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## **The Role of Multimodality Imaging in Multiple Valvular Heart Diseases. A Clinical Consensus Statement of the European Association of Cardiovascular Imaging (EACVI) of the ESC**

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## 1 ABSTRACT

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

11  
12 **Key words:** multimodality imaging, multivalvular disease, heart team, myocardial damage  
13

## 14 INTRODUCTION

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

22 Management of patients with MVD presents several important challenges. In terms of diagnosis,  
23 although echocardiography remains the cornerstone investigation, the impact of MVD on cardiac  
24 flow and loading conditions can invalidate or reduce the accuracy of several echocardiographic  
25 parameters routinely used to assess isolated valve lesions. (Figure 1 and Table 1) (3, 4). As

1 examples, the continuity equation may be inaccurate when flow through different valves is  
2 unequal, and pressure half time-derived methods cannot be applied when left ventricular (LV)  
3 diastolic properties are altered by the presence of MVD. For risk stratification, prognostic tools  
4 recommended for single VHD have not been substantially validated in MVD, and accepted cut-  
5 off values may not be applicable in these patients. Finally, in terms of therapeutic decision making,  
6 the management of associated lesions that are less than severe in nature, as well as the timing  
7 (combined vs. sequential) and the type (surgical vs. percutaneous) of intervention, are challenging  
8 clinical choices.






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

15

## 16 **Methodology**

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

20 Table 2. Categories of clinical advice

STRENGTH OF ADVICE	DEFINITION	SYMBOL
	Clinical advice, based on robust published evidence	
	Clinical advice, based on uniform consensus of the writing group	
	May be appropriate, based on published evidence	
	May be appropriate, based on consensus within writing group	
	Area of uncertainty	

1

2

### 3 **MVD: prevalence and evidence from registries**

4 In a large nationwide hospital-based registry in Sweden, Andell et al.(5) reported an overall  
 5 incidence of VHD of 63.9 cases per 100,000 persons years, and 10.4% of these cases had MVD or  
 6 mixed VHD, with a higher incidence in men. In this study, the most frequent combination was  
 7 aortic stenosis (AS) + aortic regurgitation (AR), followed by AS + mitral regurgitation (MR), and







1 measurements (24) (Table 3 and Figure 4). Of note in this setting, dobutamine stress  
2 echocardiography is often unable to induce a significant increase in LV forward stroke volume  
3 and is therefore not of help for the confirmation of AS severity.

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

15 The myocardial damage (or remodelling) that occurs secondary to the combined effects of  
16 significant AS together with MR is frequently greater than with single lesions, combining both  
17 pressure and volume overload of the LV (6). However, LV contractility might be overestimated in  
18 the presence of MR, so that a careful assessment of LV size and function should always be  
19 performed. (Table 1 and 3). Advanced echocardiographic tools such as global longitudinal strain  
20 (GLS) may help better estimating myocardial contractility in this setting and should be combined  
21 with the standard assessment. In addition, CMR can be used to detect and quantify the extent of  
22 both replacement (using late gadolinium enhancement) and interstitial (by T1 mapping with extra

1 cellular volume (ECV) calculation) myocardial fibrosis (25). This provides an objective  
2 assessment of the severity of myocardial damage in response to both AS and MR. Fibrosis  
3 assessment by CMR has also been shown to be valuable for risk stratification in AS (25, 26) (Table  
4 3).

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

10  
11 Finally, the management of concomitant AS and MR remains a clinical challenge. MMI can  
12 provide important information for the decision-making process (Table 3), but local resources, cost,  
13 expertise, and the individual patient's wishes, are also to be considered by the Heart team. Accurate  
14 assessment of the severity of each valvular lesion and the impact on the myocardium and  
15 pulmonary vasculature is crucial for the indication and timing of intervention, and as above  
16 mentioned should include a multi-parametric and imaging approach. The difficulty to predict the  
17 course of MR after aortic valve intervention represents a major issue in decisions regarding the  
18 optimal treatment strategy (29). Reduced afterload after aortic valve intervention may initially  
19 reduce MR, but whether this reduction is sufficient over both the short and long-terms depends on  
20 several factors, including the mechanism of MR and the chance of progressive cardiac reverse  
21 remodeling after intervention (30). Currently, both American and European Guidelines  
22 recommend concomitant mitral valve surgery in patients with severe MR undergoing aortic valve  
23 surgery (1, 31), as surgery is typically intended as "one-stop-shop" procedure. However, in case



1       ⇒ *The aetiology of the MR in patients with severe AS should be precisely defined by*  
2             *imaging, since it will impact the management of these patients and particularly the*  
3             *choice of timing (and type) for intervention.*

4       ⇒ *The extent of myocardial damage, resulting from both heart valve diseases, should be*  
5             *reported precisely, using echocardiography and CMR as required.*

### 6

### 7 **b)Tricuspid regurgitation**

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

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







1 Key messages:

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

17  
 18     **c) Ascending aorta, aortic root involvement and aortic regurgitation**

