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Is There Currently a Place for Combined Mitral and Aortic Transcatheter Interventions?

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Abstract

Purpose of Review The goal was to evaluate published data on the incidence, diagnosis, and management of symptomatic combined mitral and aortic valvular disease. Furthermore, to identify the role of treatment using contemporary transcatheter techniques.

Recent Findings Up to a quarter of symptomatic adult valvular disease is caused by multiple left-sided valvular lesions. The etiologic spectrum of this combined disease has shifted from rheumatic to degenerative. Both presentation and diagnosis of lesions are modified compared with isolated disease. Based upon narrative review, there are only limited observational experiences, insufficient to provide robust guidance. These data, however, indicate the feasibility of interventions such as transcatheter aortic valve replacement and edge-to-edge mitral valve repair to treat such disease and mitigate the risks of open surgery.

Summary Combined aortic and mitral valve disease is commonly encountered. There is a role for transcatheter interventions based on limited data; however, more research is needed.

Keywords Multivalve · Multiple valve disease · Combined valve disease · Transcatheter intervention

Introduction

Valvular heart disease in the twentieth century was dominated by inflammatory rheumatic disease and was primarily an affliction of the young. The new millennium has witnessed a gradual change in the epidemiology of disease to degenerative pathology in older patients as the most prevalent cause [1]. Multiple co-existent valve disease or multivalve disease (a combination of moderate or severe stenosis and/or moderate or severe regurgitation of two or more cardiac valves) comprises a substantial proportion of these cases. Limited data exist on optimal treatment efficacy and safety in part due to the numerous possible combinations, with observational data being dominated by retrospective analyses. In this context, strong evidence-based recommendations are precluded. In this narrative review, we explore the consequences of the changing spectrum, focussing on left-sided multiple valve disease, and how the development and rapid adoption of percutaneous cardiovascular medicine has the potential to affect the traditional paradigm of treatment.

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Epidemiology and Natural History of Multivalve Disease

Rheumatic heart disease has declined over the last 40 years and been overtaken by degenerative disease as the prime cause of valvular heart disease, particularly in high-income countries [2, 3]. Less frequently, infective endocarditis affecting the aortic valve can spread to the nearby mitral valve and vice-versa. Rarer causes must also be considered if there is no clear etiology after initial evaluation (Table 1).

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Table 1 Etiology of left-sided multivalve disease

Acquired	Rheumatic heart disease
	Degenerative calcific
	Infective endocarditis
	Mediastinal radiation
	Drugs (ergotamines, fenfluramine and phentermine, pergoline)
Congenital	Marfan syndrome
	Ehlers-Danlos syndrome
	Mucopolysaccharidosis

Based upon population and community studies, the prevalence of moderate or severe left-sided valvular heart disease (either stenosis or regurgitation) is 2.5% across all age groups. The aortic and mitral valve account for a prevalence of up to 16% in the > 75 demographic.

In the EORP registry VHD II ($n = 7247$) [4•], 25% of patients with valvular disease had multiple left-sided lesions. Of these, one-third of patients were over 80 years of age, 52% were highly symptomatic (NYHA III/IV), and 29% presented with heart failure. In the EuroHeart survey, 20.2% had multivalve disease with a mean age of 64 and predominantly male sex [2].

Both coronary artery disease and previous myocardial infarction pre-dispose to ischaemic mitral regurgitation and aortic root dilation can lead to secondary aortic regurgitation [5].

The commonest pathological combination leading to multiple valve surgery (15% of all valve surgery) is aortic and mitral followed by mitral and tricuspid, accounting for > 85% of multivalve procedures. Both aortic and tricuspid as well as triple valve surgery (aortic, mitral, and tricuspid) is relatively infrequent [6].

Isolated surgical aortic valve replacement with concomitant > grade 2 mitral regurgitation (MR) is associated with worse clinical outcomes [7].

Assessment of Left-Sided Multivalve Disease

Clinical and echocardiographic evaluation in multivalve disease is frequently misleading due to haemodynamic interaction of the proximal valve on the distal valve and vice-versa so accurate assessment is challenging (Table 2). In particular, echocardiographic parameters have only been validated in isolated valve disease. For example, the combination of severe aortic stenosis and severe mitral regurgitation reduces transaortic flow, which may result in low-flow, low-gradient aortic stenosis. This may lead some clinicians to erroneously conclude that the aortic stenosis severity is not severe. The risks of a second valve lesion being under or overestimated at the time of an index procedure places even more reliance on multimodality imaging within a Heart team environment. Quantitative echo methods based more on direct plannimetry rather than loading conditions are less prone to misinterpretation [9••].

