European Heart Journal Supplements (2023) **25** (Supplement B), B21–B24
The Heart of the Matter
https://doi.org/10.1093/eurheartjsupp/suad061

Treatment of multiple valve disease: surgery, structural intervention, or both?

Sergio Berti[1]*, Michela Bonanni[2], Andreina D'agostino[1], Simona Celi[1], and Massimiliano Mariani[1]

[1]CNR Foundation of the Tuscany Region G. Monasterio; and [2]Department of Biomedicine and Prevention, Policlinico Tor Vergata, Rome

KEYWORDS
Multiple valve heart disease; Treatment of combined valvular defects; Management strategies of multiple valve diseases

Multiple valve heart disease refers to the simultaneous presence of several valvular anomalies, while mixed valvular heart disease refers to the combination of stenotic lesions or regurgitation affecting the same valve. The pathophysiology of multiple and mixed valvular heart disease depends on the combination of affected valves and the severity of the individual valvular defects. Imaging is essential for diagnosis and assessment of disease severity. The treatment of combined valvular defects currently represents a challenge for both cardiac surgeons and interventional cardiologists since only few data in the literature address the clinical and therapeutic decision-making process related to these complex lesions. These are heterogeneous conditions, which differ from each other in the combination of the valves involved, in the pathogenesis with which they develop, in the severity of the individual lesions, in the associated surgical risk, in the possibility of being repaired, and in the undergoing transcatheter treatments. In addition to the severity of the individual valve defects, the choice of treatment also depends on the ventricular function and the general condition of the patient. This work aims to provide a review of the state of the art regarding the possible management strategies of the most common multiple valve diseases in clinical practice.

Introduction

Combined valvular heart disease is highly prevalent, and the most frequent combinations are aortic stenosis (AS) with mitral regurgitation (MR), AS with aortic regurgitation (AR), and AR plus MR. Combined valve disease can be found in rheumatic heart disease and congenital heart disease but especially in the context of degenerative heart disease.[1] In industrialized countries, the most frequent pathogenesis is degenerative, in accordance with the ageing of the population and the reduction of rheumatic heart disease.[2] Degenerative AS is often associated with degeneration of the mitral valve apparatus which can generate a mixed defect with concomitant stenosis and insufficiency.[3] The prevalence of congenital heart disease in adults is also steadily increasing, and many of these subjects have multiple or mixed heart disease. The haemodynamic and clinical consequences of a given valve lesion can be modulated by the concomitant presence of another stenotic or regurgitant lesion on the same valve, in the case of mixed valve disease, or on another valve, in the case of multiple valve disease. These consequences depend not only on the specific combination of interest but also on the severity and timing of onset of each single lesion, on the loading conditions, and on the ventricular systolic or diastolic performance. When two or more severe lesions are present, the likelihood of ventricular dysfunction is high. Identifying the pathogenesis of the valve defects involved is essential to direct the patient to a targeted treatment that considers the anatomy of the valve disorders as well as the specific characteristics of the patient. The decision to operate on multiple valves should be considered after a quantification and evaluation of individual valve lesions and their mutual interactions. It must also consider age, comorbidities, and the risk of

*Corresponding author. Email: berti@ftgm.itb

combined procedures.[4] Before intervening, it is necessary to balance the evolution of the untreated valvular disease with the risk of combined intervention.[5] Current evidence on medical, surgical, and interventional management is limited, and most recommendations made on the treatment of combined valvular defects are established by C levels of evidence.[5,6] In current European and American guidelines, when two severe lesions are present, it is recommended to treat both lesions during surgery, with a Class I recommendation.[5,6] When, on the other hand, a severe lesion is associated with a non-severe lesion, the clinical management refers to that envisaged for the more severe pathology. Treating the moderate injury is in most situations a Class II recommendation.[5,6] When, on the other hand, two moderate lesions are present, the intervention can be taken into consideration when there are symptoms referable to valve disease, an impairment of the contractile function is evident, and pulmonary hypertension is present. In this case, the evaluation of the ventricular volumes, the pulmonary pressure at rest and during exercise, and the measurement of natriuretic peptides are particularly important.[5,6] Despite this general evidence, it is limiting to establish a standardized and unambiguous therapeutic approach that includes all possible combinations of valvular lesions. In this work, we will look at the most frequent and relevant combined valve defects from a clinical point of view and their possible therapeutic strategies.