19 AS is commonly associated with ascending aorta and/or aortic root disease, particularly in  
 20 patients with congenital heart disease, such as bicuspid aortic valve (BAV), or in those with  
 21 connective tissue disease (46, 47)). For example, at the time of aortic valve intervention for  
 22 severe AS, approximately 30% of patients with BAV have been reported to require concomitant  
 23 aortic root replacement (48). In case of significant AS, measurements of the proximal aorta  
 24 should be reported and typically require MMI, as outlined by the recent dedicated EACVI

1 document on imaging in thoracic aortic disease (49). Cross-sectional imaging with CT or CMR  
2 should always be used when there is evidence of dilatation by echocardiography or in patients  
3 with BAV, especially for the assessment of the ascending aorta which may not be fully  
4 visualised with echocardiography (Figure 4). The “root phenotype” or “ascending phenotype”  
5 can be therefore also identified as it has impact on the chosen cut-off value of aortic dilatation  
6 for surgery indication. In any case, current ESC-guidelines recommend surgery for aortic  
7 dilatation in patients undergoing aortic valve surgery at a root or ascending aorta diameter  $\geq 45$ mm  
8 (50, 51).

9

10 Key message

11  $\Rightarrow$  **CT or CMR must be used to confirm echocardiographic measurements in patients**  
12 **with aortic root or ascending aorta dilatation associated with aortic valve disease.**

13  $\Rightarrow$  CT or CMR should be used to assess the entire thoracic aorta in patients with bicuspid  
14 aortic valve disease being considered for valve intervention

15

## 16 COMBINATION OF MITRAL REGURGITATION WITH

### 17 a) Aortic regurgitation

18 The combination of MR and AR is common. In the European Valvular Heart Disease II Survey,  
19 183 of the 1516 patients (12.1%) with at least one severe and one moderate valve disease had a  
20 combination of AR and MR (10). The presence of MR can be secondary to the LV dilatation  
21 induced by severe AR and could therefore resolve if the aortic valve is treated before the





1 could complete the assessment of the severity of both AR and MR especially when  
2 echocardiographic assessments are discrepant (60, 61) (Table 3). Good CMR scan quality is  
3 required for both phase contrast flow-mapping sequences and for the short-axis cine stack that  
4 enables LV and RV volume quantification (**Figure 7**). In cases of combined MR and AR, the aortic  
5 regurgitant volume is quantified directly from diastolic flow on velocity encoded images  
6 positioned in the proximal aorta, while mitral regurgitant volume is calculated as the difference  
7 between the LV stroke volume, measured from a short-axis cine of the LV, the aortic regurgitant  
8 volume and the aortic stroke volume measured in the proximal aorta (62).

9 In these patients, assessment of myocardial damage is again very important (Table 3). LV ejection  
10 fraction is load dependent, and most of the time overestimates ventricular systolic performance.  
11 The GLS has been proposed both in MR and AR as a more sensitive marker of LV dysfunction  
12 and to improve risk-stratification, although no specific studies have been performed in patients  
13 with combined MR and AR(63, 64). Accordingly, also no specific cut-off values for GLS have  
14 been validated in these patients. A threshold of 19% could be considered extrapolating the results  
15 from the data available on the single valve lesion (64). In addition, CMR can be used for accurate  
16 assessment of LV remodelling providing reference standard assessments of the degree of left  
17 ventricular dilatation that can be monitored over time. Myocardial tissue characterization using  
18 late gadolinium enhancement and extra cellular volume (ECV) analysis, can also be used, which,  
19 although not yet extensively studied, seem promising to help identify irreversible myocardial  
20 damage and therefore patients at higher risk(65) (Table 3).

21 The combination of MR and AR is poorly tolerated and therefore concomitant double valve  
22 surgery is normally recommended when one valve lesion is severe and the other moderate or even  
23 in cases where both valve lesions are moderate(1). When the patient is considered inoperable,



1 (Figure 2). Presence of a cardiac implantable electronic device (CIED) might also contribute to the  
2 severity of TR in these patients (70, 71). (8). The identification of TR and MR aetiology has  
3 important implications in patient management as in some cases surgical and transcatheter  
4 interventions should be considered only after optimal heart failure therapy (including cardiac  
5 resynchronization) or treatment of underlying rhythm abnormalities (70, 71). Also, resolution of  
6 the MR by surgical or transcatheter intervention might lead in some cases to a significant  
7 improvement of the TR. Recent findings have highlighted the importance of understanding  
8 predictors of lack of TR improvement after intervention. Key predictors include RA dilation, TR  
9 severity, tricuspid annular dilation, and the presence of atrial fibrillation. These factors often  
10 indicate advanced disease stage and may require tailored therapeutic strategies. Adamo M et al.  
11 (72) emphasized the critical role of atrial dimension and of follow-up assessment after mitral valve  
12 intervention. Furthermore, Basman et al. (73) underscored the importance of procedural planning  
13 and outcomes in patients undergoing mitral valve interventions.