A careful assessment using multimodality imaging is therefore paramount with decision-making guided by the dominant severe valvular lesion and based on symptoms, ventricular function, and pulmonary artery pressure.

Current Status of Open Surgical Multivalve Repair and Replacement

The operative mortality of combined procedures is highly relative to isolated lesions. The Society of Thoracic Surgeons STS database of more than 50,000 operations for 2000–2010 reported a 30-day mortality of 10.7% for combined open surgical aortic and mitral valve procedures with triple valve (aortic, mitral, and tricuspid) procedures carrying a 14% mortality. Even higher mortality is reported if combined valve procedures are performed with coronary artery bypass grafting [10] Whilst the overall trend has been for decreasing mortality for both isolated and combined procedures, the patient comorbidities have worsened over time also and latter still are associated with a higher mortality.

For aortic and mitral pathology, SAVR and mitral valve repair is preferable to double valve replacement at long-term follow-up [11, 12]. If both aortic and mitral valve mechanical replacement are undertaken, then the incidence of long-term thrombo-embolism is higher than isolated replacement but can be partially mitigated by higher intensity of anticoagulation with the lowest event rate between INR 2.5–4.9, giving rise to a target INR 3.0–4.0 [13].

Current Status of Transcatheter Multivalve Intervention

Percutaneous interventions, in particular transcatheter aortic valve replacement (TAVR) and transcatheter edge-to-edge mitral valve repair (MitraClip), supported by a series of randomised controlled clinical trials and large registries, have revolutionised the management of isolated valvular disease. By comparison, the percutaneous management of multivalve disease has a very limited evidence base from which to draw. Thus far, only observational cohort, case series, and isolated case reports have reported on the application of transcatheter therapies for multivalve disease [14••].

Table 2 The interaction of left-sided multivalve disease and echocardiographic evaluation

Primary lesion	Effect on AS evaluation	Effect on AR evaluation	Effect on MS evaluation	Effect on MR evaluation
AS		• Pressure half-time unreliable due to left ventricular hypertrophy prolonging flow	• Pressure half-time unreliable as may be shortened •Low-flow-low-gradient possible	• Overestimation of severity possible due to high volume load. • Effective regurgitant orifice area less affected
AR	• Overestimation of severity possible due to increased forward flow		• Pressure half-time unreliable • Continuity equation unreliable	• Volumetric methods unreliable
MS	• Low-flow-low-gradient possible • Aortic valve area (continuity) remains valid	• Underestimation possible (left ventricular chamber dilatation may be less evident)		• Standard methods reliable
MR	• Low-flow-low-gradient possible • MR may be mistaken for the AS flow envelope	• Pressure half-time unreliable	• Pressure half-time unreliable • Continuity equation unreliable	

AS aortic stenosis, *AR* aortic regurgitation, *MS* mitral stenosis, *MR* mitral regurgitation

Adapted by permission from Springer Nature: Unger et al. Nat Rev Cardiol. 2016, 13: 429–440 [8••]

Adapted from: Zoghbi et al. J Am Soc Echocardiogr 2017;30:303–371, with permission from Elsevier [9••]

Aortic Valve Stenosis and Mitral Regurgitation

Careful integration of clinical evaluation and multimodality imaging is required for this pathological combination as the severity of aortic stenosis can be underestimated due to mitral regurgitation, and conversely, the severity of mitral regurgitation can be overestimated due to aortic stenosis. The more severe the aortic stenosis, the more likely the association with MR.

Aortic stenosis can cause > grade 2 functional (secondary) MR or to a worsening of pre-existing primary degenerative MR and conveys a poor prognosis if it remains after aortic valve intervention regardless of mechanism [15•]. In the case of the former, aortic valve intervention (surgical or transcatheter) should partially or completely resolve the secondary effect, whilst with the latter mitral valve intervention may be required. Independent predictors, using multivariate analysis, of continued moderate or severe MR or progression of disease after TAVR include mitral valve and/or leaflet calcification, new-onset atrial fibrillation, depressed left ventricular function, left atrial enlargement, and a mitral annulus of > 35 mm. The key feature, however, is whether the predominant mechanism of MR is due to degenerative change or functional.