Aortic stenosis and mitral regurgitation

About 20–30% of patients with severe AS have MR. Mortality in patients with severe AS is significantly higher in patients with moderate or severe MR.[7] Mitral regurgitation associated with AS can be either primary, characterized by degeneration of the mitral apparatus, or secondary or functional, i.e. secondary to increased left ventricular systolic pressure, increased afterload with subsequent ventricular remodelling. However, functional MR appears to be more frequent than primary mitral disease. In addition to evaluating each valvular lesion separately, the interaction between the different valvular lesions should be considered. The presence of severe MR may underestimate the extent of AS as the decrease in stroke volume, linked to MR, reduces the flow through the aortic valve and therefore the aortic gradient.[3] Conversely, the severity of MR accompanying AS may be overestimated due to elevated left ventricular pressures.[8] The main factor to consider in the therapeutic choice is the possibility of improvement of the MR after the correction of the aortic valve defect. In fact, the resolution of AS and the consequent reduction of afterload and left ventricular pressures should reduce MR.[8] Most of the data available in the literature show a reduction of MR after treatment of AS. These findings are more evident in patients with secondary MR than in those with primary MR. An integrated clinical-instrumental evaluation is therefore essential, with transthoracic and, when necessary, transoesophageal echocardiogram in order to identify the mechanism underlying the MR itself and its anatomy. In this way, it is possible to hypothesize a possible improvement after treatment of AS in functional mitral valves or, conversely, to consider it improbable in primitive mitral valves disease. Since in addition to risk scores such as EuroSCORE 2 or Society of Thoracic Surgeons (STS) score, there are no standardized prognostic indicators for this type of patient, all these aspects must be taken into consideration when choosing the therapeutic strategy to adopt. The therapeutic options are surgical aortic valve replacement (SAVR) and subsequent re-evaluation of the mitral valve, SAVR and mitral valve repair/replacement, transcatheter aortic valve replacement (TAVR) with subsequent re-evaluation of MR and TAVR with subsequent transcatheter MR treatment [transcatheter edge-to-edge repair (TEER)].[5,6] In patients with primary severe MR, mitral valve surgery at the time of SAVR is recommended. In patients with severe secondary MR, however, surgery may be considered in the presence of significant annular dilatation and marked left ventricular dilatation. In high-risk or inoperable patients with severe AS and severe MR, combined TAVI and TEER at the same time or sequentially may be an alternative. Data on the choice between the two possible timescales are insufficient to be able to formulate solid recommendations.[9] In particular, in patients with severe primary MR, TEER should be considered early if the patient is symptomatic and if MR is still severe after TAVI. Conversely, in patients with severe functional MR, after TAVI, the MR should be re-evaluated, and a careful echocardiographic follow-up should be carried out to identify the correct timing for any correction of the mitral valve defect.[9,10] Particularly in functional MR, the absence of pulmonary hypertension, as well as the absence of atrial fibrillation, had positive effects on the reduction of MR after TAVR.[10]

