

Assessment of Complex Multi-Valve Disease and Prosthetic Valves



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Multivalvular heart disease (MVD) is a highly prevalent condition causing significant morbidity and mortality. The complex haemodynamic interactions between coexisting valve lesions makes the diagnosis and treatment challenging. Current guidelines may not be adequate for managing the varying clinical scenarios of MVD and, therefore, the expertise of a multidisciplinary Heart Valve Team is of paramount importance. The indications for intervention should be based on a global assessment of the consequences of the multiple valve lesions after a careful estimation of the added surgical risk of combined procedures, the long-term risk of morbidity and mortality associated with multiple valve prostheses and the risk of reoperation if less-than-severe valve lesions are left untreated at the time of first evaluation. Echocardiography plays an important role in assessing patients and, as a general rule, an accurate echo diagnosis needs to combine different measurements. The emerging transcatheter valve therapies should be considered an option for high risk patients. More data on the natural history of MVD and the impact of intervention on outcome are required to better define the optimal management strategy.

Keywords

Multiple valve disease • Multiple prostheses • Echo cardiac imaging • Multidisciplinary heart valve team

Introduction

Multivalvular heart disease (MVD), referred to as concomitant stenosis or regurgitation of the same valve or two or more cardiac valves, is a highly prevalent condition causing significant morbidity and mortality [1]. Recently, MVD was identified in over one-third of individuals over the age of 65 years from a primary care centre screened for undiagnosed valvular heart disease (VHD) using echocardiography [2]. In the EuroHeart Survey, 20% of patients with native valve disease, and 15% of those undergoing valvular surgery, had MVD [3]. Among more than 600,000 patients undergoing valvular surgery included in the Society of Thoracic Surgeons (STS) database, 11% had multiple-valve procedures, of whom 58% underwent aortic and mitral valve surgery, 31% had mitral and tricuspid valve surgery, 3% had aortic and tricuspid valve surgery and 8% underwent triple valve surgery [4]. In the Placement of Aortic Transcatheter Valves

(PARTNER) trials of severe aortic stenosis (AS), the incidence of concomitant moderate-to-severe mitral regurgitation (MR) was approximately 20%, and of moderate-to-severe tricuspid regurgitation (TR) was 27% [5]. Despite the prevalence of MVD, most published studies have focussed on regurgitation or stenosis of single valve lesions. Consequently, there is a lack of data on patients with combined valvular lesions and therefore current guidelines offer limited evidence, largely based on small studies or a consensus opinion [6,7]. The main difficulty in acquiring good data on MVD lies in the heterogeneity of valve disease combinations and variations in the severity of disease among the valve lesions, leading to a wide spectrum of clinical scenarios. In this review, we discuss (1) aetiology of the valve lesions; (2) pathophysiological considerations; (3) common combinations of MVD in everyday practice; (4) primary role of echocardiography; and (5) treatment strategies in MVD. It is beyond the scope of this review to discuss MVD in the context of congenital heart disease.

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Aetiology

Primary

Rheumatic heart disease is the predominant aetiology of valvular dysfunction in developing countries, whereas degenerative aetiology is more common in developed countries owing to the ageing population [8,9]. Marfan syndrome and other connective tissue disorders may cause multivalvular regurgitation and aortic dilatation [8]. Less frequent causes of primary MVD include endocarditis, genetic syndromes, thoracic and mediastinal radiation therapy and adverse effects of drugs [10].

Secondary

Mitral and tricuspid regurgitation can develop in a structurally normal valve owing to malcoaptation, secondary to alterations of the geometry of the left or right ventricle, respectively [11,12]. In addition, especially in the elderly population, the possibility of coexisting primary and secondary aetiologies should be kept in mind.

Pathophysiological Considerations

In patients with MVD, owing to the haemodynamic interactions between valve lesions, a given valve lesion may exacerbate or, indeed, blunt the clinical expression of a concomitant valve lesion [8]. For example, a patient with severe aortic regurgitation (AR) may better tolerate this condition in the presence of a concomitant mitral stenosis (MS) which would serve to mitigate the left ventricular volume overload of the AR. By contrast, the presence of primary MR instead of MS would add to the volume overload in the same patient. The clinical effect of MVD depends on multiple factors, such as the severity of each individual valve lesion, which combination of valves are involved, the chronicity of the lesions, loading conditions and ventricular function. Moreover, the severity and clinical effect of one valve lesion can be altered if another valve is treated. For example, in some patients, the reduction in left ventricle pressures after the correction of aortic stenosis (AS) may rapidly reduce the severity of concomitant functional MR [8,12].

Common Combinations of MVD

Mixed Single-Valve Disease

Aortic Valve

Mixed aortic valve (AV) disease is a common entity in both rheumatic and degenerative disease. One lesion usually predominates over the other, the pathophysiology resembles that of the pure dominant lesion and symptoms develop early, especially with coexisting coronary artery disease [8]. The available studies show that asymptomatic patients with moderate, mixed AV disease are at a similar risk of a

major event as those with isolated severe AS [13,14]. Moreover, their outcome is poor without surgery [15] and, therefore, they require the same level of surveillance given to those with isolated severe AS, because half of them will become symptomatic and require aortic valve replacement (AVR) within 12 months. Aortic valve intervention needs to be considered based not just on the severity of the individual lesions, but on the overall haemodynamic burden indicated by the transaortic peak velocity, left ventricular (LV) size and function and pulmonary artery pressure [13,16].

Mitral Valve

In patients with MS, a degree of coexisting MR is common. The severity of MR and its haemodynamic consequences can be evaluated using standard echocardiographic parameters. If significant, MR may elevate the transmitral pressure gradient making the planimetric valve area the most accurate measurement for evaluating the degree of concomitant MS [16]. In the setting of degenerative disease, it is important to appreciate that heavy mitral calcification may cast acoustic shadows that prevent the visualisation of colour flow jets and, therefore, off axis views may be necessary.

Double-Valve Disease

Aortic Stenosis and Mitral Regurgitation

Aortic stenosis and MR are the most prevalent valvular heart diseases in Western countries [3]. In severe AS, the afterload mismatch, the concomitant ischaemic cardiomyopathy, or both may result in left ventricular (LV) dilatation and dysfunction causing mitral annular dilatation and leaflet tethering with consequent secondary MR [17]. Alternatively, patients with AS can have concomitant primary MR due to mitral valve prolapse (MVP) or degenerative annular calcification. Moderate or severe MR may reduce the stroke volume through the aortic valve causing a low-flow low-gradient condition leading to a possible underestimation of the severity of AS [18]. On the other hand, severe AS, by causing high ventricular pressures, may cause an increase in the mitral regurgitant jet, which reflects the haemodynamic burden and correlates with symptoms, but tends to be disproportionately elevated as compared with the effective regurgitant orifice area. In addition, AS and MR have opposite effects on LV systolic performance. Therefore, the early detection of LV dysfunction in patients with AS can be impeded by the presence of MR if LV ejection fraction (EF) alone is considered to represent systolic function. Some studies suggest that global longitudinal strain (GLS) may be a more robust parameter in assessing myocardial systolic function in patients with valvular heart disease especially if LVEF appears preserved [19]. In the specific setting of low-flow low-gradient AS due to significant MR, the use of dobutamine stress echo (DSE) should be considered in an attempt to normalise flow rate and discriminate true severe AS from 'pseudosevere' AS [18]; this information may provide useful prognostic information [20].

