Mitral regurgitation in patients with severe aortic stenosis: diagnosis and management

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ABSTRACT

Severe aortic stenosis (AS) and mitral regurgitation (MR) frequently coexist. Although some observational studies have reported that moderate or severe MR is associated with higher mortality, the optimal management of such patients is still unclear. Simultaneous replacement of both aortic and mitral valves is linked to significantly higher morbidity and mortality. Recent advances in minimally invasive surgical or transcatheter therapies for MR allow for staged procedures in which surgical or transcatheter aortic valve replacement (SAVR/TAVR) is done first and MR severity re-evaluated afterwards. Current evidence suggests MR severity improves in some patients after SAVR or TAVR, depending on several factors (MR aetiology, type of valve used for TAVR, presence/absence of atrial fibrillation, residual aortic regurgitation, etc). However, as of today, the absence of randomised clinical trials does not allow for evidence-based recommendations about whether or not MR should be addressed at the time of SAVR or TAVR. A careful patient evaluation and clinical judgement are recommended to distinguish patients who might benefit from a double valve intervention from those in which MR should be left alone. The aim of this review is to report and critique the available data on this subject in order to help guide the clinical decision making in this challenging subset of patients.

INTRODUCTION

Mitral regurgitation (MR) is commonly observed in patients with severe aortic stenosis (AS).[1] However, conflicting data exist regarding the impact of MR on outcomes after surgical or transcatheter aortic valve replacement (SAVR or TAVR). It is known that simultaneous surgical replacement of both aortic and mitral valves significantly increases morbidity and mortality, especially in elderly patients (in-hospital mortality rates 5%–12.5%).[2 3] The success of TAVR as a therapy for severe AS, along with the development of transcatheter therapies for MR, offers the option of a staged procedure to address AS first, and then reassess MR severity afterwards. This is particularly relevant since moderate or severe MR may improve in some patients following SAVR or TAVR. Because of the paucity of high-quality data on this topic, the 2014 American Heart Association/American College of Cardiology guidelines opted not to make recommendations regarding double valve procedures in patients with AS and MR.[4] This review focuses on the available evidence regarding 1) the impact of MR on outcomes of patients with severe AS, 2) spontaneous improvement in MR severity after SAVR or TAVR and 3) when it is reasonable to intervene on mitral valve at the time of SAVR or TAVR, versus a staged procedure or leaving MR untreated.

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Assessment of MR in patients with concomitant AS

The valve guidelines emphasise the importance of distinguishing whether MR is primary (ie, caused by leaflet abnormality) or secondary to left ventricular (LV) dilation and dysfunction.[4] The most common cause of primary MR in the general population of high-income countries is mitral valve prolapse,[5] whereas the most common cause of secondary MR is ischaemic cardiomyopathy.[6] In secondary MR, the leaflets are normal (or have only minor age-related thickening), with restricted systolic closure caused by tethering because of outward displacement of the LV walls and papillary muscles, with or without annular dilation.[6 7] However, in patients with severe AS, the mitral annulus, leaflets and subvalvular apparatus often are calcified to varying degrees and the LV size and function are typically normal. Thus, the classical definition of secondary MR is seldom met. Patients with AS and LV dysfunction, either due to ischaemic heart disease or the effects of chronic pressure overload, may have leaflet tethering, but usually also have some degree of leaflet or annular calcification, and thus mixed aetiology MR. The presence of normal mitral valve leaflets in a patient with severe AS may be a clue to the presence of a bicuspid valve. Occasionally, patients with AS are observed to have mitral valve prolapse or a flail leaflet, often with mitral annular calcification. Figure 1 shows examples of mitral valve pathologies in patients with severe AS. Transthoracic or transoesophageal echocardiography is the reference standard for determining the mechanism of MR and the feasibility of mitral valve repair.[8] However, the echocardiographic evaluation of the severity of MR is complex with no single parameter having sufficient accuracy and reproducibility to serve as the sole arbiter of MR severity. Thus, integration of multiple echocardiographic findings, including quantitative measurements, is recommended in clinical practice.[8–11] This can be more challenging in AS due to attenuation of ultrasound by calcification. Colour Doppler jet size tends to overestimate MR severity in classic AS due to the increased LV pressure which often causes MR jet velocities to be above 6 m/s.[11] Because colour Doppler jet area is determined by jet momentum flux, a 6 m/s jet appears 44% larger than a 5 m/s jet through the same regurgitant orifice area. A large colour Doppler jet with a high driving velocity but small effective regurgitation orifice area is probably not severe MR, and is likely to appear less severe after SAVR/TAVR. Conversely, moderate or severe MR may lead to underestimation of the severity of AS, since decreased forward stroke volume due to MR lowers the flow across the aortic valve and, hence,