For degenerative disease, if a percutaneous treatment is contemplated, then the procedure should be staged with mitral valve edge-to-edge repair performed first as the results are less predictable in this setting. A successful result then supports a second procedure with TAVR; conversely, a sub-optimal result supports a second procedure with surgical AVR.

In the case of a pre-existing TAVR prosthesis, then edge-to-edge repair may be performed as a single procedure.

For functional disease, the place of surgery is not clear as mitral regurgitation may improve after TAVR. If there is no improvement, then mitral edge-to-edge repair can be performed with high procedural success.

When treated with TAVR, a meta-analysis of cohort studies ($n = 8015$) reveals an association with a higher mortality at 30 days and 1 year (HR 1.49, 95% CI 1.16 to 1.92, and HR 1.32, 95% CI 1.12 to 1.55, respectively) compared with isolated aortic stenosis irrespective of valve prosthesis design (self or balloon-expandable) [16]. Predictors of improvement of MR grade after TAVR, which occurs in up to half of cases especially if non-severe, includes secondary MR, reduced LVEF, and an absence of mitral annular calcification (MAC) or pulmonary hypertension [17]. Interestingly in one cohort undergoing TAVR ($N = 813$) with non-severe MR, the presence or absence of moderate or severe tricuspid regurgitation may be the key determinant of outcome (HR, 18.4; 95% CI, 10.2–33.3; $P < .001$) [18]. Furthermore, patients with combined low-flow, low-gradient severe AS with moderate to severe MR have a 3-fold higher rate of all-cause mortality compared with similar patients with mild or less MR. However, the former patient subgroup have a particularly dismal prognosis if medically managed [19]. Recently published data from randomised studies are conflicting on the benefit of edge-to-edge repair in the setting of functional MR. The MITRA-FR trial reported no benefit of MitraClip for moderate-severe functional MR in terms of a reduction of mortality or heart failure hospitalisations at 1-year follow-up whereas conversely, the COAPT trial showed a reduction in mortality and heart failure hospitalisation with a large effect size [20••, 21••]. The apparently contradictory findings may have been due to a combination of more stringent selection criteria, less procedural complications, and echocardiographically more severe MR in COAPT compared with the former. The absence of echocardiographic core laboratory evaluation in both studies, non-specialist monitoring of guideline heart failure medical management in MITRA-FR, and the very slow recruitment rate in the COAPT study indicate the need for further trial evaluation, particularly of the subset of patients with the most severe MR. It thus currently appears justified to closely follow patients that undergo TAVR and have concomitant MR and if the MR remains moderate to severe after TAVR, edge-to-edge repair should be considered.

A proposed algorithm incorporating percutaneous intervention is outlined (Fig. 1) and an example of mitral edge-to-edge repair in the presence of a pre-existing TAVR prosthesis (video 1-3, Fig. 2).

Aortic Valve Stenosis and Mitral Stenosis

Combined left-sided stenotic lesions usually present early as the additive haemodynamic strain rapidly produces symptoms with signs dominated by aortic stenosis. Degenerative mitral valves are less prone to severe stenosis than their rheumatic counterpart and so the frequency of critical mitral stenosis has reduced in high-income countries making this double valve lesion less frequent [22].

A large registry has demonstrated that combined stenoses occurred in 11.6% of patients undergoing TAVR ($n = 44{,}755$); 2.7% were severe combined lesions. In case of severe combine lesions, there was an associated increase in mortality at 1 year after TAVR compared with TAVR for isolated aortic disease (1.2, 95% CI 1.0 to 1.4, $p = 0.046$) and in addition, an increase in heart failure related re-hospitalisation (HR 1.3, 95% CI 1.1–1.5, $p < 0.009$) and mitral valve intervention. Patients with mitral stenosis had a higher NYHA class, a history of previous valve intervention, and more frequent need for dialysis [23••].

In aortic stenosis, concomitant mitral stenosis is now typically non-rheumatic affecting the basal portions of the leaflets, so the absence of commissural fusion precludes percutaneous transluminal mitral commissurotomy (PTMC) although it may accommodate a transcatheter aortic valve in mitral position if there is sufficient annular calcification. This procedure is however hampered by high morbidity and mortality [24–26]. Studies on dedicated transcatheter mitral valves have until now largely excluded patients with mitral stenosis but it would be the obvious next step for these devices as the safety and efficacy data on MR is growing.

A proposed algorithm incorporating percutaneous intervention is outlined (Fig. 3).