Aortic Stenosis and Mitral Stenosis

In developed countries, the combination of critical aortic and mitral stenosis is rare because, typically, the MS is the result

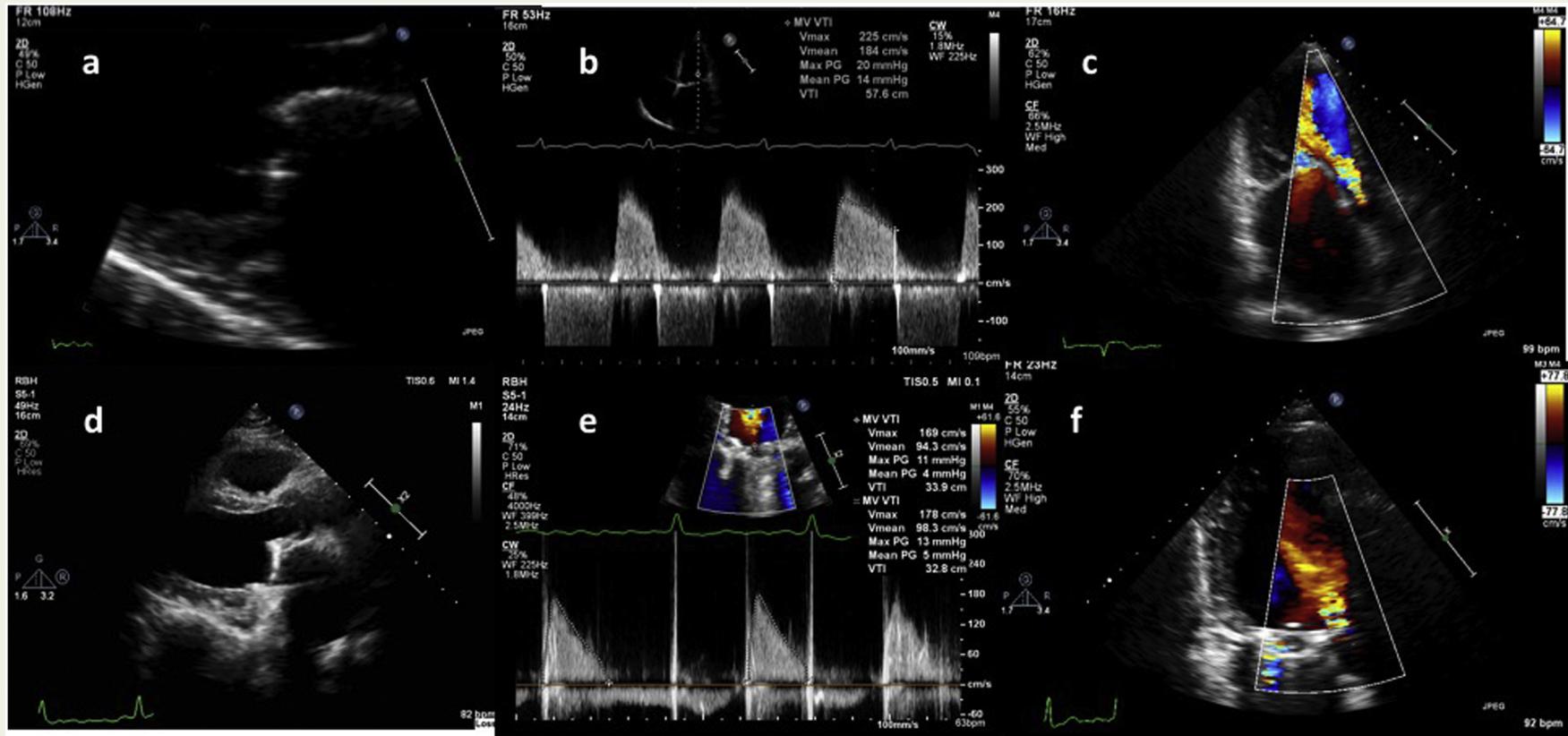


Figure 1 A patient with rheumatic MS and AR. a) Severe, symptomatic MS with b) a mean transmitral gradient of 14 mmHg and c) a concomitant moderate AR. Left ventricular ejection fraction was 60%. d) The same patient, 10 years after mechanical MVR (29 mm St Jude Medical, Uppsala, Sweden), well seated with good valve opening. e) Mean gradient 4.5 mmHg at heart rate of 63 bpm. f) The aortic valve shows systolic doming of the cusps consistent with rheumatic disease. Appearance and Doppler parameters are consistent with mild AS (Ava by continuity equation 1.55 cm², AVAi 0.85 cm²/m², peak velocity 2.4 m/s, mean gradient 12 mmHg, DVI 0.5 and flow rate 283 ml/s) and still moderate AR (vena contracta 0.4 cm, ERO 0.06 cm², average PHT 431 ms. No diastolic flow reversal seen at the proximal Desc-Ao). Left ventricle is normal in size and function (Simpson EF 58%). Estimated PASP 40 mmHg.

Abbreviations: PASP, pulmonary artery systolic pressure; AS, aortic stenosis; AR, aortic regurgitation; MS, mitral stenosis; AVA, aortic valve area; AVAi, indexed aortic valve area; ERO, effective regurgitant orifice; PHT, pressure half time.