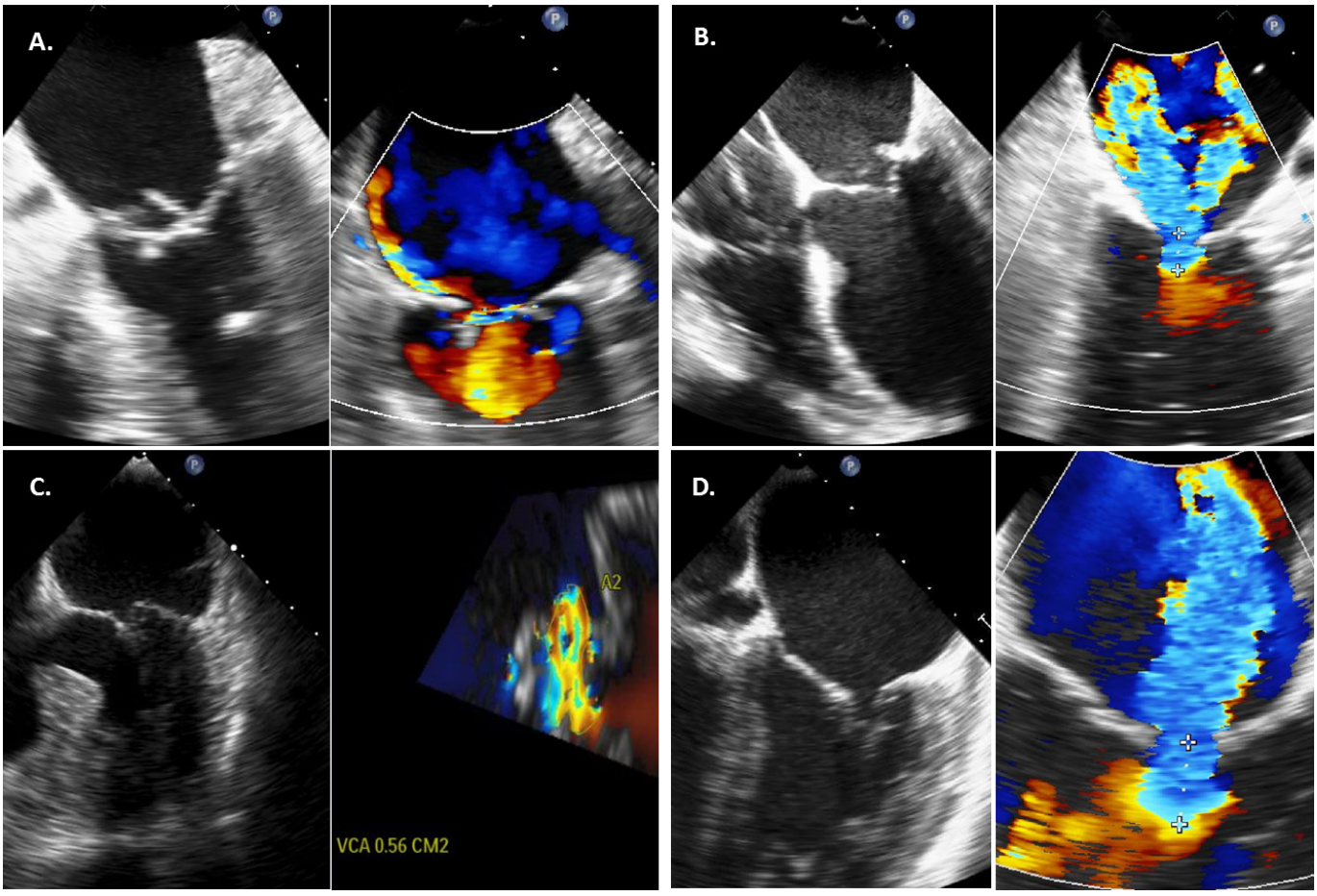

Figure 1 Examples of different mitral regurgitation (MR) etiologies in patients with severe aortic stenosis. (A) Mitral valve with flail middle scallop of posterior leaflet (P2) and severe eccentric MR. (B) Mitral annulus calcification with bileaflet thickening and severe central MR. (C) Severe prolapse of middle scallop of posterior leaflet (P2) and severe MR by vena contracta area. (D) Normal mitral valve structure with restricted motion of the posterior leaflet due to inferior wall motion abnormality and associated severe MR.

the aortic velocity and gradient (paradoxical low-flow low-gradient aortic stenosis with preserved ejection fraction). In patients with combined AS and MR, these factors highlight the critical need for careful quantitative assessment of both lesions, using multiple quantitative and qualitative parameters.

Does MR impact the outcomes of patients with severe aortic valve stenosis?

Role of MR on SAVR outcomes

Whereas isolated AVR in elderly patients carries an acceptable mortality rate (estimated approximatively 1%–3%), the operative risk is significantly increased when double valve surgery is performed, with or without revascularisation. Indeed, in the Euro Heart Survey on Valvular Heart Disease, perioperative mortality for double valve intervention was 6.5% compared with 2.7% for isolated SAVR and 4.3% for SAVR combined with revascularisation.[12] The latest report from the Society of Thoracic Surgeons reported a 3.5% mortality for double valve intervention over the last decade; however, when specifically looking at AVR combined with mitral valve surgery, perioperative mortality ranged from 8.2% to 11%.