with at least one severe and one moderate valve disease had a combination of AR and MR.[10] The presence of MR can be secondary to the LV dilatation induced by severe AR and could, therefore, resolve if the aortic valve is treated before the development of irreversible LV remodelling.[52] However, AR and MR can also share a common aetiology. For examples in cases of radiotherapy, specific drugs use or RHD, systolic and diastolic restriction of valve leaflets is frequently observed in both aortic and mitral valves. Also, in patients presenting acutely with the combination of MR and AR, IE should be excluded.[53,54]

Both AR and MR increase LV pre-load, and, by increasing the total stroke volume and systolic blood pressure, AR also increases afterload. The co-existence of MR and AR, therefore, often results in severe LV dilatation with increased sphericity and eccentric hypertrophy, which

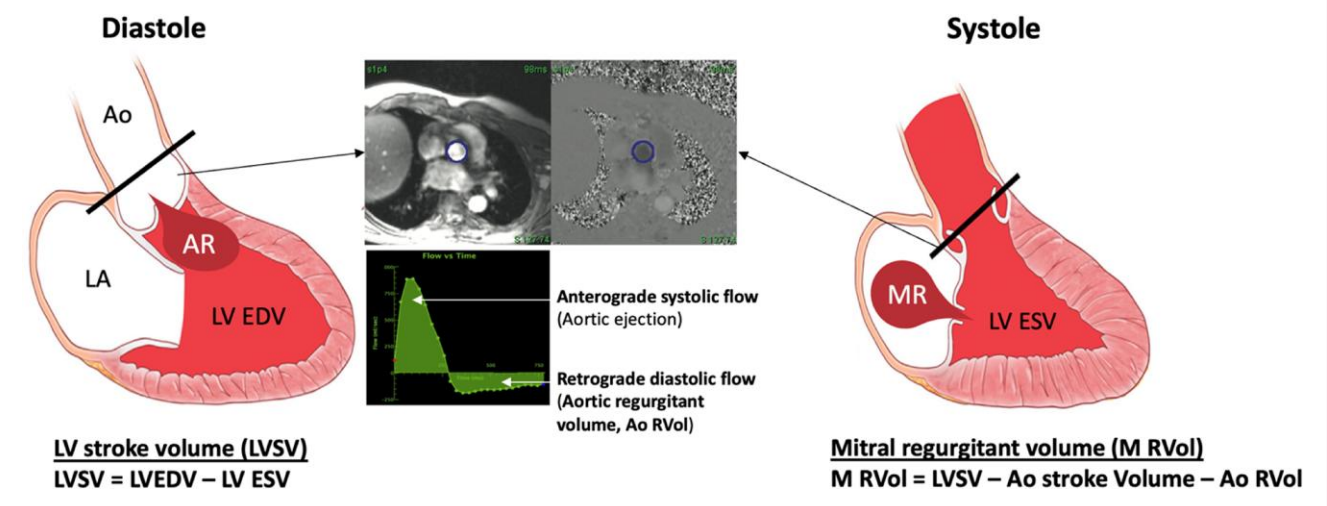


Figure 7 CMR for the assessment of the severity of valvular regurgitation in patients with combined significant mitral regurgitation and aortic regurgitation. LV volume measurements in end-diastole (LV EDV) and end-systole (LV ESV) are performed using short-axis views cine-MRI. Then, the measurement of LV stroke volume (LVSV) is obtained by the formula: LVSV = LV EDV – LV ESV. By performing a 2D flow sequence 1 cm above the aortic valve, measurement of the volume of systolic anterograde flow in the aorta and the regurgitant volume (Ao RVol) can be performed. Finally, the mitral regurgitant volume (M RVol) is obtained by the following formula: M Rvol = LVSV – Ao stroke volume – Ao RVol.

may occur even in case of moderate AR and moderate MR, because of the combined effect of the valve lesions (*Table 3*). Whilst initially compensatory and reversible, this LV remodelling eventually results in irreversible myocardial damage and impaired systolic function, which is more frequently observed following valve intervention than in case of isolated AR or MR.[53–55] In these patients, assessment of the aortic root and ascending aorta dimension remains important, as aortic dilatation may also progress more rapidly according to the blood pressure control or the phenotype of the aortic root disease.