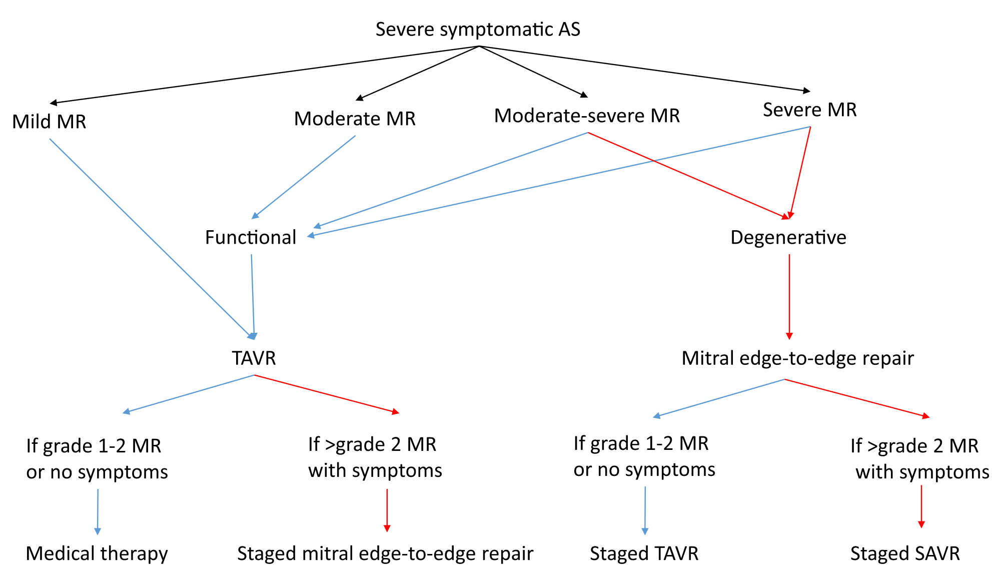

Fig. 1 A proposed algorithm for integrating transcatheter intervention in the management of severe combined aortic stenosis and mitral regurgitation. AS, aortic stenosis; MR, mitral regurgitation; SAVR, surgical aortic valve replacement; TAVR, transcatheter aortic valve replacement