[13] The decision to perform a single versus a double valve intervention should therefore be based on the severity of the disease, on the clinical status of the patient, the surgical risk evaluation and on the likelihood that MR will improve after SAVR. Table 1 lists the available studies observing the natural history of MR left untreated at the time of SAVR. Overall, these data suggest that MR is not a predictor of either early or late mortality, particularly when multivariate analysis was performed.[1 14–22] However, Ruel *et al* found MR to be associated to a higher rate of heart failure (HF) symptoms, HF death and mitral valve repair/replacement need at follow-up, while Cutinho *et al* reported a 4.9-fold increased risk of mortality for patients in whom MR failed to improve after isolated SAVR.[14 15] Barreiro *et al* examined a series of 408 patients (62.8% primary MR), excluding severe MR, and found that moderate MR was a significant predictor of cumulative late mortality.[21] In the Placement of Aortic Transcatheter Valve (PARTNER) trial, moderate-to-severe MR was linked to higher 2-year mortality, with only a trend towards higher 30-day mortality.[22] A meta-analysis by Harling *et al* reported poorer early and late outcomes associated with moderate-to-severe MR left untreated at the time of SAVR.[23] However, this analysis included only four studies and a limited number of patients. The conclusions should be therefore considered provisional. This disparity between studies is likely due to different design and inclusion criteria; indeed, some studies included both primary and secondary MR and in some cases the MR group included trivial or mild MR. The studies are also confounded by lack of detail regarding mechanism of MR, or complete absence of such. Several studies reported 100% secondary MR in AS, which is highly doubtful because, as noted above, the mitral apparatus is usually calcified to some degree in patients with severe AS.