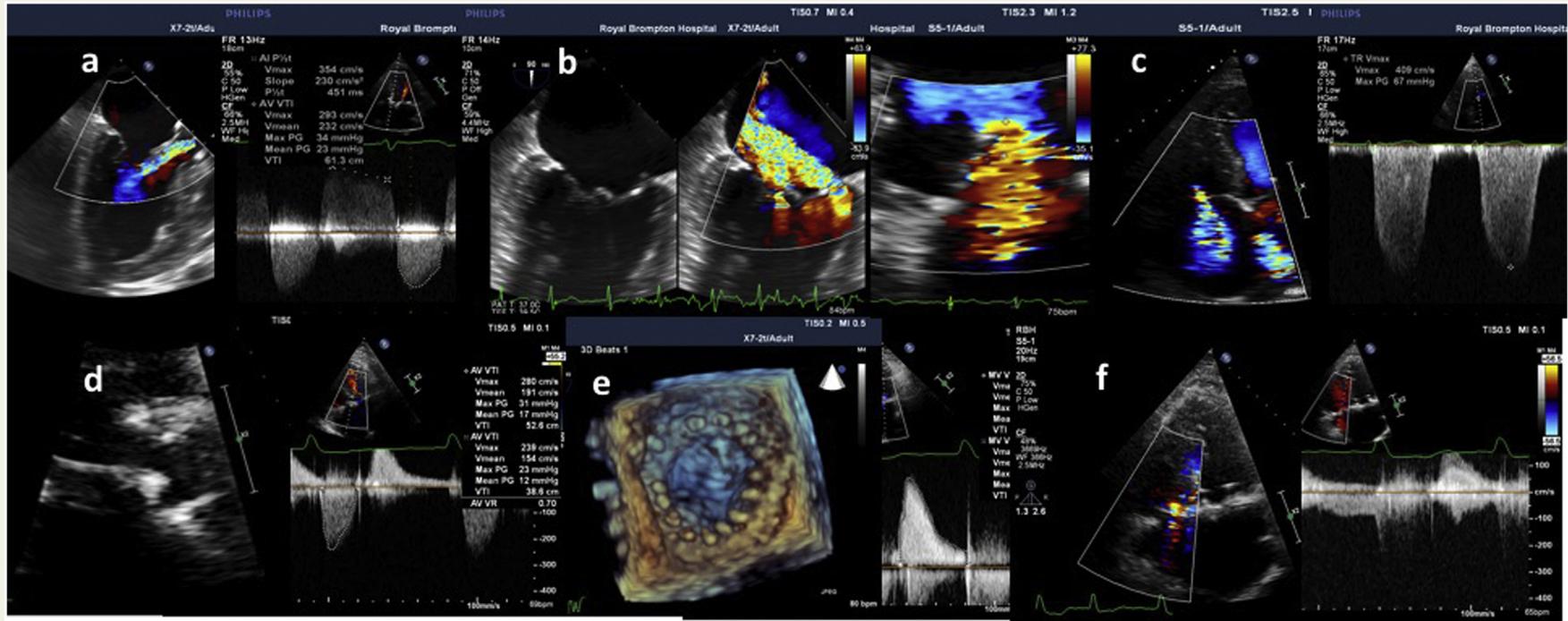


Figure 2 A patient with triple valve disease.

Top images: a) Mixed degenerative aortic valve disease with moderate AS (AVA by continuity equation 1.2 cm^2 , peak velocity 3.3 m/s , mean gradient 23 mmHg , DVI 0.36) and moderate regurgitation b) Severe eccentric primary MR (E vel 1.5 m/s , PISA radius 0.9 cm , ERO 0.3 cm^2 , Reg volume 50 ml) with no stenosis (MVA 3.3 cm^2 by planimetric area) c) Concomitant moderate TR with dilated annulus (5.0 cm) and PH (PASP 80 mmHg). Normal LV cavity size with preserved ejection fraction. Visual EF 55–60%.

Bottom images: 2 weeks after the triple valve operation d) 23 mm Mosaic aortic bioprosthesis, well seated, mean gradient 15 mmHg . e) 33 mm Perimount mitral bioprosthesis well seated, mean gradient 5 mmHg at heart rate of 65 bpm . f) tricuspid annuloplasty with Carpentier-Edwards 32 ring , mild residual TR, insufficient to accurately estimate PASP. Normal LV cavity size with preserved ejection fraction. Visual EF 55–60%.

Abbreviations: PASP, pulmonary artery systolic pressure; EF, ejection fraction; LV, left ventricular; TR, tricuspid regurgitation; PH, pulmonary hypertrophy; AS, aortic stenosis; MR, mitral regurgitation; MVA, mitral valve area; AVA, aortic valve area; DVI, dimensionless velocity index; ERO, effective regurgitant orifice; PISA, proximal isovelocity surface area.

Table 1 Echocardiographic diagnosis of multivalvular disease.

Valvular lesion	AS	AR	MS	MR	TR
AS	NA	a) VC b) PISA method c) LV size, shape, function d) PHT method unreliable e) Mean gradient > 40 mmHg suggests severe mixed AV disease	a) planimetric mitral area b) LF-LG MS can occur c) PHT method unreliable	a) VC b) ERO c) Doppler volumetric method d) Color Doppler jet area unreliable	Little impact unless PH develops
AR	a) continuity equation applicable b) simplified Bernoulli formula not applicable if significant AR (elevated V_{LVOT}) c) LV size, shape and function	NA	a) planimetric area b) PISA c) AR jet and MS jet could be mistaken d) continuity equation unreliable (unequal flows) e) PHT unreliable, significant AR shortens PHT	a) PISA b) GLS for assessing LV function c) volumetric methods challenging (use RVOT forward flow)	Little impact unless PH develops
MS	a) LF-LG AS consider DSE for AVA (continuity equation)	a) VC b) PHT unreliable (delayed LV filling might lengthen AR PHT)	NA	a) PISA applicable b) Volumetric method applicable c) if MV heavily calcified may shadow and decrease jet area and appearance of jet	a) if PH RVol and jet area increased. b) if RV dysfunction ROA may increase
MR	a) LF-LG AS consider DSE for AVA (continuity equation) and contractile reserve	a) VC b) Volumetric method challenging (use RVOT forward flow) c) PHT unreliable (rapid filling shortens AR PHT)	a) planimetric area (TTE or TEE) b) continuity equation unreliable c) PHT unreliable d) Mean gradient > 10 mmHg suggest severe mixed MV disease	NA	a) if PH RVol and jet area increased. b) if RV dysfunction ROA may increase
TR	Little direct impact	Little direct impact	Little direct impact	Little direct impact	NA

Abbreviations: AS, aortic stenosis; MS, mitral stenosis; AR, aortic regurgitation; MR, mitral regurgitation; TR, tricuspid regurgitation; Reg, regurgitation; VC, vena contracta; PISA, Proximal isovelocity surface area; PHT, pressure half time; LF-LG, low-flow low-gradient; AVA, aortic valve area; LV, left ventricle; GLS, global longitudinal strain; RV, right ventricle; RVOT, right ventricle tract flow; NA, not applicable; PH, pulmonary hypertension; TEE, transoesophageal echocardiography; DSE, dobutamine stress echo; ERO, effective regurgitant orifice.

This table illustrates both the applicable and unreliable echocardiographic methods for a given valvular lesion (vertical columns) in presence of a concomitant valvular lesion (horizontal rows).

of progressive mitral annular calcification involving the base of the leaflets with progressive reduction in the functional valvular orifice, but without commissural fusion, resulting in less severe stenosis than in rheumatic valve disease [21]. In addition, this combination is very poorly tolerated from a haemodynamic point of view, and therefore intervention is indicated early during the course of the disease before both valve lesions become severe [22]. Other causes of concomitant MS and AS are congenital (Shone's complex, mucopolysaccharidosis) and drug-induced or post-radiation therapy. Echocardiography usually provides the diagnosis, recording the typical high pressure gradients across both valves. However, when both stenoses are severe, a greater reduction in cardiac output occurs than with just one severe stenosis, decreasing the flow rate and pressure gradients leading to underestimation of the severity of both valve stenoses [23]. Underestimating the concomitant severe AS may lead to dramatic clinical consequences if isolated mitral valve intervention is then considered, as relief of the mitral stenosis would suddenly increase the preload to a small, hypertrophied, and stiff left ventricle, resulting in pulmonary oedema [24].