14  
15 The imager is therefore required to provide an accurate assessment of both valve disease severity  
16 and of the respective mechanism, including also the quantification of left and right chamber size  
17 and function (myocardial damage) and pulmonary pressures (Table 3). In the presence of  
18 significant TR, MR could be underestimated due to a decreased LV preload; TR severity could  
19 also be dynamic in relation to changes in MR severity and pulmonary pressures (Figure 1).  
20 Echocardiography is the first-line imaging technique and most of the standard measures can still  
21 be applied reliably in these patients; however, 3D echocardiography (by TTE or when need by  
22 TOE), is strongly suggested for the assessment of the 3D vena contracta area (often with a non-  
23 circular shape in case of TR) and of the tricuspid valve anatomy (annulus geometry and dimension,

1 leaflet tenting), and for the quantification of RV and RA size and function. (74)(Figure 6). Right  
2 ventricular-arterial coupling (TAPSE/sPAP<0.4 mm/mm Hg) might help in monitoring cardiac  
3 performance in these patients in relation to the changes in pulmonary pressures (for example after  
4 correction of the MR) (70, 71). Also strain analysis can be applied to both left and right chambers  
5 to better depict systolic dysfunction(75), but specific cut-off values are not available in patients  
6 with combined TR and MR. CMR can be of important additional help for quantifying TR severity  
7 using a similar method as for MR, based upon the difference between pulmonary forward flow  
8 and RV stroke volume measurements. (62). CMR is also the most robust technique for assessing  
9 RV volumes and ejection fraction (Table 3).

10 When there is an indication for MR surgery, current ESC-guidelines recommend concomitant  
11 tricuspid valve annuloplasty in case of moderate or severe secondary TR or in patients with a  
12 tricuspid annulus >40 mm or 21 mm/m<sup>2</sup> (1), as these are considered predictors of lack of TR  
13 improvement or even progression after mitral valve surgery. Recent trials (76, 77) have confirmed  
14 the value of concomitant tricuspid valve surgery mainly in patients with moderate TR, however  
15 annulus dimensions represent an important anatomical consideration. Currently, tricuspid annular  
16 diameters are measured in diastole from a RV focus apical 4-chamber view. This gives a  
17 measurement from approximately the mid-septal annulus to the mid-anterior annulus (although it  
18 could be the posterior) and has been shown to be a predictor of the severity of TR(78). On top of  
19 the echocardiographic assessment, CT should be considered, especially for planning in patients  
20 where tricuspid valve annuloplasty or replacement is considered (79) (Table 3).In cases where the  
21 patient is not eligible for surgery and a transcatheter intervention is considered, the treatment  
22 strategy may involve either a one-step or two-step approach. This decision should primarily be

1 guided by the underlying TR mechanism and the extent of myocardial damage, which can be  
2 evaluated through a comprehensive imaging assessment (80).

3 .

#### 4 **Key messages**

5 ⇒ *In the context of MR, careful evaluation of TR severity is required and the underlying*  
6 *mechanisms should be clearly identified.*

7 ⇒ *Echocardiography, including advanced techniques such as 3D echocardiography and*  
8 *strain imaging, is the first-line imaging technique for the assessment of these patients*  
9 *but CMR and CT are of additional value for both valve disease severity and myocardial*  
10 *damage (CMR) assessments and for transcatheter procedures planning (CT)*

11

## 12 **ASSOCIATION OF MITRAL STENOSIS WITH**

### 13 **a) Aortic stenosis**

14 RHD is the most common cause of the association of MS with AS, especially in low-middle-  
15 income countries. However, this combination is nowadays rare. It could also be observed in  
16 patients exposed to a thoracic radiotherapy. Also, especially in industrialized countries, combined  
17 MS and AS is usually due to calcific degeneration as in patients with chronic kidney disease and  
18 in dialysis (81). Combined severe MS and AS represented 17% of consecutive patients undergoing  
19 combined mitro-aortic surgery (82, 83).

20 Severe MS combined with severe AS results in a marked reduction in cardiac output, which is  
21 poorly tolerated both hemodynamically and clinically. The low pressure gradient across both





1 3). As in other cases of significant AR, dilatation of the aortic root and ascending aorta should be  
2 identified and quantified using cross sectional imaging and followed-up over time for potential  
3 progression.

4 Double valve replacement is usually considered if MS and AR are severe. However, if severe MS  
5 is the predominant lesion and the valve anatomy is suitable, PBMV may be proposed first (92) and  
6 the heart team might further consider the indication and the risks for the surgical or percutaneous  
7 (still very limited) treatment of AR.

#### 8 **Key messages**

9     ⇒ *Association of MS and AR gives important challenges for the diagnosis of valve disease*  
10         *severity and for the therapeutic decision making (timing and type of intervention).*

11     ⇒ *Advanced echocardiography should be used, particularly with a 3D and TOE approach,*  
12         *alongside CMR as required to overcome these challenges and optimize management of*  
13         *these patients.*

#### 15 **c) Tricuspid regurgitation**

16 Primary (rheumatic) tricuspid valve involvement, resulting in regurgitation and/or stenosis, is  
17 observed in up to 10% of rheumatic MS patients (93). In addition, up to 38% of rheumatic MS  
18 patients and up to 30% of severe calcific degenerative MS patients have at least moderate  
19 secondary TR (19, 94), which portends a worse prognosis (95). In these cases, secondary TR  
20 develops either due to post-capillary pulmonary hypertension and RV dilatation/dysfunction  
21 (ventricular TR), or due to MS-related atrial fibrillation causing concomitant RA enlargement and











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39

#### 40 **FIGURES LEGENDs**

41

42 Central Figure. The prevalence of MVD (according to the 2017 VHD II Survey) is high and the  
 43 management of these patients requires specific assessment, for which the role of MMI is  
 44 pivotal.