Table 1 Association of MR severity with early and late mortality after SAVR

Author (ref)	Year	n	MR aetiology	MR grading	Early mortality	Time	p Value	Late mortality	Time (years)	Value	Multivariate analysis HR (95% CI)*
Absil[18]	2003	116	Secondary MR 100%	None/mild Moderate/severe	3.5% 7.0%	Perioperative	0.67	60.9% 55.0%	3.2±2.4	0.10	NR
Moazami[1]	2004	107	Secondary MR 100%	Trivial/mild (72) Moderate/severe (35)	NR NR	–	NR	10.9% 28.6%	5	0.04	NR
Barreiro[21]	2005	408	Myxomatous 34.3% Calcific 28.5% Ischaemic 15.7% Non-ischaemic 21.4%	None/mild (338) Moderate (70)	3.8% 7.1%	In-hospital	0.21	40.8% 41.4%	10	1.0	1.43 (1.32 to 1.976)
Ruel[14]	2006	848	Secondary MR 100%	None/mild (741) Moderate/severe (107)	NR	–	NR	N/A	10	NR	1.8 (0.9 to 3.4)
Caballero-Borrego[20]	2008	572	Secondary MR 100%	No MR (419) Non-severe MR (153)	5.6% 10.5%	NR	0.02	N/A	–	NR	NR
Wan[17]	2009	182	Secondary MR 100%	None/mild (91) Moderate/severe (91)	NR	30 days	NR	56.6% 51.7%	3.8±3.6	0.33	NR
Takeda[16]	2010	193	NR	None/mild (134) Moderate/severe (59)	1.7% 2.9%	Operative	0.6	8.2% 8.5%	3.3±0.5	0.49	NR
Barbanti[22]	2012	299	NR	None/mild (240) Moderate/severe (59)	7.1% 13.6%	30 days	0.09	71.9% 50.2%	1	0.04	1.77 (1.17 to 2.68)
Cotinho[15]	2013	255	Secondary MR 100%	Severe MR untreated Severe MR surgically treated	0.0% 1.1%	30 days	0.19	44.4% 23.3%	4.48±2.93	0.44	NR
Schubert[19]	2016	423	Secondary MR 96% Rheumatic 3% Leaflet prolapse 1%	Mild (319) Moderate/severe (105)	NR	–	NR	28.3% 38.2%	5	0.212	NR

MR, mitral regurgitation; NR, not reported; SAVR, surgical aortic valve replacement.
*Significant MR and late mortality.

The majority of studies used only qualitative, subjective grading of MR severity or failed to report the methodology of MR grading. Only the PARTNER trial used core-laboratory adjudication of MR severity, but noted that the core laboratory did not perform any quantitative measures of MR severity.[22] Most studies lumped moderate and severe MR together, presumably because severe MR is not commonly present in patients with severe AS. These limitations strongly limit the conclusions that can be drawn from the current literature.

Role of MR on TAVR outcomes

Significant MR (moderate or severe) appears to be present in 15%–20% of patients undergoing TAVR and in this setting, it is often left untreated.[24] How MR impacts on TAVR outcomes and how it changes after TAVR has been a focus of observational studies from single-centre and multicentre TAVR studies, with often conflicting results. Pooled results coming from two different meta-analyses have shown a higher mortality rate at 30 days, 1 year and 2 years following TAVR in patients with significant MR.[25 26] However, some of the primary studies (table 2), suggested an increase in early mortality after TAVR, whereas others did not.[27–36] Moreover, MR was not been found to be a predictor of mortality in registries used to build the risk scores that are used or have been used for SAVR and/or TAVR.[37 38] This might be due to the same limitations noted above. Most studies do not report the mechanism or aetiology of MR in patients who have undergone TAVR, nor is guideline-recommended integration of multiple quantitative and qualitative parameters used to grade MR. Moreover, different studies used different transcatheter heart valves (balloon-expandable vs self-expandable), frequently reporting different results. Whether the type of transcatheter heart valve has an influence on the impact of significant MR in TAVR patients will require confirmation in well-designed prospective studies.

Does surgical or transcatheter AVR (SAVR or TAVR) reduce MR severity?