Echocardiography remains the first-line imaging modality for assessing MR and AR severity, although when these two valve lesions are combined, standard echocardiographic approaches may be unreliable (*Table 3* and *Figure 1*).[3] When quantifying AR, pressure half-time assessments are often unreliable as LV relaxation/compliance is altered in case of significant MR. Similarly, when quantifying MR, mitral to aortic velocity time integral measurements cannot be trusted in the presence of AR. Also, Doppler volumetric methods using left-sided assessment of net forward flow are invalid in case of both AR and MR. The use of the proximal iso-velocity surface area (PISA) method and of the vena contracta width should be still valid and especially the 3D vena contracta area measurement should be considered in centres with the enough expertise.[47] CMR could complete the assessment of the severity of both AR and MR especially when echocardiographic assessments are discrepant (*Table 3*).[56,57] Good CMR scan quality is required for both phase-contrast flow-mapping sequences and for the short-axis cine stack that enables LV and RV volume quantification (*Figure 7*). In cases of combined MR and AR, the aortic regurgitant volume is quantified directly from diastolic flow on velocity-encoded images positioned in the proximal aorta, while mitral regurgitant volume is calculated as the difference between the LV stroke volume, measured from a short-axis cine of the LV, the aortic regurgitant volume and the aortic stroke volume measured in the proximal aorta.[58]

In these patients, assessment of myocardial damage is again very important (*Table 3*). LV ejection fraction is load dependent, and most of the time overestimates ventricular systolic performance. The GLS has been proposed both in MR and AR as a more sensitive marker of LV dysfunction and to improve risk stratification, although no specific studies have been performed in patients with combined MR and AR.[59,60] Accordingly, also no specific cut-off values for GLS have been validated in these patients. A threshold of 19% could be considered extrapolating the results from the data available on the single-valve lesion.[60] In addition, CMR can be used for accurate assessment of LV remodelling providing reference standard assessments of the degree of LV dilatation that can be monitored over time. Myocardial tissue characterization using late gadolinium enhancement and ECV analysis, can also be used, which, although not yet extensively studied, seem promising to help identify irreversible myocardial damage and therefore patients at higher risk (*Table 3*).[61]

The combination of MR and AR is poorly tolerated and therefore concomitant double valve surgery is normally recommended when one valve lesion is severe and the other moderate or even in cases where both valve lesions are moderate.[1] When the patient is considered inoperable, transcatheter interventions should be considered and the imager is required to identify the most severe valvular lesion so that this can be treated first. However, the anatomical suitability for each procedure should be also assessed (by using TOE and

Key messages

- When the valvular lesions are combined, quantification of aortic and MR severity is challenging. Advanced imaging techniques, such as 3D echocardiography and CMR should be used
- Accurate assessment of LV remodelling and myocardial damage should be performed for clinical decision-making and include echocardiography (with strain analysis) and CMR as required

potentially CT, *Table 3*), considering that limited transcatheter options are currently available for the treatment of AR.

Tricuspid regurgitation

The combination of significant MR with secondary TR is relatively common,[10] (while MR with primary TR is very rare) and is associated with worse prognosis.[62,63] In a cohort of echocardiographic studies of patients with MR, 19% of patients had a TR of at least moderate grade.[64] According to a recent classification of secondary TR, in these patients TR could be often classified as ventricular (tenting of tricuspid valve leaflet and RV remodelling), as direct consequence of long-standing primary MR or of LV dysfunction with secondary MR (with increased pulmonary pressure and RV/RA remodelling).[65] However, it could be classified also as atrial secondary TR (annular dilatation and flattening with RA dilatation but no RV remodelling), when present in patients with atrial fibrillation and concomitant atrial FMR (*Figure 2*).[9] The presence of a cardiac implantable electronic device (CIED) might also contribute to the severity of TR in these patients.[8,66,67] The identification of TR and MR aetiology has important implications in patient management as in some cases surgical and transcatheter interventions should be considered only after optimal heart failure therapy (including cardiac resynchronization) or treatment of underlying rhythm abnormalities.[66,67] Also, resolution of the MR by surgical or transcatheter intervention might lead in some cases to a significant improvement of the TR. Recent findings have highlighted the importance of understanding predictors of lack of TR improvement after intervention. Key predictors include RA dilation, TR severity, tricuspid annular dilation, and the presence of atrial fibrillation. These factors often indicate an advanced disease stage and may require tailored therapeutic strategies. Adamo *et al.*[68] emphasized the critical role of atrial dimension and of follow-up assessment after mitral valve intervention. Furthermore, Basman *et al.*[69] underscored the importance of procedural planning and outcomes in patients undergoing mitral valve interventions.