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

4  
5 Figure 2. Contributing factors and physiopathology underlying the presence of concomitant  
6 secondary mitral and/or tricuspid valve regurgitation in patients with severe aortic stenosis

7 Figure 3. Proposed algorithm for the management of patients with severe aortic stenosis  
8 combined with severe MR. MMI plays a crucial role in identifying the etiology and mechanism  
9 of MR, and the anatomical details to be considered (favorable or unfavorable) when referring  
10 patients for surgical or transcatheter interventions.

11  
12 Figure 4 : Value of computed tomography for the measurements of aortic valve calcium scoring  
13 (Left Panel) in the assessment of aortic stenosis severity, and of the aortic valve and aorta  
14 dimensions (Right Panel) for the correct planning of surgical and transcatheter interventions.

15 Figure 5. Example of the value of cardiac computed tomography for assessing mitral valve  
16 calcifications (Panel A-B = echocardiographic versus cardiac computed tomography  
17 assessment). Panel C and D: example of the fundamental role of cardiac computed tomography  
18 for planning of transcatheter atrio-ventricular valve prosthesis implantation, in this case of a Lux  
19 valve in tricuspid valve position.

20  
21 Figure 6. Comprehensive transthoracic and trans-esophageal echocardiographic assessment of  
22 a patient with severe tricuspid regurgitation associated with left-sided valvular heart disease.  
23 Panel A-C: quantification of RV function by global (GS) and free wall (FWS) strain analysis (Panel  
24 A) and 3D volumetric measure of the RV (Panel B), and of the RA (Panel C), which provide  
25 crucial information for decision-making;

26 In addition, the assessment of TR severity can be improved by measuring the 3D vena contracta  
27 area (Panel D) using multi-planar reformatting planes, 3D evaluation of valve geometry  
28 including the quantification of annulus dimension and leaflet tenting (Panel E), but also the  
29 measure of the coaptation gap (Panel F)

1 Figure 7: CMR for the assessment of the severity of valvular regurgitation in patients with  
 2 combined significant mitral regurgitation and aortic regurgitation.  
 3 LV volume measurements in end-diastole (LV EDV) and end-systole (LV ESV) are performed using short-  
 4 axis views cine-MRI. Then, measurement of LV stroke volume (LVSV) is obtained by the formula:  $LVSV =$   
 5  $LV\ EDV - LV\ ESV$ . By performing a 2D flow sequence one centimeter above the aortic valve,  
 6 measurement of the volume of systolic anterograde flow in the aorta and the regurgitant volume (Ao  
 7 RVol) can be performed. Finally, the mitral regurgitant volume (M RVol) is obtained by the following  
 8 formula:  $M\ RVol = LVSV - Ao\ stroke\ volume - Ao\ RVol$ .  
 9

	<b>Diagnostic challenges in the assessment of myocardial damage</b>	<b>Diagnostic challenges in the quantification of valvular heart diseases severity</b>
<b>Combination of AS and MR</b>	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.	Misinterpretation 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.
<b>Combination of AS and TR</b>	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
<b>Combination of MR and AR</b>	Severe LV remodelling due to the significant increase in preload (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 aortic root and ascendens dimension are 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.

<b>Combination of MR and TR</b>	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.
<b>Combination of MS and AS</b>	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 underestimation of both valvular heart diseases. MS pressure half-time method becomes unreliable.
<b>Combination MS and AR</b>	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 overestimation. Mitral valve area could be assessed by direct planimetry (3D preferred)

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

3  
4 Table 3: Value of each imaging modality in the assessment of both valve disease severity and subsequent  
5 myocardial damage according to the different combination of valvular heart diseases. The role of each  
6 imaging modality for the assessment of the feasibility and the planning of surgical and transcatheter  
7 interventions is also highlighted. Abbreviations...

	<b>TTE</b>	<b>TOE</b>	<b>Cardiac CT</b>	<b>Cardiac MR</b>	<b>Exercise stress echocardiography</b>	<b>Dobutamine Stress Echocardiography</b>
<b>Combination of AS and MR</b>	+++ severity of valve disease.	++ Mechanism of the MR.	++ Severity of AS (calcium	+ Myocardial damage including	+ Severity of MR in	+ Severity of AS in case of low flow