The resolution of AS leads to an immediate drop in LV systolic pressure, which reduces the pressure gradient across the mitral valve, and therefore should improve MR severity. However, patient-prosthesis mismatch after SAVR or TAVR may limit the anticipated reduction LV pressure and thereby attenuate MR reduction. In the presence of secondary MR with mitral tethering, the resolution of the AS can reduce mitral tenting area in the acute phase, which in turn leads to a decrease in MR severity. In the late postoperative period, reversed LV remodelling and/or regression of LV concentric hypertrophy, could potentially reduce MR weeks after the intervention. In the PARTNER trial, MR improved in the majority of patients after SAVR and TAVR (69.4% vs 57.7%, respectively). However, it also worsened after SAVR or TAVR (2.8% and 5.8%, respectively). Although haemodynamic success of SAVR or TAVR would be expected to improve MR severity, other factors could potentially worsen MR severity

Table 2 Association of MR severity with early and late mortality after TAVR

Author (ref)	Year	n	MR aetiology	MR grading	Early mortality	Time	p Value	Late mortality	Time	p Value	Multivariate analysis HR (95% CI)
Bedogni[28]	2005	1007	Secondary MR 50.3%	None/mild (670) Moderate (243) Severe (94)	5.0% 9.5%	30 days	<0.001	10.0% 13.4%	1	<0.001	2.9 (2.5 to 3.8)
Leon[36]	2010	171	NR	Moderate/severe (38)	N/A	30 days	NR	23.7% vs 32.2%	1	0.307	NR
Rodes-Cabau[29]	2010	339	NR	Severe (27)	16.7%	30 days	0.049	10.7%	8 months	0.447	NR
D'Onofrio[34]	2011	176	Secondary MR 100%	None/Mild (133) Moderate/severe (43)	3.0% 9.3%	In-hospital	0.10	15.5% 20.5%	10.4±7.7 months	0.46	NR
Toggweiler[32]	2012	451	Secondary MR 56%	None/mild (319) Moderate/severe (132)	8.0% 15.0%	30 days	0.02	15.5% 20.5%	1 year	ns	0.82 (0.50 to 1.34)
Barbanti[22]	2013	331	Secondary MR 17.4%	None/mild (266) Moderate/severe(65)	5.6% 4.6%	30 days	0.76	32.7% 37.0%	2 years	0.58	1.14 (0.72 to 1.78)
Hutter[35]	2013	268	NR	No MR (208) Non-severe MR (60)	9.6% 13.3%	30 days	ns	21.2% 30.2%	1 year	0.068	NR
Di Mario[31]	2013	4571	NR	Moderate/severe (950)	1.45 (1.08–1.93)	In-hospital	0.010	N/A	–	N/A	NR
Sabate'[30]	2013	1416	NR	Mild (565) Moderate/severe (55)	N/A	–	NR	N/A	1 year	N/A	1.67 (0.94 to 2.96)
Zahn[27]	2013	1391	NR	Moderate/severe (42)	N/A	–	NR	N/A	1 year	N/A	1.70 (1.19 to 2.42)
Cortes[32]	2016	1110	Secondary MR 29.2%	MR<3 (933) MR≥3 (177)	4.6% 9.0%	In-hospital	0.016	10.2% 35.0%	6 months	<0.001	4.288 (2.852 to 6.447)
Kiramijyan[33]	2016	589	NR	None/mild (521) Moderate/severe (68)	6.5% 14.7%	30 days	0.016	20.0% 22.1%	1 year	0.685	NR

N/A, not available; NR, not reported; ns, not significant; MR, mitral regurgitation; TAVR, transcatheter aortic valve replacement.
*Significant MR and late mortality.