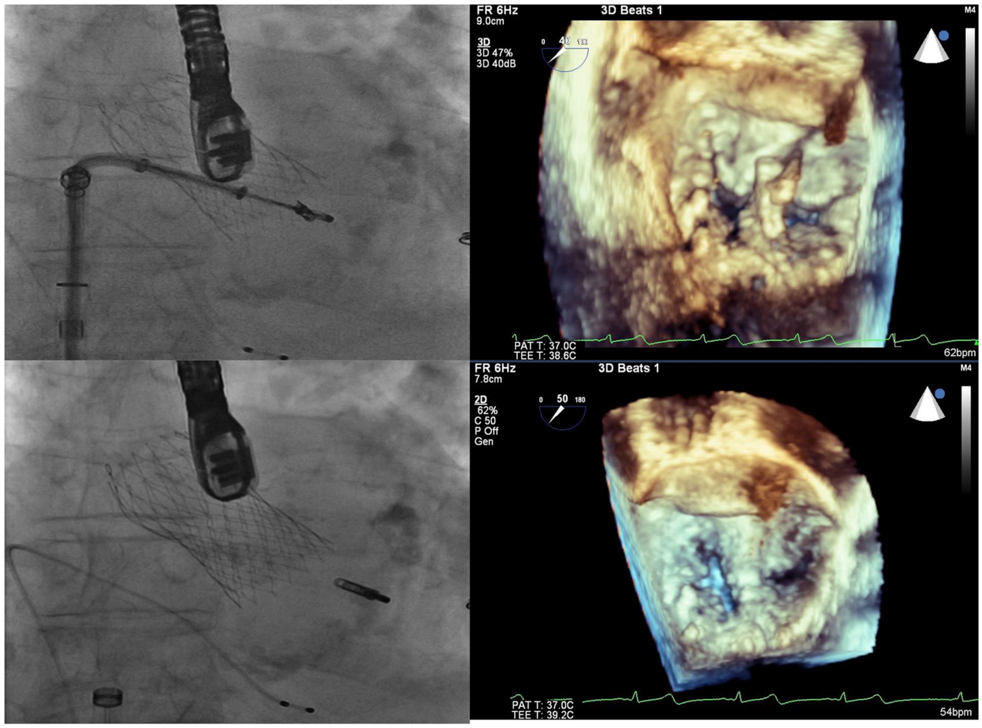

Fig. 2 Composite still frame collage. Left upper frame: fluoroscopic image of edge-to-edge repair being performed with transesophageal guidance. A self-expanding aortic valve prosthesis and temporary pacing wire can also be seen. Right upper frame: 3-dimensional image of the delivery system and device being positioned via transseptal puncture and the left atrium. Left lower frame: Fluoroscopic image demonstrating the position of a released clip on the mitral valve leaflets. Right lower frame: 3-dimensional image demonstrating the final anatomical result with a double orifice appearance to the mitral valve

Aortic Regurgitation and Mitral Regurgitation

Aortic regurgitation (AR) leads to secondary MR in up to one quarter of patients with an associated worse prognosis [27]. Less frequently primary myxomatous degeneration of the aortic and mitral valves, Marfan syndrome (mitral valve prolapse and aortic annular dilatation), and Ehlers-Danlos syndrome also associated with multivalve regurgitation. In all etiologies, combined regurgitant lesions are poorly tolerated relative to stenotic lesions due to the immense left ventricular volume overload. This leads to ventricular dilatation with displaced papillary muscles and mitral annular dilatation causing an increased regurgitant orifice area secondary MR.

The efficacy of percutaneous treatment is dependent on anchoring of TAVR prosthesis. The mechanism of anchoring relies on annular calcification for the majority of valve designs but can be performed in its absence although data are very limited [28]. Moreover, specific TAVR prostheses have been designed which anchor onto the aortic valve leaflets themselves obviating a need for excess calcific deposits (e.g. the Jena Valve) and have been used with encouraging results [28•, 29•]. Similarly, efficacy of percutaneous mitral valve replacement depends on the presence and extent of mitral annular calcification. Thus, surgical treatment of both valves is currently favoured, however a hybrid approach with surgical replacement for AR and then followed by percutaneous edge-to-edge repair or percutaneous direct annuloplasty for MR and appears feasible [30]. The efficacy of TAVR and MitraClip for

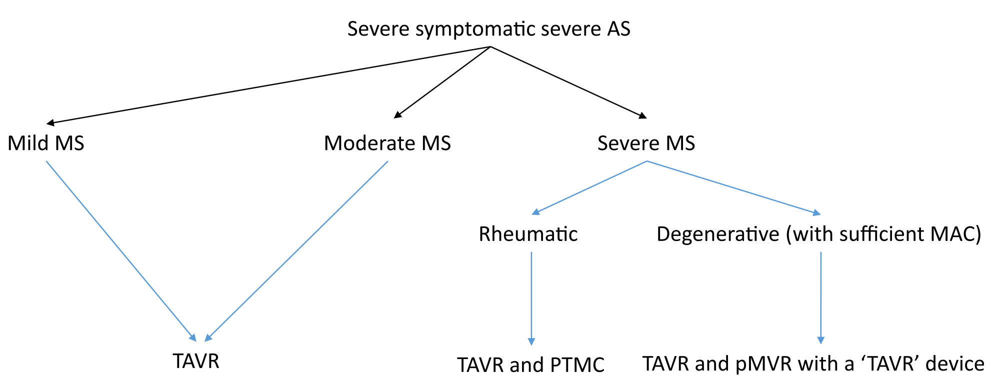

Fig. 3 A proposed algorithm for integrating transcatheter intervention in the management of severe combined aortic stenosis and mitral stenosis. AS, aortic stenosis; MAC, mitral annular calcification; MS, mitral stenosis; pMVR, percutaneous mitral valve replacement; PTMC, percutaneous transluminal mitral commissurotomy; TAVR, transcatheter aortic valve replacement

concomitant AR and MR in patients not fit for surgery is unknown.

Mitral Stenosis and Aortic Regurgitation

Rheumatic disease frequently causes aortic regurgitation and mitral stenosis; however, a combination of severe valve pathology is uncommon. The valve lesions generate opposite loading conditions which can make each appear less severe. If the mitral stenosis is rheumatic in origin, then it may be amenable to PTMC in an attempt to postpone SAVR or TAVR (in those unfit for open surgery). There are very limited data on combined or hybrid percutaneous procedures.