	Mechanism of MR. Myocardial damage.	Feasibility/planning and guidance of surgical or transcatheter interventions mainly for MR.	scoring). Planning for transcatheter procedures for both AS and MR (replacement).	assessment of myocardial fibrosis. Severity of MR.	selected cases.	(stroke volume <35ml/m <sup>2</sup> ) low gradient (mean pressure gradient < 40 mmHg) And depressed LVEF.
<b>Combination of AS and TR</b>	+++ 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 <35ml/m <sup>2</sup> ) low gradient (mean pressure gradient < 40 mmHg) and depressed LVEF
<b>Combination of MR and AR</b>	+++ 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
<b>Combination of MR and TR</b>	+++ Severity of valve disease. Mechanism of MR and TR. Myocardial damage.	++ Mechanism of the MR and TR. Feasibility/planning and guidance of	+ Planning for transcatheter tricuspid valve	++ Severity of TR and MR. Myocardial damage including	+ Severity of MR in selected cases	-

		surgical or transcatheter interventions both for TR and MR.	annuloplasty or replacement or mitral valve replacement.	assessment of myocardial fibrosis.		
<b>Combina tion of MS and AS</b>	+++ 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.		+	-
<b>Combina tion MS and AR</b>	+++ 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.	+	-

1

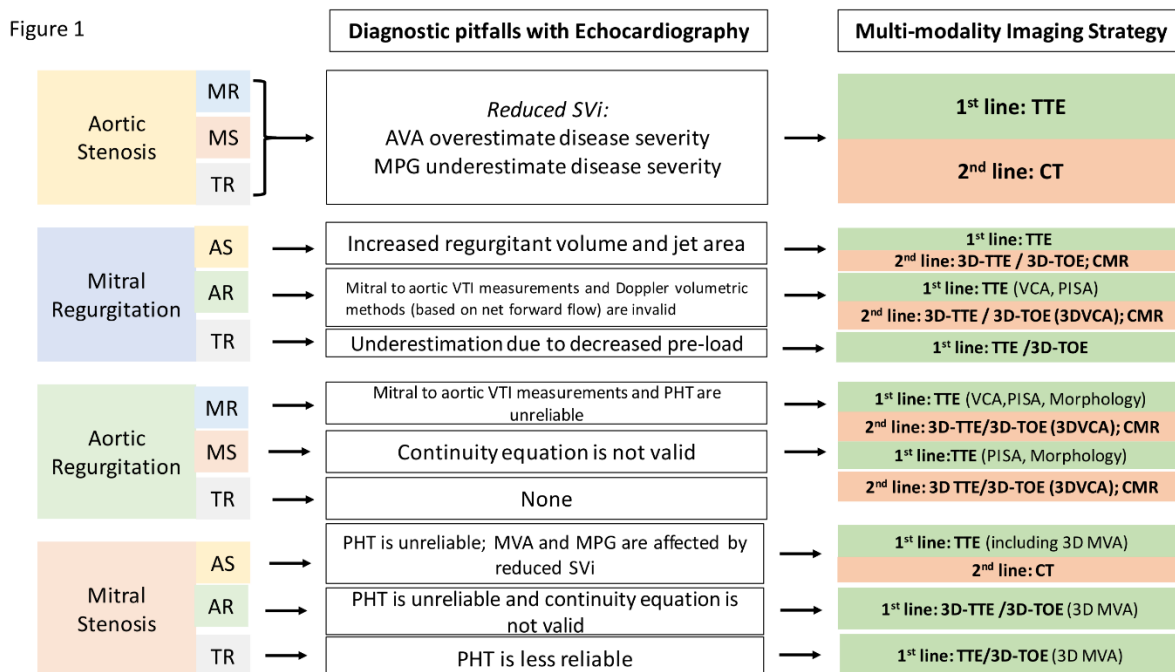


Figure 1  
339x190 mm (x DPI)

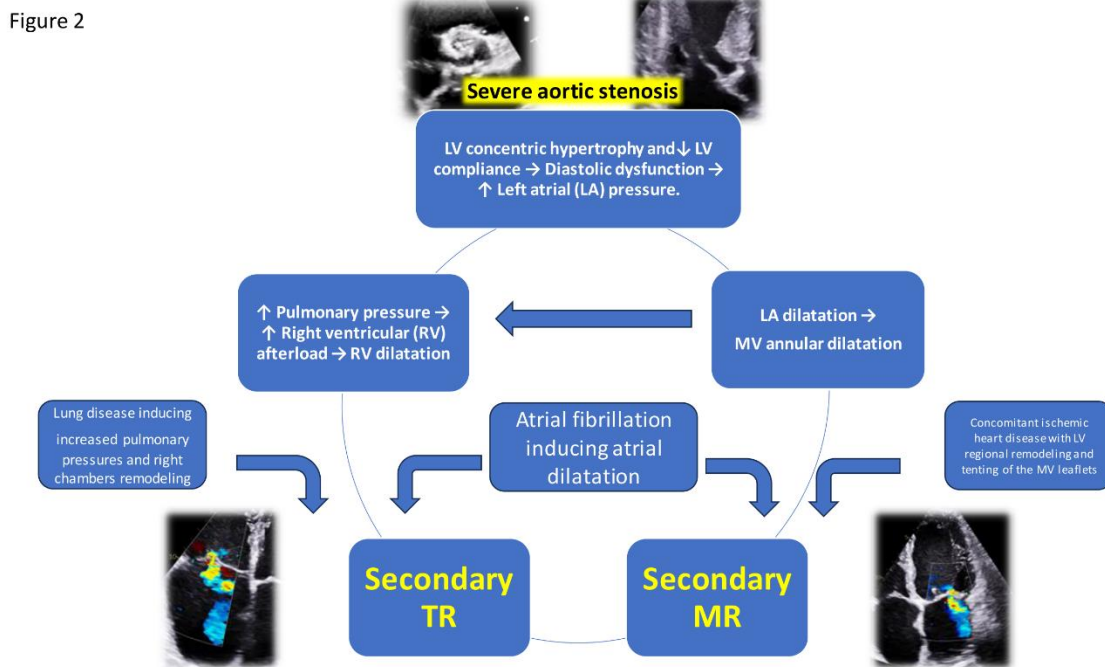


Figure 2  
339x190 mm (x DPI)