The imager is, therefore, required to provide an accurate assessment of both valve disease severity and of the respective mechanism, including also the quantification of left and right chamber size and function (myocardial damage) and pulmonary pressures (*Table 3*). In the presence of significant TR, MR could be underestimated due to a decreased LV pre-load; TR severity could also be dynamic in relation to changes in MR severity and pulmonary pressures (*Figure 1*). Echocardiography is the first-line imaging technique and most of the standard measures can still be applied reliably in these patients; however, 3D echocardiography [by *trans*-thoracic echocardiography (TTE) or when need by TOE], is strongly suggested for the assessment of the 3D vena contracta area (often with a non-circular shape in case of TR) and of the tricuspid valve anatomy (annulus geometry and dimension, leaflet tenting), and for the quantification of RV and RA size and function (*Figure 6*).[70] RV–arterial coupling (TAPSE/sPAP < 0.4 mm/mmHg) might help in monitoring cardiac performance in these patients in relation to the changes in pulmonary pressures (for example after correction of the MR).[66,67] Also, strain analysis can be applied to both left and right chambers to better depict systolic dysfunction,[71] but specific cut-off values are not available in patients with combined TR and MR. CMR can be of important additional help for quantifying TR severity using a similar method as for MR, based upon the difference between pulmonary forward flow and RV stroke volume measurements.[58] CMR is also the most robust technique for assessing RV volumes and ejection fraction (*Table 3*).

When there is an indication for MR surgery, current ESC guidelines recommend concomitant tricuspid valve annuloplasty in case of moderate or severe secondary TR or in patients with a tricuspid annulus >40 mm or 21 mm/m^2,[1] as these are considered predictors of lack of TR improvement or even progression after mitral valve surgery. Recent trials[72,73] have confirmed the value of concomitant tricuspid valve surgery mainly in patients with moderate TR; however, annulus dimensions represent an important anatomical consideration. Currently, tricuspid annular diameters are measured in diastole from an RV focus apical four-chamber view. This gives a measurement from approximately the mid-septal annulus to the mid-anterior annulus (although it could be the posterior) and has been shown to be a predictor of the severity of TR.[74] On top of the echocardiographic assessment, CT should be considered, especially for planning in patients where tricuspid valve annuloplasty or replacement is considered (*Table 3*).[75] In cases where the patient is not eligible for surgery and a transcatheter intervention is considered, the treatment strategy may involve either a one-step or two-step approach. This decision should primarily be guided by the underlying TR mechanism and the extent of myocardial damage, which can be evaluated through a comprehensive imaging assessment.[76]

Key messages

- In the context of MR, careful evaluation of TR severity is required and the underlying mechanisms should be clearly identified
- Echocardiography, including advanced techniques such as 3D echocardiography and strain imaging, is the first-line imaging technique for the assessment of these patients but CMR and CT are of additional value for both valve disease severity and myocardial damage (CMR) assessments and for transcatheter procedures planning (CT)

Association of mitral stenosis with

Aortic stenosis

RHD is the most common cause of the association of MS with AS, especially in low-middle-income countries. However, this combination is nowadays rare. It could also be observed in patients exposed to a thoracic radiotherapy. Also, especially in industrialized countries, combined MS and AS are usually due to calcific degeneration as in patients with chronic kidney disease and in dialysis.[77] Combined severe MS and AS represented 17% of consecutive patients undergoing combined mitro-aortic surgery.[78,79]

Severe MS combined with severe AS results in a marked reduction in cardiac output, which is poorly tolerated both haemodynamically and clinically. The low-pressure gradient across both valves induced by the low cardiac output, often leads to underestimate both AS and MS severity.[80] Also, the MS pressure half-time method is unreliable in this setting (*Figure 1* and *Table 1*). Mitral valve area might be better assessed by direct planimetry with 3D echocardiography (TTE and TOE); however, recent studies showed that mitral valve area may increase after AS interventions (pseudo-severe MS), confirming the flow dependency of this parameter.[81] In these cases, aortic valve CT calcium scoring can help to rule out pseudo-severe low-flow low-gradient AS (*Figure 4*). CT assessment of the extension of mitral valve calcifications from the annulus to the leaflets (*Figure 5*) has been shown to be associated with less MS improvement after aortic valve interventions, although no specific quantification of cut-off of the mitral valve calcium has been provided yet (*Table 3* and *Figure 1*).[81]

When deciding upon potential treatment strategies, assessing the aetiology of MS is crucial in these patients, because percutaneous