Aortic Regurgitation and Mitral Stenosis

Aortic valve involvement, in the form of primary regurgitation, stenosis, or mixed stenosis and regurgitation, is present in approximately one-third of patients with rheumatic MS (Figure 1) [8]. The combination of AR and MS imposes opposite loading conditions on the left ventricle. Both LV end-diastolic and end-systolic volume are lower than with isolated AR. Therefore, the increase in stroke volume typically associated with AR might be blunted in the presence of MS, and the clinical signs associated with increased pulse pressure might not be observed [8].

Aortic Regurgitation and Mitral Regurgitation

This condition may be caused by rheumatic heart disease, prolapse of both the aortic and mitral valves secondary to myxomatous degeneration, or dilation of both annuli in patients with connective tissue disease. The severe volume overload caused by the two regurgitant lesions and some pressure overload typically associated with AR, is very poorly tolerated. Patients with this combination of valve lesions may develop progressive LV dysfunction, resulting in a high incidence of postoperative LV dysfunction, reduced postoperative survival and more frequently persistent symptoms after surgery than those with single-valve disease [25].

Tricuspid Valve Lesion with Left-Sided Valve Disease

Rheumatic heart disease may cause haemodynamically significant disease involving the mitral, aortic, and tricuspid valves. In this scenario, correction of all three valvular lesions is imperative although triple valve replacement is a long, complex and high risk operation [6,7]. In developed countries, the most common tricuspid valve lesion is secondary TR which is highly prevalent in patients presenting with left-side valve disease (Figure 2) [26]. Many studies suggest that

the severity of TR, both isolated or in the presence of left-sided valvular disease, is associated with reduced exercise capacity, long-term mortality and reduced postoperative survival [27,28]. The severity of TR is highly sensitive to changes in loading conditions, and the absence of regurgitation at the time of treatment of the left-sided valve lesion does not guarantee long-term freedom from it. Echocardiography plays an important role in evaluating several factors, including tricuspid annular (TA) dilatation, right ventricular (RV) enlargement and dysfunction, pulmonary artery pressure and right atrial enlargement, all of which are useful in assessing the severity of secondary TR [16] and the timing of surgery.

Role of Advanced Echocardiography

A recently published document addressed the use of multimodality imaging in the diagnosis and management of valvular heart disease (VHD) to improve and standardise the decision making process [29]. Transthoracic echocardiography (TTE) is the primary investigation for the detection of VHD with a high level of appropriateness (score 7-9) at the stage of initial evaluation and during serial follow-up. The assessment is based on a multiparametric analysis which includes two-dimensional (2D), three-dimensional (3D) and Doppler parameters for evaluating valve anatomy and function providing a clear description of the aetiology, mechanism and severity of dysfunction. Moreover, an assessment of the haemodynamic consequences of the specific combination of valve lesions is readily made by evaluating the left and right ventricular volumes and function along with an estimation of the pulmonary pressure. As reported in Table 1, according to international guidelines [16], the haemodynamic interactions between valves may interfere with several Doppler parameters, most of which have been validated only in patients with a single-valve disease and might not be valid in the setting of MVD [22]. As a general rule, an accurate echo diagnosis needs to combine different measurements, possibly using methods that are less dependent on loading conditions, such as direct planimetry of a stenotic valve or, for regurgitant lesions, the assessment of the effective regurgitant orifice or the vena contracta. Moreover, all information regarding the suitability of valve repair and the presence of unfavourable factors for a specific procedure, such as the presence of more than mild MR in rheumatic MS under consideration for percutaneous mitral commissurotomy (PMC), is required [6,7]. Stress echocardiography (SE) is indicated when symptoms are disproportionate to the resting haemodynamics [6,7,18]. Particularly in the case of combined non-severe lesions, patients may be asymptomatic at rest but exercise may worsen the haemodynamic consequences of dominant lesions and produce symptoms. Exercise haemodynamic parameters, such as an increase in transvalvular gradients, elevations in pulmonary artery pressure, and the absence of LV contractile reserve might be relevant in deciding the appropriateness and timing of

Table 2 Indications for concomitant valve surgery in patients undergoing surgery on another valve.

Valve lesion	ESC/EACTS guidelines (2017) ⁶	AHA/ACC guidelines (2017) ⁷
Aortic stenosis	<ul style="list-style-type: none"> • AVR is indicated in patients with severe aortic stenosis undergoing CABG surgery, or surgery on the ascending aorta or another valve (class I, LOE C) • AVR should be considered in patients with moderate aortic stenosis undergoing surgery on the ascending aorta or another valve after Heart Team decision (class IIa, LOE C) 	<ul style="list-style-type: none"> • AVR is indicated for patients with severe aortic stenosis undergoing other cardiac surgery (class I, LOE B) • AVR is reasonable for patients with moderate aortic stenosis undergoing other cardiac surgery (class IIa, LOE C)
Aortic regurgitation	<ul style="list-style-type: none"> • Surgery is indicated in patients with severe aortic regurgitation undergoing surgery on another valve (class I, LOE C) 	<ul style="list-style-type: none"> • AVR is indicated for patients with severe aortic regurgitation (stage C or D) undergoing cardiac surgery for other indications (class I, LOE C) • AVR is reasonable in patients with moderate aortic regurgitation undergoing other cardiac surgery (class IIa, LOE C)
Mitral stenosis	<ul style="list-style-type: none"> • Surgery is preferable to PMC in patients with severe mitral stenosis combined with severe aortic valve disease • In patients with severe mitral stenosis and moderate aortic valve disease, PMC can be performed to postpone the surgical treatment of both valves • Severe concomitant aortic valve disease is a contraindication to PMC 	<ul style="list-style-type: none"> • Concomitant mitral valve surgery is indicated for patients with severe mitral stenosis undergoing other cardiac surgery (class I, LOE C) • Concomitant mitral valve surgery may be considered for patients with moderate mitral stenosis (mitral valve area 1.6–2.0 cm²) undergoing other cardiac surgery (class IIb, LOE C)
Mitral regurgitation	<ul style="list-style-type: none"> • No clear position on moderate secondary MR in patients undergoing cardiac surgery for other indications 	<ul style="list-style-type: none"> • Concomitant mitral valve repair or replacement is indicated in patients with chronic severe primary mitral regurgitation undergoing cardiac surgery for other indications (class I, LOE B) • Concomitant mitral valve repair is reasonable in patients with chronic moderate primary mitral regurgitation (stage B) undergoing cardiac surgery for other indications (class IIa, LOE C) • Mitral valve surgery (repair or replacement) is reasonable for patients with chronic severe secondary mitral regurgitation (stages C and D) undergoing AVR (class IIa, LOE C) • The usefulness of mitral valve repair is uncertain in patients with chronic moderate secondary mitral regurgitation (stage B) undergoing other cardiac surgery (class IIb, LOE B-R)
Tricuspid stenosis	<ul style="list-style-type: none"> • Tricuspid valve surgery is indicated in patients with severe tricuspid stenosis undergoing left-sided valve intervention (class I, LOE C) • Percutaneous balloon valvuloplasty can be attempted if PMC can be performed on the mitral valve 	<ul style="list-style-type: none"> • Tricuspid valve surgery is recommended for patients with severe tricuspid stenosis at the time of operation for left-sided valve disease (class I, LOE C)

Table 2. (continued).