Clinical Scenarios Frequently Encountered

Two severe lesions (particularly aortic stenosis and mitral regurgitation), one severe and one moderate lesion or two or more moderate lesions, are the typical scenarios encountered in clinical practice. The presence of severe aortic and mitral stenosis or severe aortic and mitral regurgitation is conventionally rectified by SAVR unless significant co-morbidity preclude it. In this situation, therefore, transcatheter therapies such as a staged percutaneous approach with TAVR followed by edge-to-edge repair after a period of medical therapy may be performed [8••, 31•, 32•].

In the case of one severe and one moderate lesion, the decision for treatment is dominated by the severe lesion and the anticipated progression of the moderate lesion.

For moderate degenerative aortic stenosis, the average annual increase in peak gradient is 4 ± 3 mmHg with a slower rate of increase in rheumatic disease. Moderate aortic regurgitation (grade $> 2+$) progresses to severe at a relatively slow rate of an annual increase in grade of $+0.07$ per annum [33, 34]. Mitral valve stenosis, however, declines at a variable rate dependent on the severity of calcification and the presence or absence of commissural fusion.

The presence of two or more moderate lesions poses perhaps the greatest challenge in assessment and for which no data on the benefits of different interventional therapies exist. Currently, a global approach using detailed functional assessment, pulmonary artery pressure at rest and on exercise, right ventricular indices, and natriuretic peptides may aid clinical decision-making [35]. In the context of decreased left ventricular function related to combined valve disease, percutaneous or surgical replacement may be of benefit.

The calculus of decision-making for valve disease should include an evaluation of the patient co-morbidities, the risk of the procedure (surgical or transcatheter), the projected life expectancy, the risk of long-term morbidity (particularly in regard to chronic anticoagulation, and pacemaker implantation), and the sequencing or procedures (particularly in the case of transcatheter therapies) or likely need for future procedures. This level of decision-making complexity necessitates a multidisciplinary approach based on a Heart team.

Current Guidelines

The lack of definitive data on the optimal management of multivalve disease limits the ability to form strong recommendations. The current (2017) and previous (2012) European guidelines in respect of multivalve interventions emphasise, in a very limited but dedicated section, the importance of using the dominant valvular lesion (whether stenosis or regurgitation) to inform decision-making. In addition, the importance of considering the haemodynamic interactions between valves and global clinical assessment is stressed. In combined valve disease, severity is inferred if there are symptoms associated with two moderate lesions [36]. The guidelines advise against surgical intervention of mitral regurgitation if there is mitral annular dilatation, morphological abnormalities of the mitral valve, or marked abnormalities of LV geometry. In patients with secondary mitral regurgitation combined with sequential TAVR and edge-to-edge mitral valve repair is described as feasible but without sufficient evidence to make a recommendation [37•, 38•]. North American guidelines, in contrast, focus almost entirely on isolated valve disease management and do not suggest approaches to the interventional management of multivalve disease [36, 39].

Future Perspectives

The management of multivalve disease has a limited evidence base. The advent of TAVR and edge-to-edge percutaneous transcatheter therapies allows for minimally invasive solutions to combinations of valve lesions which would ordinarily be too high risk to tackle with open surgery particularly in patients with co-morbidities and the increasingly ageing demographic in high-income countries. Although percutaneous valve strategies have been deployed in the context of isolated valve disease, they have the potential to help manage multivalve disease. The advent of percutaneous mitral valve replacement brings with it the possibility of combined left-sided valve replacement [40].

The relative merits of sequencing and different percutaneous or hybrid approaches (surgical and percutaneous) are unclear, as is the management of less frequently encountered valve disease combinations. As current percutaneous valve therapies diffuse and newer technologies enter the clinical arena, more clinical experience and observational and economic data will accumulate and allow for a more informed management strategy to evolve.

Conclusion

Multivalve disease is frequently encountered and challenging to manage. The standard paradigm for both diagnosis and treatment is based on data from isolated valve disease and cannot always be applied. A systematic approach which identifies the primary severe valve pathology in multivalve disease is of key importance before planning treatment. Contemporary open surgical therapies are associated with high morbidity and mortality, whereas transcatheter therapies offer a lower risk alternative that can be staged if necessary. Such treatments are feasible and therefore very attractive from a clinical perspective. Outcome data from clinical trials and registries, including health economic analyses, are needed to advance the field of percutaneous therapies in this challenging subset.

Compliance with Ethical Standards

Conflict of Interest Rodney De Palma, Crochan J. O'Sullivan, and Magnus Settergren declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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