Key messages

- The association of MS and AS is uncommon but poorly tolerated due to the marked reduction in cardiac output
- Echocardiography is crucial in these patients, for the assessment of the haemodynamic status and to determine the aetiology of MS and suitability of the mitral valve for PMBV; however, the assessment of valve disease severity is challenged by the low-pressure gradients across both valves
- CT is of important additional value for the assessment of the extent of valve calcifications of both valves

mitral balloon valvuloplasty (PMBV) should only be performed in patients with rheumatic MS and in the presence of suitable mitral valve anatomy as assessed by echocardiography. Hence, PMBV should be proposed to treat severe MS in cases of less than severe AS in patients with favourable anatomy. If both MS and AS are severe, double valve surgery, or TAVR with PMBV should be considered.[1,77] It is important to emphasize the risks of performing PMBV while neglecting concomitant severe AS. In this setting, PMBV could lead to an abrupt increase in LV pre-load causing pulmonary oedema.[82] Acute severe LV dysfunction related to this acute change in loading condition must be anticipated.

Aortic regurgitation

The prevalence of MS and AR is strongly related to the prevalence of RHD and may differ across different countries.[10] In most reports, AR is of mild or moderate severity, being severe in only 10% of patients with severe MS.[83] The effects of AR and MS on loading conditions are the opposite: the increase in stroke volume usually seen in isolated AR is attenuated in the presence of severe MS.[84] Therefore, the presence of severe MS may delay the AR-related LV dilatation and dysfunction and accordingly the indication for surgery.[85] The diagnosis of valve disease severity is also challenging in these patients (*Figure 1* and *Table 1*); MS severity should not be evaluated using the continuity equation since flow across the aortic valve and the mitral valve is different; pulmonic flow should be used instead as the reference. Moreover, due to the presence of AR, the MS pressure half-time decay may be shortened, leading to over-estimation of the mitral valve area.[86,87] Mitral valve area should, therefore, be obtained using direct planimetry, preferably using 3D echocardiography. For AR severity assessment, 2D or, better 3D vena contracta area, could be used and preferably by TOE. CMR using phase-contrast imaging might be useful for confirming the severity of AR regardless of the presence of concomitant MS (*Table 3*). As in other cases of significant AR, dilatation of the aortic root and ascending aorta should be identified and quantified using cross-sectional imaging and followed-up over time for potential progression.

Key messages

- Association of MS and AR gives important challenges for the diagnosis of valve disease severity and for the therapeutic decision-making (timing and type of intervention)
- Advanced echocardiography should be used, particularly with a 3D and TOE approach, alongside CMR as required to overcome these challenges and optimize the management of these patients

Double valve replacement is usually considered if MS and AR are severe. However, if severe MS is the predominant lesion and the valve anatomy is suitable, percutaneous ballooning of the mitral valve (PBMV) may be proposed first[88] and the heart team might further consider the indication and the risks for the surgical or percutaneous (still very limited) treatment of AR.

Tricuspid regurgitation

Primary (rheumatic) tricuspid valve involvement, resulting in regurgitation and/or stenosis, is observed in up to 10% of rheumatic MS patients.[89] In addition, up to 38% of rheumatic MS patients and up to 30% of severe calcific degenerative MS patients have at least moderate secondary TR,[19,90] which portends a worse prognosis.[91] In these cases,

Key message

- When MS is associated with significant TR, an accurate assessment of TR mechanism and severity as well as right heart remodelling should be performed by echocardiography, in combination with CMR and right heart catheterization as required

secondary TR develops either due to post-capillary pulmonary hypertension and RV dilatation/dysfunction (ventricular TR), or due to MS-related atrial fibrillation causing concomitant RA enlargement and central leaflet mal-coaptation (atrial TR/FTR).[92] Of note, TR related to the presence of CIED should also be considered.

Therefore, as for the other combinations of TR and left-sided VHD, a thorough assessment of the precise TR mechanism and severity is crucial to decide the most appropriate treatment approach. For this purpose, echocardiography is the first-line imaging modality, including also the assessment of RV and RA size and function and the estimation of pulmonary pressures (*Table 3*).[93] However, an integrated approach, including cardiac magnetic resonance (CMR), might be considered as described in previous chapters (*Figure 1*). Integrating advanced imaging findings and haemodynamic assessments is critical for optimizing patient selection and tailoring interventions.