Valve lesion	ESC/EACTS guidelines (2017) ⁶	AHA/ACC guidelines (2017) ⁷
Tricuspid regurgitation	<ul style="list-style-type: none"> • Tricuspid valve surgery is indicated in patients with severe primary or secondary tricuspid regurgitation undergoing left-sided valve surgery (class I, LOE C) • Surgery should be considered in patients with moderate primary tricuspid regurgitation undergoing left-sided valve surgery (class IIa, LOE C) • Surgery should be considered in patients with mild or moderate secondary tricuspid regurgitation with annular dilatation (≥ 40 mm or > 21 mm/m²) (class IIa, LOE C) or in absence of annular dilatation when previous recent right heart failure has been documented (class IIb, LOE C) undergoing left-sided valve surgery • After previous left-sided surgery and in absence of recurrent left-sided valve dysfunction, surgery should be considered in patients with severe tricuspid regurgitation who are symptomatic or have progressive RV dilatation/dysfunction, in the absence of severe RV or LV dysfunction and severe pulmonary vascular disease/hypertension. 	<ul style="list-style-type: none"> • Tricuspid valve surgery is recommended for patients with severe tricuspid regurgitation (stages C and D) undergoing left-sided valve surgery (class I, LOE C) • Tricuspid valve repair can be beneficial for patients with mild, moderate, or greater functional tricuspid regurgitation (stage B) at the time of left-sided valve surgery with either tricuspid annular dilatation or prior evidence of right-sided heart failure (class IIa, LOE B) • Tricuspid valve repair may be considered for patients with moderate functional tricuspid regurgitation (stage B) and pulmonary artery hypertension at the time of left-sided valve surgery (class IIb, LOE C)

Abbreviations: AVR, aortic valve replacement; LOE, level of evidence; PMC, percutaneous mitral commissurotomy.

intervention [18,30]. The assessment of multiple valves during semi-supine bicycle exercise is feasible, and mixed stenotic and regurgitant lesions can be evaluated with a combination of colour flow and Doppler imaging [18]. Dobutamine stress echo might be useful in the low-flow, low-gradient states related to the combination of severe AS and MS or MR, providing useful diagnostic and prognostic information [20]. Transoesophageal echocardiography (TEE) is of paramount importance for precise anatomic and functional imaging before and during percutaneous and surgical procedures [29,31]. Real-time 3D TEE is considered useful to accurately measure mitral valve area in rheumatic MS especially if mitral disease is combined with aortic valve involvement because anatomical measurements are considered more reliable than Doppler methods under these circumstances [32]. If the echo evaluations are inconclusive or discordant with clinical assessment, the current guidelines recommend proceeding to cardiac magnetic resonance (CMR) or invasive haemodynamic assessment for further clarification [6,7,33]. Multislice cardiac tomography (MSCT) is the preferred imaging tool in the preoperative diagnostic work-up of aortic valve percutaneous procedures [34] and in equivocal cases of low-flow low-gradient AS [35].

Treatment

Despite the paucity of data on the management of MVD, the American Heart Association/American College of Cardiology (AHA/ACC) and European Society of Cardiology (ESC) guidelines suggest following two general principles. Firstly, the management of MVD should be dictated by the predominant valve lesion and secondly, when both valve lesions are of at least moderate severity, the overall impact of the multi-valve pathology should be considered severe. These recommendations are summarised in Table 2.

Two or More Severe Lesions

In patients with two or more severely stenotic or regurgitant lesions, and who are symptomatic or have ventricular dysfunction or dilatation, all lesions should be surgically corrected during a single procedure. As such, in patients with combined severe aortic and mitral valve disease, despite the higher morbidity and mortality of double-valve surgery compared with isolated aortic valve surgery [36], concurrent mitral valve intervention should be considered at the time of AVR [6,7]. Similarly, despite higher operative risk, concomitant tricuspid valve repair or replacement is recommended (class I) in patients with severe TR undergoing surgery for aortic or mitral valve disease [6,7].

One Severe Lesion Plus One Non-Severe Lesion

In this situation, the decision to perform an intervention should be based on the recommendations concerning the predominant valvular lesion. In patients undergoing surgery for a severe valve lesion or coronary artery bypass graft (CABG), then moderate AS, moderate AR, moderate primary

MR, and moderate primary or secondary TR (if tricuspid annulus is dilated) are all class IIa recommendations for performing concomitant valve surgery [6,7]. Moderate MS, moderate secondary MR, and moderate TR (in the presence of pulmonary hypertension or prior evidence of right-sided heart failure) are considered class IIb indications. The guidelines considered some specific settings such as patients with severe rheumatic MS and only moderate aortic valve disease, in whom percutaneous mitral commissurotomy could be performed to postpone double-valve surgery [6].

Based on conflicting results [37,38], there is continuing debate on the management of patients with severe AS and moderate functional MR. Although in most cases of severe AS, the concomitant MR is mild to moderate and tends to improve following isolated AV surgery [4,5,39], in one-third of patients the MR does not improve or even worsens [37,38]. Consequently, current guidelines do not have a clear position regarding the usefulness of mitral valve repair in this clinical scenario [6,7]. Recently, in high risk patients with combined AS and MR, a concomitant or staged percutaneous approach has been demonstrated to be feasible, but there is not enough experience to make clear recommendations [38,40]. Regarding the surgical options, several studies suggest that, in the setting of primary MR, repair offers an advantage over replacement in patients undergoing AVR [41,42]. Controversy exists, however, as to whether repair or replacement of the mitral valve is preferred in patients with secondary MR undergoing AVR. In one study, reduced in-hospital mortality was reported with mitral valve repair (11% versus 18% for replacement), but survival after discharge from hospital did not differ significantly between the two strategies [42]. Conversely, other studies that included patients with primary or secondary MR reported no survival benefit of mitral valve repair with AVR over double-valve replacement, and an increased long-term incidence of mitral valve failure in patients undergoing mitral repair was observed [37,43–45]. In high to intermediate surgical risk, percutaneous treatment of AS and MR is increasingly used [46,47], but data are lacking [47,48]. Single-centre experiences have demonstrated that in selected patients, a staged percutaneous approach—treating the AS first, followed by a MitraClip® (Evalve, Inc., Menlo Park, CA, USA) procedure if moderate-to-severe MR with symptoms persists—has been associated with good procedural success rates and acceptable functional outcomes and survival at 6 months [49].

Moderate to severe functional TR may improve after MVR or AVR as a result of the decreased pulmonary vascular pressure and RV overload. However, the pathophysiological links between left-sided valve disease and secondary TR are not linear or predictable. Based on the strong evidence that secondary moderate-to-severe TR is an independent predictor of long-term mortality [50–53], and that the reoperation for secondary TR is associated with operative mortality of 10–25% [54]; even patients with mild-to-moderate secondary TR in the presence of right-sided heart failure or annular dilatation are generally recommended to undergo tricuspid valve surgery when the left-sided valve lesion is corrected

[6,7]. Tricuspid annuloplasty is the preferred technique for the surgical treatment of TR at the time of left-sided valve surgery [55,56] with a lower rate of complications than tricuspid valve replacement [57].