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Figure 3

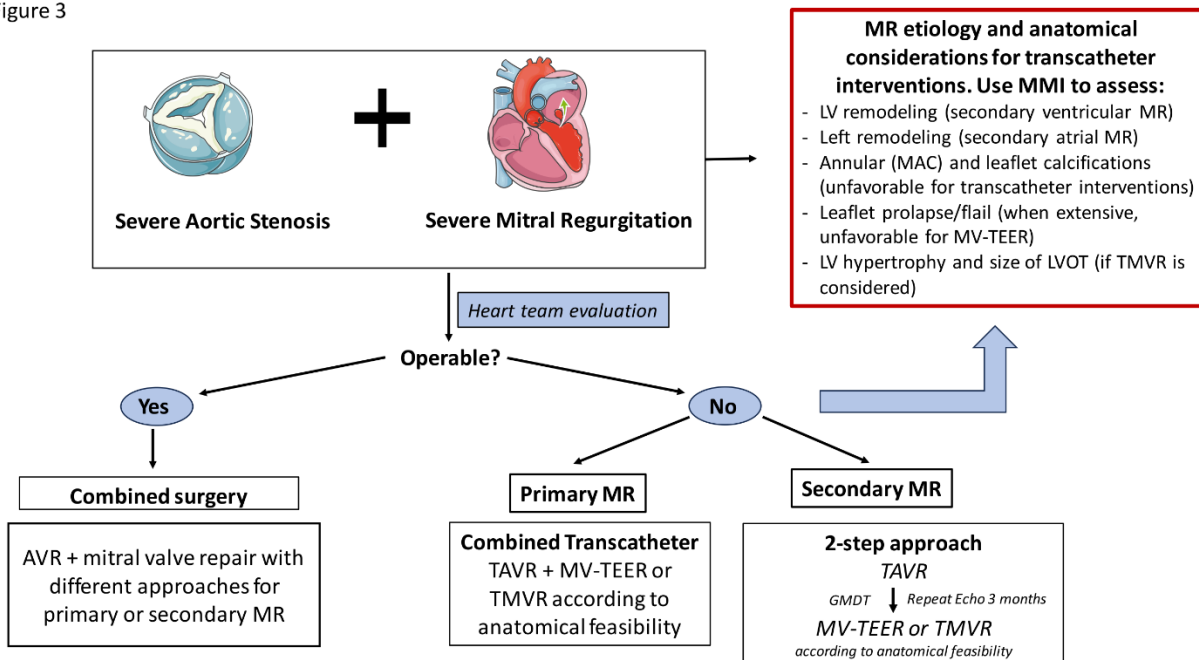


Figure 3  
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Figure 4

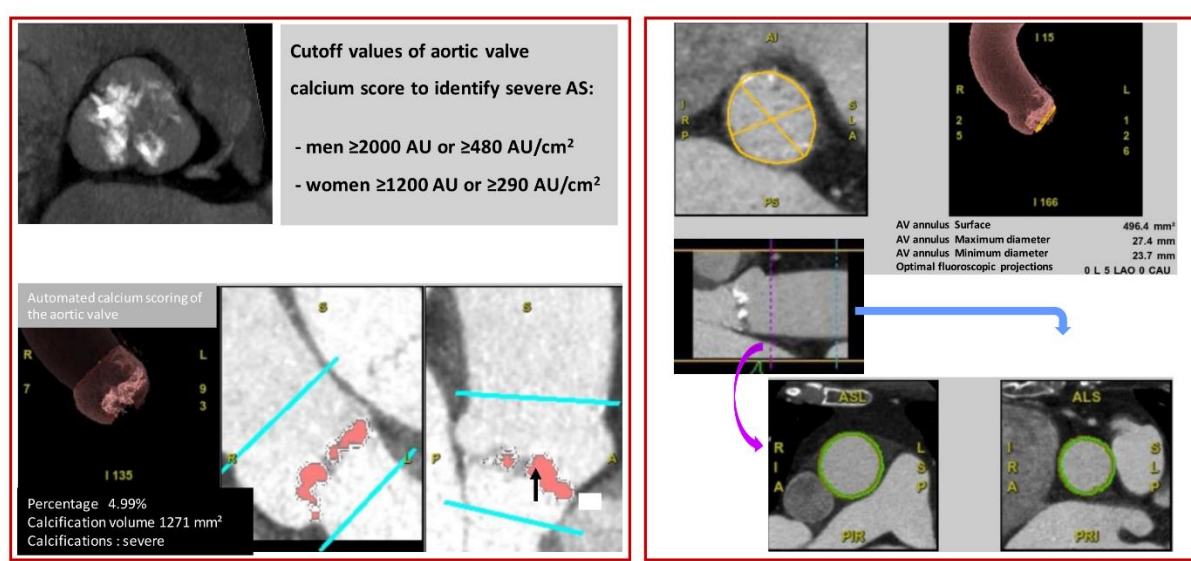


Figure 4  
339x190 mm (x DPI)