Aortic stenosis and mitral stenosis

Almost half of patients with AS undergoing TAVI have calcifications of the mitral annulus (MAC), which lead to severe mitral disease in 9.5% of cases. Severe MAC can cause MR, or more frequently mitral stenosis, or both, generating a mixed disorder. Although less frequent in industrialized countries, another cause of mixed mitro-aortic valve disease is rheumatic heart disease.[5,6] Aortic stenosis and MS together are poorly tolerated by patients as the reduction in cardiac output is usually greater than that seen in isolated disorders. As a result, aortic and mitral pressure gradients may be lower than expected, which may lead to an underestimation of the severity of both AS and MS. Severe MS generates a small stroke volume, and, therefore, the concomitant AS will be low-flow and low-gradient. Therefore, careful assessment of the severity of AS using an integrative approach, including quantification of aortic valve calcium using computed tomography, is needed. Also in this case, establishing the pathogenesis of the valve defects is essential for identifying an appropriate therapeutic procedure. Severe rheumatic mitral stenosis, caused by commissural fusion, can be treated effectively by percutaneous balloon valvuloplasty. In this case when associated with moderate AS, percutaneous mitral commissurotomy (PMC) can be performed to postpone surgical treatment of both valves. Degenerative mitral disease is associated with a poorer prognosis and poses specific therapeutic challenges, as balloon commissurotomy or surgical mitral valve replacement is often not an option in these patients due to extensive calcifications.[5] Usually, these are elderly patients with significant comorbidities.[11] Since there is no commissural fusion,

degenerative mitral stenosis cannot be subjected to PMC. Treatment options, including transcatheter and surgical approaches, are high-risk procedures, and evidence from randomized trials is lacking. In inoperable patients with severe mitral stenosis, symptomatic, and with adequate anatomy, transcatheter mitral valve implantation (ViMAC) is feasible, when performed by experienced operators after careful pre-planning with multimodality imaging. However, the technical complexity and operative mortality are high, particularly due to the risk of LVOT obstruction, and the medium-term results are less favourable when compared with mitral valve in valve (ViV) procedures.[12]

Aortic insufficiency and mitral insufficiency

Multiple valve disease including AR and MR is often poorly tolerated due to severe volume overload, leading to left ventricular eccentric hypertrophy and decreased contractile function. Mitral regurgitation is often secondary to volume overload caused by AR which in turn leads to ventricular remodelling. In patients undergoing aortic valve replacement for severe regurgitation, the presence of concomitant MR has a negative prognostic effect. Simultaneous mitral valve repair improved survival. Based on the anatomical characteristics of the valve, AR can be treated with TAVR devices developed for AS, however taking into account the increased risk of paravalvular leak, valve embolization, and pacemaker implantation. After treatment of aortic valve regurgitation, it is possible to re-evaluate MR and left ventricular function and possibly perform percutaneous mitral repair surgery at a later stage.

Tricuspid regurgitation and left heart valve disease

Functional tricuspid regurgitation (TR) is common in patients with left heart valve disease. The increase in left ventricular filling pressures and, consequently, in left atrial pressures causes post-capillary pulmonary hypertension, with significant increase in right ventricular afterload and eventually right ventricular dilatation and dysfunction. The main anatomical features of functional TR are dilatation of the tricuspid annulus and tethering of the valve leaflets, with subsequent coaptation deficit. Furthermore, atrial fibrillation, very common in patients with moderate aortic and/or mitral valve disease, constitutes an additional cause of tricuspid annular dilatation, contributing to the genesis of functional TR. Several studies have shown that TR can improve in patients with mitral valve disease undergoing surgery or percutaneous repair but that it can also remain unchanged or worsen, negatively influencing the long-term outcome.[13,14]