In the past 5 years, several percutaneous procedures have been developed and successfully used to treat secondary TR [58,59]. These emerging techniques provide a valuable alternative to surgery to correct TR at the time of other percutaneous intervention on the aortic or mitral valve, or as a staged procedure after surgical or percutaneous treatment of another valve. More studies are needed to clarify these treatment pathways and to implement these evolving transcatheter options as a clinical standard.

Two or More Non-Severe Lesions

The combination of multiple non-severe lesions is the most challenging scenario in terms of therapeutic decision-making. Concomitant moderate valve dysfunction may be haemodynamically severe causing functional intolerance and symptoms or LV/RV dilatation and dysfunction. Therefore, indications for interventions should be based on symptoms and objective haemodynamic consequences rather than on the indices of severity of stenosis or regurgitation. Given the absence of strong evidence on the management of multiple non-severe lesions [6,7] a multidisciplinary approach to decision making has become increasingly important [60]. The Heart Valve Team may be required to discuss and identify patients in whom the less than severe coexisting valve lesion may be at risk of rapid progression, wherein concomitant treatment of the valve lesion could be advocated to avoid the less desirable prospect of ‘redo’ valve surgery [60]. The early management of less-than-severe MVD, before the onset of symptoms and irreversible LV/RV dysfunction is probably the key for improving prognosis. In this setting, the exercise-induced increase in transvalvular gradients and pulmonary artery pressure along with the N-terminal pro B-type natriuretic peptide (NT-pro BNP) estimations may be helpful in predicting outcomes and in determining the optimal timing for intervention [18,61].

Multiple Prosthetic Valves

Biologic prosthetic valves are associated with a high risk of reoperation because of structural valve deterioration, whereas mechanical valves typically necessitate lifelong anticoagulation, which increases the risk of haemorrhage and thromboembolism [62]. Obviously, this risk is considered higher in patients undergoing double- or triple-valve replacement. The use of the same type of prosthesis in both locations (bioprosthesis or mechanical) has been recommended so as not to lose the advantages of each valvular option. In addition, to reduce the risks associated with multiple prosthetic valves, surgical valve repair should be considered whenever possible [1].

Echocardiography plays an important role in assessing patients with multiple prostheses and recent advances in 3D imaging may offer additional information [63]. However, there

is a lack of data regarding the appropriate evaluation of multiple prosthetic valves because in most studies, the presence of MVD is considered among the exclusion criteria [62]. In addition, the current guidelines are based in part on data from underpowered trials of now-obsolete valves that were implanted more than 30 years ago [63]. In the Echo assessment of multiple prostheses, the use of multiple and sometimes off-axis views is crucial to overcome the problem of acoustic shadowing, reverberations and mirror artefacts that are more pronounced for mechanical valves. Besides the classical mechanical and bio-prosthetic valves, a steady increase in the number of percutaneous procedures is seen each year [64], including the complex transcatheter valve-in-valve and valve-in-ring implantations in patients with documented prosthetic valve dysfunction [65]. More long-term outcome data are required in transcatheter aortic and mitral valve interventions which still carry significant peri-procedural risks and often leave varying degrees of residual paravalvular regurgitation [49,62,64].

Conclusions

Multivalvular disease (MVD) is common among patients with VHD. Due to the complex haemodynamic interactions between coexistent valve lesions, several diagnostic tools validated in patients with single-valve disease might not be transferable to patients with MVD. In the absence of relevant outcome data and evidence-based guidelines, the management of patients with MVD remains empirical and most often challenging. Therapeutic decisions should be made by a Heart Valve Team, based on symptoms, severity and the haemodynamic significance of MVD, the extra surgical risk of a combined procedure, the long-term risk of morbidity and mortality associated with multiple valve prostheses and the risk of reoperation. The introduction of transcatheter valve therapies is changing the therapeutic paradigm, but further studies are needed to guide therapeutic decision-making and to appreciate the real benefits of these emerging treatments.

Declarations of Interest

None.