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7  
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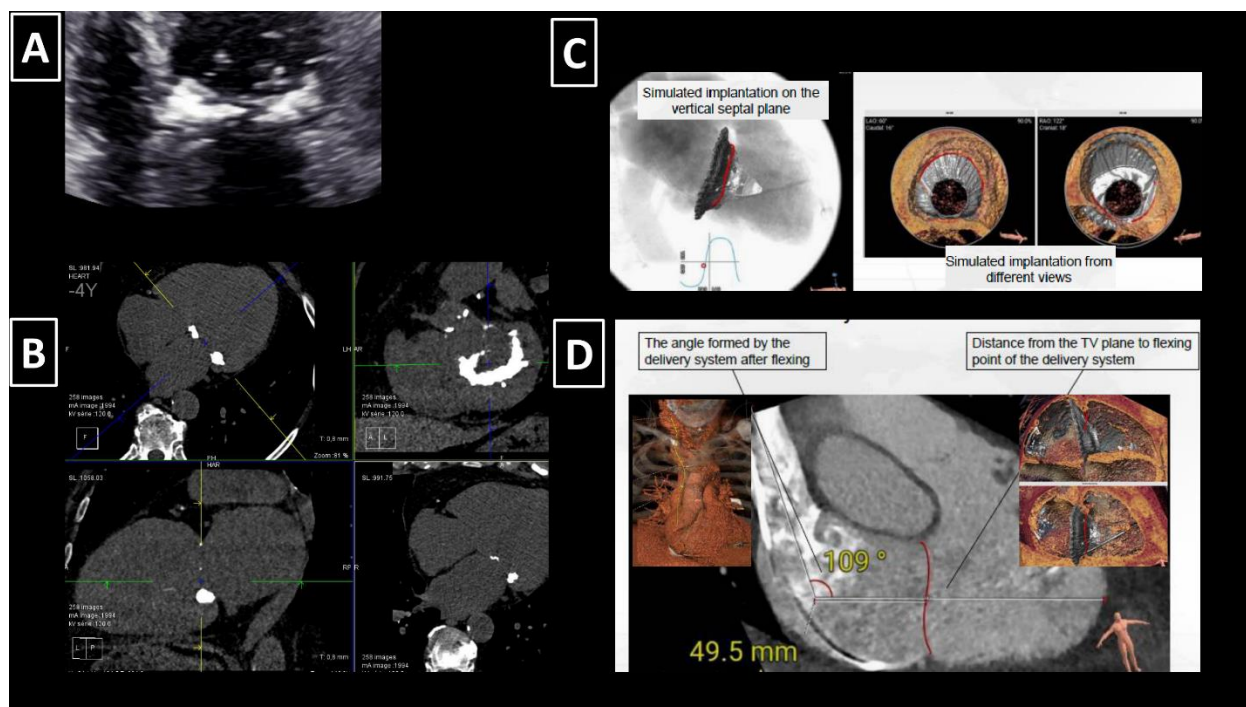


Figure 5  
339x190 mm (x DPI)