Among the factors recognized as predictors of progression of TR after mitral valve surgery, we find dilatation of the tricuspid annulus, atrial fibrillation, at least moderate preoperative TR, and extreme atrial dilatation. Although predominantly secondary to mitral valve disease, TR is present in up to 40% of patients with severe degenerative AS. Compared to other combined valve diseases, the presence of multiple valve disease AS–TR generally does not influence the assessment of the respective degree of severity. However, in the case of particularly severe TR, if associated with right ventricular dysfunction, a low-flow condition can be generated which can alter the echocardiographic evaluation of the severity of AS. In recent decades, the negative prognostic impact of significant TR in patients undergoing SAVR has been widely demonstrated.[15,16] Surgical or percutaneous aortic valve replacement reduces the severity of TR in 15–30% of patients.[15,16] However, the progression of TR despite correction of the aortic defect is not an infrequent event and is associated with the degree of dilatation of the tricuspid annulus (septolateral diameter greater than 40 mm or 21 mm/m^2 in end diastole) and the presence of preoperative atrial fibrillation. Identifying the correct timing to intervene on the TR is essential to prevent right ventricular dysfunction. The most recent European and American guidelines on the management of heart valve disease recommend surgery of the tricuspid valve, favouring repair to replacement in conjunction with surgery for left heart valve disease in cases of severe primary or secondary TR (Class I), or moderate primary TR (Class IIa).[5,6] Since reoperation after mitral or aortic valve surgery in case of worsening pre-existing TR carries a high surgical risk, combined correction should be considered even in still asymptomatic patients if there are initial signs of right ventricular dilatation and/or dysfunction but in the absence of severe pulmonary hypertension or severe right ventricular dysfunction because in the latter case, the prognosis is not determined by TR.[5,6] Whenever possible, repair with annuloplasty is preferred to replacement, which should be considered only in cases of severe annular dilatation or leaflets tethering. Where transcatheter repair/replacement of a left heart valve defect is chosen due to excessive surgical risk, it is necessary to identify the mechanism of the TR, its aetiopathogenetic characteristics and haemodynamic aspects.[17] In the presence of predictive factors of reduction of the TR after reduction of the mitro-aortic valve disease, a follow-up of the TR can be opted for, in order to plan, if necessary, a possible subsequent percutaneous repair/replacement. In the case of an unfavourable phenotype, such as severe atrial functional TR, a combined approach with concomitant mitral/aortic and tricuspid repair can be opted for. Conversely, patients with valvular anatomy not amenable to transcatheter treatment, or in case of low probability of clinical benefit due to the presence of end-stage disease or severe pre-capillary and post-capillary pulmonary hypertension, treatment of left valve defect alone is opted for. The transcatheter therapeutic techniques of TR are relatively new and need further randomized clinical trials to confirm their long-term efficacy and safety results.

Consequently, in the European guidelines, the indication for this therapy is in Class IIb recommendation, only in symptomatic, inoperable patients, in whom a prognostic benefit is expected.[5] Based on the target mechanism and anatomical features, treatment options include direct or indirect tricuspid restrictive annuloplasty, edge-to-edge leaflet coaptation restoration, heterotopic tricuspid valve implantation, and transcatheter tricuspid valve replacement.[18]

In conclusion, the treatment of combined valvular defects represents a challenge for cardiac surgeons and interventional cardiologists and requires careful evaluation of the patient, the combination of associated defects, and

the interaction between them. Cardiovascular surgery and percutaneous treatment are both valid options, but the choice between the two options and the timing of the intervention strongly depend on multiple factors that need to be analysed in a multidisciplinary way. Further data are needed to identify patients for combination treatment and those in whom a re-evaluation in time is indicated for.

Funding

None declared.

Conflict of interest: None declared.

Data availability

No new data were generated or analysed in support of this research.