Table 3 Factors related to a decrease/increase in MR severity after aortic valve interventions (either surgical and percutaneous)

Factors related to decrease in MR severity	Factors related to increase in MR severity
Reduced LV systolic pressure (haemodynamic success of SAVR/TAVR) Reversal of LV remodelling	Patient-prosthesis mismatch (persistently high LV pressure) Continued LV remodelling
Absence of mitral annular calcification	Dilated mitral annulus
Secondary mitral regurgitation	Primary mitral regurgitation
LVEDD≥50 mm	Dilated left atrium
LVESD≥36 mm	Dilated mitral annulus
Absence of atrial fibrillation	Self-expanding valve with deep implant
Absence of pulmonary hypertension	Moderate or greater aortic regurgitation
Mean gradient ≥40 mm Hg	
Valve type (balloon-expandable)	
Previous coronary artery disease or myocardial infarction	

LVEDD, left ventricle end-diastolic diameter; LVESD, left ventricle end-systolic diameter; SAVR, surgical aortic valve replacement; TAVR, transcatheter aortic valve replacement.

(table 3). Among these are atrial fibrillation, LV dyssynchrony to to new left bundle branch block or right ventricular pacing or ischaemic wall motion abnormalities.[39] It has been reported that self-expandable valves have a higher incidence of residual AR mainly due to paravalvular leaks, particularly with deep implants that may result in the valve cage impinging on the anterior mitral leaflet.[40] Severe MR due to a flail mitral leaflet would not be expected to improve after SAVR or TAVR, and likely requires either double valve replacement, or TAVR following by minimally invasive or transcatheter mitral valve repair. The presence of patient-prosthesis mismatch, which is overall more common with SAVR than TAVR, might limit improvement in MR severity due to persistently high LV pressure. No studies have directly compared SAVR and TAVR in terms of MR reduction related to the presence of patient-prosthesis mismatch.

Is it necessary to intervene on mitral valve at the time of aortic valve intervention or should MR be left alone?

Based on the existing literature, which is fraught with limitations, there is still no clear pathway to follow when dealing with patients with concomitant AS and MR. However, a common sense approach based on symptoms, classification of AS severity, mechanism and severity of MR is proposed (figure 2). In