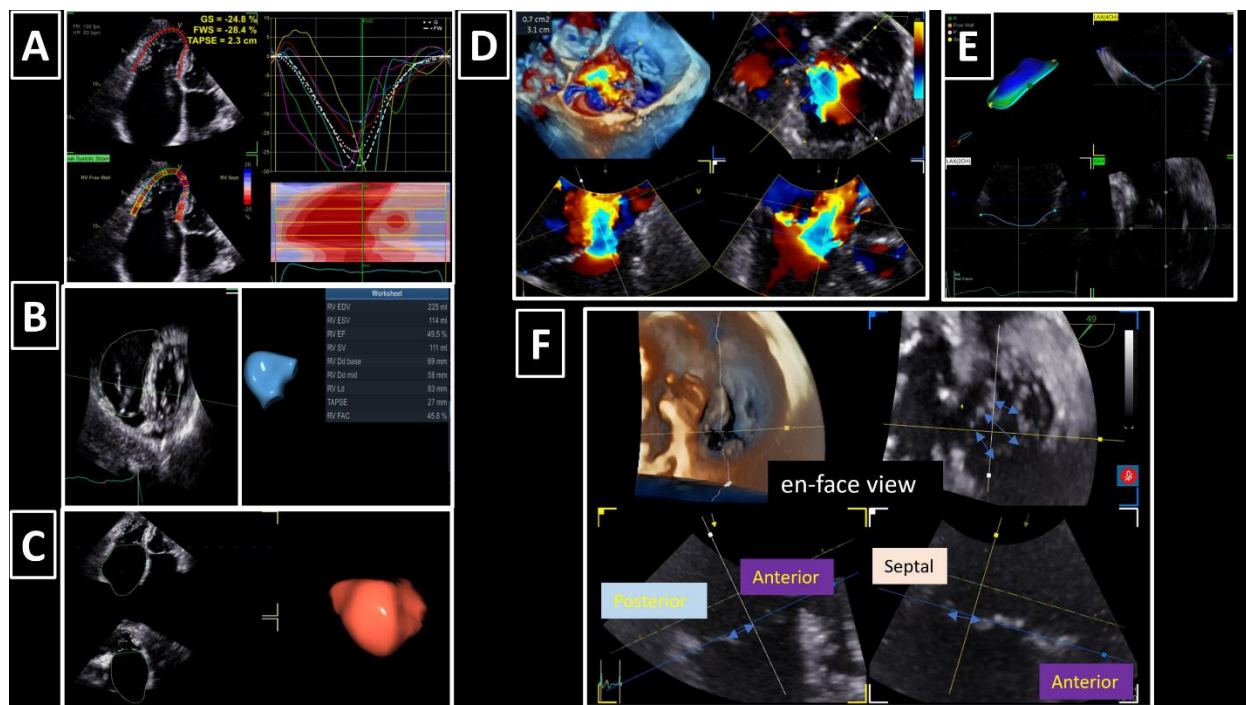
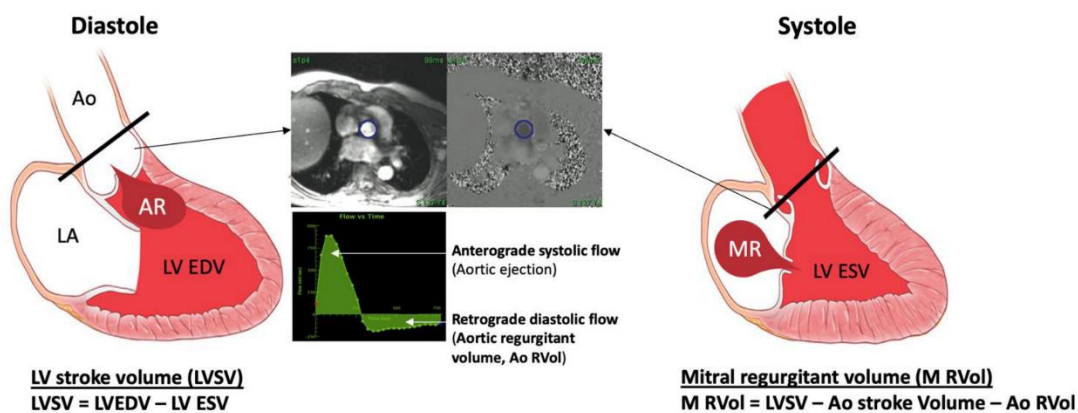


Figure 6  
339x190 mm (x DPI)

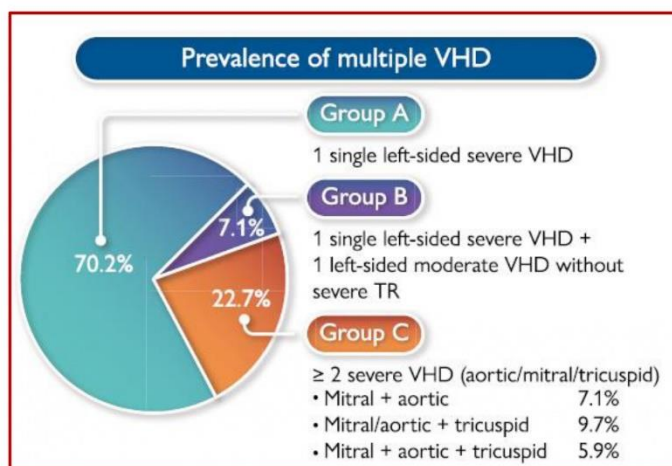
Figure 7

1  
2  
3Figure 7  
339x190 mm (x DPI)**Abbreviations figures.**

MR: mitral regurgitation  
 MS: mitral stenosis  
 TR: tricuspid regurgitation  
 TTE: transthoracic echocardiography  
 TOE: transoesophageal echocardiography  
 SVi: stroke volume indexed  
 AVA: aortic valve area  
 PHT: pressure half time  
 MPG: mean pressure gradient  
 VTI: velocity time integral  
 LVOT: left ventricular outflow tract  
 MRI: magnetic resonance imaging  
 ERO : effective regurgitant orifice  
 LVESP: Left ventricular end-systolic pressure  
 GDMT: guideline directed medical therapy  
 LV: Left ventricle  
 LVOT: Left ventricle outflow tract  
 MAC: mitral annular calcifications  
 TAVR: transcatheter aortic valve replacement  
 TEER: transcatheter edge-to-edge repair  
 TMVR: transcatheter mitral valve replacement

4  
5  
6  
7Figure 8  
339x190 mm (x DPI)

Central Figure



- 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.

1  
2  
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*Graphical Abstract*  
339x190 mm (x DPI)