References

1. Yang LT, Enriquez-Sarano M, Scott CG *et al*. Concomitant mitral regurgitation in patients with chronic aortic regurgitation. *J Am Coll Cardiol* 2020;**76**:233–246.
2. Unger P, Pibarot P, Tribouilloy C *et al*. Multiple and mixed valvular heart diseases. *Circ Cardiovasc Imaging* 2018;**11**:e007862.
3. Abramowitz Y, Kazuno Y, Chakravarty T *et al*. Concomitant mitral annular calcification and severe aortic stenosis: prevalence, characteristics and outcome following transcatheter aortic valve replacement. *Eur Heart J* 2017;**38**:1194–1203.
4. Mehr M, Karam N, Taramasso M *et al*. Combined tricuspid and mitral versus isolated mitral valve repair for severe MR and TR: an analysis from the TriValve and TRAMI registries. *JACC Cardiovasc Interv* 2020;**13**:543–550.
5. Vahanian A, Beyersdorf F, Praz F *et al*. 2021 ESC/EACTS guidelines for the management of valvular heart disease. *Eur Heart J* 2022;**43**:561–632.
6. Otto CM, Nishimura RA, Bonow RO *et al*. 2020 ACC/AHA guideline for the management of patients with valvular heart disease: executive summary: A report of the American College of Cardiology/American Heart Association joint committee on clinical practice guidelines. *Circulation* 2021;**143**:e35–e71.
7. Mavromatis K, Thourani VH, Stebbins A *et al*. Transcatheter aortic valve replacement in patients with aortic stenosis and mitral regurgitation. *Ann Thorac Surg* 2017;**104**:1977–1985.
8. Katte F, Franz M, Jung C *et al*. Impact of concomitant mitral regurgitation on transvalvular gradient and flow in severe aortic stenosis: a systematic ex vivo analysis of a subentity of low-flow low-gradient aortic stenosis. *EuroInterv* 2018;**13**:1635–1644.
9. Witberg G, Codner P, Landes U *et al*. Transcatheter treatment of residual significant mitral regurgitation following TAVR: a multicenter registry. *JACC Cardiovasc Interv* 2020;**13**:2782–2791.
10. D'Ancona G, Kische S, Senges J *et al*. Combined mitroaortic pathology: impact of previous aortic valve replacement upon outcomes of MitraClip therapy (from the German transcatheter mitral valve interventions registry). *EuroInterv* 2017;**13**:475–482.
11. Okuno T, Brugger N, Asami M *et al*. Clinical impact of mitral calcium volume in patients undergoing transcatheter aortic valve implantation. *J Cardiovasc Comput Tomogr* 2021;**15**:356–365.
12. Guerrero M, Vemulapalli S, Xiang Q *et al*. Thirty-day outcomes of transcatheter mitral valve replacement for degenerated mitral bioprostheses (valve-in-valve), failed surgical rings (valve-in-ring), and native valve with severe mitral annular calcification (valve-in-mitral annular calcification) in the United States: data from the Society of Thoracic Surgeons/American College of Cardiology/Transcatheter Valve Therapy Registry. *Circ Cardiovasc Interv* 2020;**13**:e008425.
13. Geyer M, Keller K, Bachmann K *et al*. Concomitant tricuspid regurgitation severity and its secondary reduction determine long-term prognosis after transcatheter mitral valve edge-to-edge repair. *Clin Res Cardiol* 2021;**110**:676–688.
14. Adamo M, Pagnesi M, Ghizzoni G *et al*. Evolution of tricuspid regurgitation after transcatheter edge-to-edge mitral valve repair for secondary mitral regurgitation and its impact on mortality. *Eur J Heart Fail* 2022;**24**:2175–2184.
15. Cremer PC, Wang TKM, Rodriguez LL *et al*. Incidence and clinical significance of worsening tricuspid regurgitation following surgical or transcatheter aortic valve replacement: analysis from the PARTNER IIA trial. *Circ Cardiovasc Interv* 2021;**14**:e010437.
16. Cremer PC, Zhang Y, Alu M *et al*. The incidence and prognostic implications of worsening right ventricular function after surgical or transcatheter aortic valve replacement: insights from PARTNER IIA. *Eur Heart J* 2018;**39**:2659–2667.
17. Sisinni A, Taramasso M, Praz F *et al*. Concomitant transcatheter edge-to-edge treatment of secondary tricuspid and mitral regurgitation. *J Am Coll Cardiol Intv* 2023;**16**:127–139.
18. Praz F, Muraru D, Kreidel F *et al*. Transcatheter treatment for tricuspid valve disease. *EuroInterv* 2021;**17**:791–808.