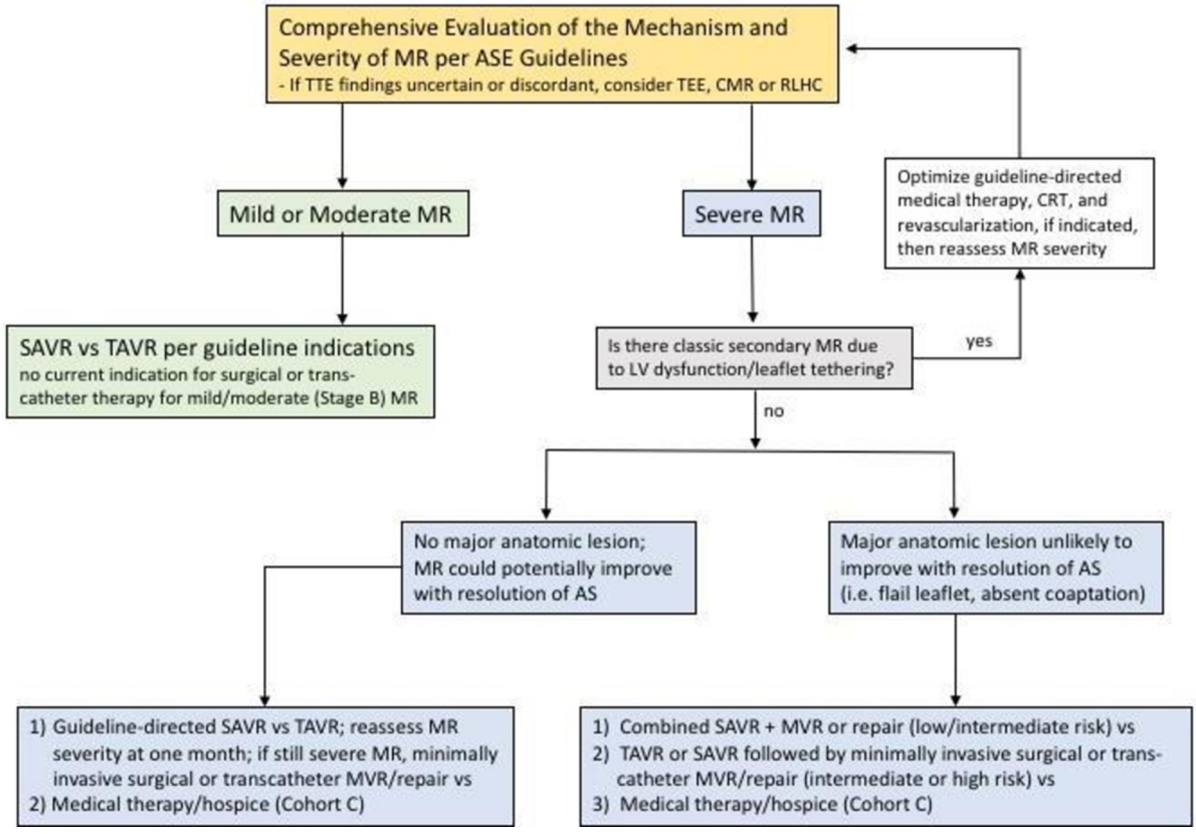

Figure 2 Proposed algorithm for the evaluation and management of patients with severe aortic stenosis (AS) and concomitant mitral regurgitation (MR). ASE, American Society of Echocardiography; CMR, Cine Magnetic Resonance; CRT, Cardiac resynchronization therapy; LV, left ventricular; MVR, mitral valve replacement; RHLC, Right and left heart catheterisation; SAVR, surgical aortic valve replacement; TAVR, transcatheter aortic valve replacement; TEE, Transesophageal Echocardiography.

symptomatic patients with severe AS, a careful evaluation of the mechanism and severity of MR should be performed according to current guideline recommendations. If mild or moderate MR (stage B) is present, SAVR or TAVR can be performed per clinical indications and MR should not be treated as there is no indication for intervention for stage B MR. If MR is severe and secondary to LV dysfunction, guideline-directed medical therapy for HF/LV dysfunction should be optimally titrated, along with cardiac resynchronisation and/or revascularisation, if indicated. MR severity should then be re-evaluated. If severe MR persists despite optimisation of therapy, or there is a major anatomic defect, such as a flail leaflet, that would preclude improvement of MR by valve replacement alone. Such patients could be considered for either a surgical double valve replacement, or a staged approach with SAVR or TAVR, followed by minimally invasive or transcatheter mitral valve intervention, depending on risk stratification, patient preference and other clinical factors. If no major anatomic defect is present, SAVR or TAVR should be performed and MR severity re-evaluated afterwards. If MR improves to mild or moderate, it can generally be left alone or managed medically. Persistence of severe MR requires careful reassessment. If the patient is asymptomatic, intervention may not be required. Resolution of AS may allow uptitration of guideline-directed medical therapy in patients with secondary MR after successful SAVR or TAVR. Symptomatic severe MR that persists or develops after SAVR or TAVR can be treated a minimally invasive surgical valve repair or replacement, depending on the valve pathology. It is also possible to use transcatheter approaches, particularly in patients at high risk for surgery. There have been several reports of transcatheter edge-to-edge repair of MR after TAVR, but all are observational studies with significant methodological limitations. Reported mortality rates up to 1 year have been high, but this may be due to patient selection. Randomised controlled trials are needed to assess the real benefit of an additional mitral valve procedure over optimised medical therapy in patients with residual severe MR after SAVR or TAVR.

CONCLUSIONS

Severe AS and MR often coexist. Despite several observational studies and a post hoc analysis of PARTNER trial data, it has not been convincingly shown that MR is an independent predictor of adverse outcomes in AS. Although MR severity can either improve or worsen after SAVR or TAVR, it is difficult to accurately predict what might happen in an individual patient. Given the lack of high-quality data on mixed and multiple valve diseases and the virtual absence of randomised clinical trials on this topic, evidence-based recommendations for double valve intervention cannot be made. For now, careful patient evaluation and clinical judgement must be used to identify those who might benefit from a double valve intervention versus a staged procedure in which mitral valve intervention is deferred until re-evaluation of MR severity after SAVR or TAVR.

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Notes