References

- Unger P, Clavel MA, Lindman BR, Mathieu P, Pibarot P. Pathophysiology and management of multivalvular disease. *Nat Rev Cardiol* 2016;13:429–40.
- d'Arcy JL, Coffey S, Loudon MA, Kennedy A, Pearson-Stuttard J, Birks J, et al. Large-scale community echocardiographic screening reveals a major burden of undiagnosed valvular heart disease in older people: the OxVALVE population cohort study. *Eur Heart J* 2016;37:3515–22.
- Iung B, Baron G, Butchart EG, Delahaye F, Gohlke-Bärwolf C, Levang OW, et al. A prospective survey of patients with valvular heart disease in Europe: the Euro heart survey on valvular heart disease. *Eur Heart J* 2003;24:1231–43.
- Lee R, Li S, Rankin S, O'Brien SM, Gammie JS, Peterson ED, et al. Fifteen-year outcome trends for valve surgery in North America. *Ann Thorac Surg* 2011;91:677–84.
- Leon MB, Smith CR, Mack MJ, Makkar RR, Svensson LG, Kodali SK, et al. Transcatheter or surgical aortic-valve replacement in intermediate-risk patients. *N Engl J Med* 2016;374:1609–20.
- Baumgartner H, Falk V, Bax JJ, De Bonis M, Hamm C, Holm PJ, et al. 2017 ESC/EACTS Guidelines for the management of valvular heart disease. *Eur Heart J* 2017;38:2739–91.
- Nishimura RA, Otto CM, Bonow RO, Carabello BA, Erwin III JP, Fleisher LA, et al. 2017 AHA/ACC Focused Update of the 2014 AHA/ACC Guideline for the Management of Patients With Valvular Heart Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Circulation* 2017;135:e1159–95.
- Eugene Braunwald. Braunwald's heart disease: a textbook of cardiovascular medicine. Philadelphia, PA: Elsevier/Saunders; 2015.
- Goldberg SH, Elmariah S, Miller MA, Fuster V. Insights into degenerative aortic valve disease. *J Am Coll Cardiol* 2007;50:1205–13.
- Unger P, Rosenhek R, Dedobbeleer C, Berrebi A, Lancellotti P. Management of multiple valve disease. *Heart* 2011;97:272–7.
- DeBonis BM, Maisano F, La Canna G, Alfieri O. Treatment and management of mitral regurgitation. *Nat Rev Cardiol* 2012;9:133–46.
- Nombela-Franco L, Barbosa Ribeiro H, Allende M, Amat-Santos I, DeLarochelière R, Dumont E, et al. Significant mitral regurgitation left untreated at the time of aortic valve replacement. *J Am Coll Cardiol* 2014;63:2643–58.
- Philip JL, Zens T, Lozonschi L, De Oliveira NC, Osaki S, Kohmoto T, et al. Outcomes of surgical aortic valve replacement for mixed aortic valve disease. *J Thorac Dis* 2018;10:4042–51.
- Egbe AC, Poterucha JT, Warnes CA. Mixed aortic valve disease: midterm outcome and predictors of adverse events. *Eur Heart J* 2016;37:2671–8.
- Zilberszac R, Gabriel H, Schemper M, Zahler D, Czerny M, Maurer G, et al. Outcome of combined stenotic and regurgitant aortic valve disease. *J Am Coll Cardiol* 2013;61:1489–95.
- Zoghbi WA, Adams D, Bonow RO, Enriquez-Sarano M, Foster E, Grayburn PA, et al. Recommendations for Noninvasive Evaluation of Native Valvular Regurgitation: A Report from the American Society of Echocardiography Developed in Collaboration with the Society for Cardiovascular Magnetic Resonance. *J Am Soc Echocardiogr* 2017;30:303–71.
- Unger P, Dedobbeleer C, Van Camp G, Plein D, Cosyn B, Lancellotti P. Mitral regurgitation in patients with aortic stenosis undergoing valve replacement. *Heart* 2010;96:9–14.
- Lancellotti P, Pellikka PA, Budts W, Chaudhry FA, Donal E, Dulgheru R, et al. The clinical use of stress echocardiography in non-ischaemic heart disease: recommendations from the European Association of Cardiovascular Imaging and the American Society of Echocardiography. *EHIJ Cardiovasc Imaging* 2016;17:1191–229.
- Galli E, Lancellotti P, Sengupta PP, Donal E. LV mechanics in mitral and aortic valve diseases. *JACC Cardiovasc Imaging* 2014;7:1151–66.
- Vamvakidou A, Jin W, Danylenko O, Chahal N, Khattar R, Senior R. Low transvalvular flow rate predicts mortality in patients with low-gradient aortic stenosis following aortic valve intervention. *JACC Cardiovasc Imaging* 2019;12:205–6.
- Tyagi G, Dang P, Pasca I, Patel R, Pai RG. Progression of degenerative mitral stenosis: insights from a cohort of 254 patients. *J Heart Valve Dis* 2014;23:707–72.
- Unger P, Lancellotti P, de Canniere D. The clinical challenge of concomitant aortic and mitral valve stenosis. *Acta Cardiol* 2016;71:3–6.
- Honey M. Clinical and haemodynamic observations on combined mitral and aortic stenosis. *Br Heart J* 1961;23:545–55.
- Zitnik RS, Piemme TE, Messer RJ, Reed DP, Haynes FW, Dexter L. The masking of aortic stenosis by mitral stenosis. *Am Heart J* 1965;69:22–30.
- Honey M, Finucane AK, Remenyi B, Kerr AR, Wilson NJ. Ventricular function before and after surgery for isolated and combined regurgitation in the young. *Ann Thorac Surg* 2015;100:1383–9.
- Guenzinger R, Lange RS, Rieß FC, Hanke T, Bischoff N, Obadia JF, et al. Six-month performance of a 3-dimensional annuloplasty ring for repair of functional tricuspid regurgitation. *Thorac Cardiovasc Surg* 2018; (November). <http://dx.doi.org/10.1055/s-0038-1673665> [Epub ahead of print].
- Dahou A, Magne J, Clavel MA, Capoulade R, Bartko PE, Bergler-Klein J, et al. Tricuspid regurgitation is associated with increased risk of mortality in patients with low-flow low-gradient aortic stenosis and reduced ejection fraction: results of the multicenter TOPAS study (true or pseudo-severe aortic stenosis). *JACC Cardiovasc Interv* 2015;8:588–96.