Association of tricuspid valve disease with pulmonary valve disease

Pulmonary valve disease is rare and mainly due to a primary aetiology, presenting as stenosis, regurgitation, or mixed valve disease. The main causes are congenital disease, carcinoid tumours, RHD, and, much less frequently, IE or iatrogenic causes.[94] Very infrequently, pulmonary regurgitation may result from secondary causes, including pulmonary arterial hypertension and idiopathic pulmonary arterial dilatation.[94]

In adult congenital heart disease, and particularly in patients with status post-complete Tetralogy of Fallot repair, the advent of transcatheter pulmonic valve replacement has allowed for safe treatment in those suitable andiming of intervention is mainly dictated by CMR-based RV dilatation. However, the presence of concomitant TR accelerates the RV remodelling and might not always improve after treatment of the upstream regurgitant lesion. e. In patients with carcinoid syndrome; the combined heart valve lesion has an incidence of 20–35% and generally occurs 2–5 years after the initial diagnosis of carcinoid syndrome. The typical presentation includes thickening and retraction of the tricuspid

and pulmonary valve leaflets, annular constriction, and fusion of the subvalvular apparatus, resulting in relatively immobile leaflets and therefore a combination of stenosis and regurgitation.[95]

Echocardiography (TTE–TOE) remains the first-line imaging modality for the assessment of patients with right-sided combined valve disease. This technique may provide a complete evaluation, including tricuspid valve and pulmonary valve morphology and function, the dimension of the pulmonary artery dimension and its branches, the presence and possibly the exact level of an RV outflow obstruction, and the assessment of size, shape, and function of the RV and RA. However, imaging of the tricuspid and pulmonary valves can be technically challenging and CMR might be needed in complex cases.[96] As mentioned earlier for congenital heart diseases, CMR is considered the gold standard for the quantification of right chamber size and function and can also provide accurate quantification of pulmonary regurgitation and stenosis and of the tricuspid valve disease, using direct (RV and LV stroke volume) and indirect (phase-contrast imaging) methods. More recently, direct measurements of the TR volume have become available with CMR 4D flow techniques.[97,98]

Key message

- An MMI approach is crucial when pulmonary and tricuspid valve diseases coexist and echocardiography cannot provide reliable imaging
- Looking for the underlying aetiology (for example carcinoid syndrome) of this specific MVD is crucial for patient management

CT may also play an important role, particularly in the guidance of percutaneous structural interventions to assess the anatomy and surrounding structures. New technologies, including 3D printing, are being used increasingly to help guide complex structural interventions involving both valves.[99] Also, the ^{68}Ga-Dotatate PET/CT is currently considered the gold standard for assessment and follow-up of neuroendocrine tumour, including those with rare sites of metastasis such as cardiac infiltration.

Gaps in evidence

The prevalence and underlying aetiology of MVD are still largely unknown and, although new European registries on this topic are ongoing, more efforts should be made to understand the true epidemiology of MVD.

Only a limited number of studies have attempted to establish specific severity thresholds for individual valve lesions when they occur in the setting of MVD. Therefore, clinical, and potentially computational modelling, research should focus on identifying and validating appropriate cut-off values for the different imaging assessments in this setting. Similar studies should be performed for the assessment of the extent of cardiac remodelling and myocardial damage accompanying MVD, which is crucial for risk stratification and therapeutic decision-making in these patients.

In addition, whilst imaging plays a crucial role also in planning, guiding, and assessing the results of both surgical and transcatheter interventions for VHD, little is known on how it can help select the best treatment approach in patients with MVD.

Due to this huge lack of evidence in the literature about multiple and mixed VHD, we advocate for the initiation of the first international registry of multiple and mixed valvular heart diseases (MMVD) proposed by the Heart Imagers of Tomorrow (HIT) of the EACVI: EACVI–MMVD study (ClinicalTrials: NCT06235385) as a large prospective, multicentre, observational 'real-life' study including all consecutive patients diagnosed with MMVD in more than one hundred centres from more than thirty different countries.

Conclusions

MVD is common, encountered in nearly 30% of patients with left-sided native VHD, and is associated with more unfavourable cardiac remodelling and worse prognosis as compared with single VHD. Moreover, diagnosis and risk stratification of MVD present significant challenges, and the scientific evidence base for MVD remains limited. Specific expertise in the use of MMI is crucial in these patients, since it provides the unique opportunity to combine different approaches for a more comprehensive assessment of the aetiology and severity of the valve disease as well as the related myocardial damage.

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Data availability

The data underlying this article will be shared on reasonable request to the corresponding author.

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