- [28] Topilsky Y, Nkomo VT, Vatury O, Michelena HI, Letourneau T, Suri RM, et al. Clinical outcome of isolated tricuspid regurgitation. *JACC Cardiovasc Imaging* 2014;7:1185–94.
- [29] Doherty JU, Kort S, Mehran R, Schoenhagen P, Soman P, Dehmer GJ, et al. ACC/AATS/AHA/ASE/ASNC/HRS/SCAI/SCCT/SCMR/STS 2017 Appropriate Use Criteria for Multimodality Imaging in Valvular Heart Disease: A Report of the American College of Cardiology Appropriate Use Criteria Task Force, American Association for Thoracic Surgery, American Heart Association, American Society of Echocardiography, American Society of Nuclear Cardiology, Heart Rhythm Society, Society for Cardiovascular Angiography and Interventions, Society of Cardiovascular Computed Tomography, Society for Cardiovascular Magnetic Resonance, and Society of Thoracic Surgeons. *Am Soc Echocardiogr* 2018;31:381–404.
- [30] Gentry III JL, Phelan D, Desai MY, Griffin BP. The role of stress echocardiography in valvular heart disease: a current appraisal. *Cardiology* 2017;137:137–50.
- [31] Zamorano JL, Badano LP, Bruce C, Chan KL, Goncalves A, Hahn RT, et al. EAE/ASE recommendations for the use of echocardiography in new transcatheter interventions for valvular heart disease. *Eur Heart J* 2011;32:2189–214.
- [32] Schlosshan D, Aggarwal G, Mathur G, Allan R, Cranney G. Real-time 3D transesophageal echocardiography for the evaluation of rheumatic mitral stenosis. *JACC Cardiovasc Imaging* 2011;4:580–8.
- [33] Muzzarelli S, Monney P, O'Brien K, Faletta F, Moccetti T, Vogt P, et al. Quantification of aortic flow by phase-contrast magnetic resonance in patients with bicuspid aortic valve. *Eur Heart J Cardiovasc Imaging* 2014;15:77–84.
- [34] Clavel MA, Malouf J, Messika-Zeitoun D, Araoz PA, Michelena HI, Enriquez-Sarano M. Aortic valve area calculation in aortic stenosis by CT and Doppler echocardiography. *JACC Cardiovasc Imaging* 2015;8:248–57.
- [35] Clavel MA, Pibarot P, Messika-Zeitoun D, Capoulade R, Malouf J, Aggarwal S, et al. Impact of aortic valve calcification, as measured by MDCT, on survival in patients with aortic stenosis: results of an international registry study. *J Am Coll Cardiol* 2014;64:1202–13.
- [36] Connelly KA, Creati L, Lyon W, Yui M, Rosalion A, Wilson AC, et al. Early and late results of combined mitral-aortic valve surgery. *Heart Lung Circ* 2007;16:410–5.
- [37] Michler RE, Smith PK, Parides MK, Ailawadi G, Thourani V, Moskowitz AJ, et al. Two-year outcomes of surgical treatment of moderate ischemic mitral regurgitation. *N Engl J Med* 2016;374:1932–41.
- [38] Chakravarty T, Van Belle E, Jilaihawi H, Noheria A, Testa L, Bedogni F, et al. Meta-analysis of the impact of mitral regurgitation on outcomes after transcatheter aortic valve implantation. *Am J Cardiol* 2015;115:942–9.
- [39] Vassileva CM, Li S, Thourani VH, Suri RM, Williams ML, Lee R, et al. Outcome characteristics of multiple-valve surgery: comparison with single-valve procedures. *Innovations* 2014;9:27–32.
- [40] del Val D, Regueiro A, Rodríguez-Gabella T, Paradis JM, Puri R, Rodés-Cabau J. Concomitant or staged transcatheter treatment for severe combined aortic and mitral valve disease. *Rev Esp Cardiol* 2018;71:676–9.
- [41] Thourani VH, Suri RM, Rankin JS, He X, O'Brien SM, Badhwar V, et al. Does mitral valve repair offer an advantage over replacement in patients undergoing aortic valve replacement? *Ann Thorac Surg* 2014;98:598–603.
- [42] Talwar S, Mathur A, Choudhary SK, Singh R, Kumar AS. Aortic valve replacement with mitral valve repair compared with combined aortic and mitral valve replacement. *Ann Thorac Surg* 2007;84:1219–25.
- [43] Leavitt BJ, Baribeau YR, DiScipio AW, Ross CS, Quinn RD, Olmstead EM, et al. Outcomes of patients undergoing concomitant aortic and mitral valve surgery in northern New England. *Circulation* 2009;120:S155–62.
- [44] Kuwaki K, Kawaharada N, Morishita K, Koyanagi T, Osawa H, Maeda T, et al. Mitral valve repair versus replacement in simultaneous mitral and aortic valve surgery for rheumatic disease. *Ann Thorac Surg* 2007;83:558–63.
- [45] Acker MA, Dagenais F, Goldstein D, Kron IL, Perrault LP. Severe ischemic mitral regurgitation: Repair or replace? *J Thorac Cardiovasc Surg* 2015;150:1425–7.
- [46] Regueiro A, Granada JF, Dagenais F, Rodés-Cabau J. Transcatheter mitral valve replacement. *J Am Coll Cardiol* 2017;69:2175–92.
- [47] Rudolph V, Schirmer J, Franzen O, Schlüter M, Seiffert M, Treede H, et al. Bivalvular transcatheter treatment of high-surgical-risk patients with coexisting severe aortic stenosis and significant mitral regurgitation. *Int J Cardiol* 2013;167:716–20.
- [48] Kische S, D'Ancona G, Paranskaya L, Schubert J, Arsoy N, Hauenstein KH, et al. Staged total percutaneous treatment of aortic valve pathology and mitral regurgitation: institutional experience. *Catheter Cardiovasc Interv* 2013;82:E552–63.
- [49] Grover FL, Vemulapalli S, Carroll JD, Edwards FH, Mack MJ, Thourani VH, et al. 2016 Annual Report of the Society of Thoracic Surgeons/American College of Cardiology Transcatheter Valve Therapy Registry. *J Am Coll Cardiol* 2017;69:1215–30.
- [50] Taramasso M, Vanermen H, Maisano F, Guidotti A, La Canna G, Alfieri O. The growing clinical importance of secondary tricuspid regurgitation. *J Am Coll Cardiol* 2012;59:703–10.
- [51] Lindman BR, Maniar HS, Jaber WA, Lerakis S, Marck MJ, Suri RM, et al. Effect of tricuspid regurgitation and the right heart on survival after transcatheter aortic valve replacement: insights from the placement of aortic transcatheter valves II inoperable cohort. *Circ Cardiovasc Interv* 2015;8:1–10.
- [52] Chikwe J, Itagaki S, Anyanwu A, Adams DH. Impact of concomitant tricuspid annuloplasty on tricuspid regurgitation, right ventricular function, and pulmonary artery hypertension after repair of mitral valve prolapse. *J Am Coll Cardiol* 2015;65:1931–8.
- [53] Groves PH, Lewis NP, Ikram S, Maire R, Roger JCH. Reduced exercise capacity in patients with tricuspid regurgitation after successful mitral valve replacement for rheumatic mitral valve disease. *Br Heart J* 1991;66:295–301.
- [54] King RM, Schaff HV, Danielson GK, Gersh BJ, Orszulak TA, Piehler JM, et al. Surgery for tricuspid regurgitation late after mitral valve replacement. *Circulation* 1984;70:193–7.
- [55] Vassileva CM, Shabosky J, Boley T, Markwell S, Hazelrigg S. Tricuspid valve surgery: the past 10 years from the Nationwide Inpatient Sample (NIS) database. *J Thorac Cardiovasc Surg* 2012;143:1043–9.
- [56] Gatti G, Dell'Angela L, Morosin M, Maschietto L, Pinamonti B, Forti G, et al. Tricuspid annuloplasty for tricuspid regurgitation secondary to left-sided heart valve disease: immediate outcomes and risk factors for late failure. *Can J Cardiol* 2016;32:760–6.
- [57] Gilard M, Schlüter M, Snow TM, Dall'Ara G, Eltchaninoff H, Moat N, et al. The 2011–2012 pilot European Society of Cardiology Sentinel Registry of Transcatheter Aortic Valve Implantation: 12-month clinical outcomes. *EuroIntervention* 2016;12:79–87.
- [58] Campelo-Parada F, Perlman G, Philippon F, Ye J, Thompson C, Bédard E, et al. First-in-man experience of a novel transcatheter repair system for treating severe tricuspid regurgitation. *J Am Coll Cardiol* 2015;66:2475–83.
- [59] Fender EA, Nishimura RA, Holmes DR. Percutaneous therapies for tricuspid regurgitation. *Expert Rev Med Dev* 2017;14:37–48.
- [60] Lancellotti P, Rosenhek R, Pibarot P, Lung B, Otto CM, Tornos P, et al. ESC Working Group on Valvular Heart Disease Position Paper—heart valve clinics: organization, structure, and experiences. *Eur Heart J* 2013;34(21):1597–606.
- [61] Bissessor N, Shanahan L, Wee YS, Stewart R, Lowe B, Kerr A, et al. The role of natriuretic peptides in patients with chronic complex (mixed or multiple) heart valve disease. *Congest Heart Fail* 2010;16:50–4.
- [62] Goldstone AB, Chiu P, Baiocchi M, Lingala B, Patrick WL, Fischbein MP, et al. Mechanical or biologic prostheses for aortic-valve and mitral-valve replacement. *N Engl J Med* 2017;377:1847–57.
- [63] Lancellotti P, Pibarot P, Chambers J, Edvardsen T, Delgado V, Dulgheru R, et al. Recommendations for the imaging assessment of prosthetic heart valves: a report from the European Association of Cardiovascular Imaging endorsed by the Chinese Society of Echocardiography, the Inter-American Society of Echocardiography, and the Brazilian Department of Cardiovascular Imaging. *Eur Heart J Cardiovasc Imaging* 2016;6:589–90.
- [64] Takagi H, Ando T, Umemoto T, ALICE (All-Literature Investigation of Cardiovascular Evidence) Group. A review of comparative studies of MitraClip versus surgical repair for mitral regurgitation. *Int J Cardiol* 2017;228:289–94.
- [65] Haji Zeinali AM, Abbasi K, Saheb Jam M, Yazdani S, Mortazavi SH. Transcatheter aortic valve in valve implantation with Edwards SAPIEN bioprosthetic valve for different degenerated bioprosthetic valve positions (First Iranian ViV report with mid-term follow up). *J Cardiovasc Thorac Res* 2017;9:152–7.