




Transcatheter aortic valve replacement in patients with severe aortic stenosis and heart failure

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Abstract

Severe aortic stenosis (AS) and heart failure (HF) represent an important and high-risk group of patients who are often referred for transcatheter aortic valve replacement (TAVR) due to high risk for surgical intervention. Thus far, randomized controlled trials have shown comparable outcomes between TAVR and surgical aortic valve replacement in patients with severe AS and heart failure with reduced ejection fraction. In the current review, we will discuss (1) the pathophysiology of HF in patients with severe AS, (2) role of imaging modalities in management, (3) role of biomarkers of HF on prognosis, (4) impact of other valvular heart diseases, (5) evidence from the contemporary trials on the role of TAVR in patients with severe AS and HF, and (6) future directions and research.

Keywords Aortic stenosis · Valvular heart disease · Heart failure

Introduction

Aortic stenosis (AS) is the most common valvular heart disease among western population, mainly among individuals older than 60 years of age [1]. The overall prevalence of severe AS in adults > 75 years of age is about 3.4% [2]. The natural history of AS is characterized by years to decades of slow progression, followed by rapid clinical deterioration with high morbidity and mortality. In symptomatic severe AS, mortality approaches > 50% at 2 years, in absence of aortic valve replacement [3]. The late stage of severe aortic stenosis invariably involves development of heart failure (HF). Transcatheter aortic valve replacement (TAVR) has revolutionized the treatment of severe AS and is currently considered the standard of care for management of severe AS in patients who are at prohibitive, or high risk for surgical aortic valve replacement (SAVR) and an alternative to SAVR in intermediate-risk patients. Furthermore, TAVR is becoming a front-line therapy in patients with severe AS and HF since the majority of such

patients possess high surgical risk. In the current review, we will discuss (1) the pathophysiology of HF in patients with severe AS, (2) role of imaging modalities in management, (3) role of biomarkers of HF on prognosis, (4) impact of other valvular heart diseases, (5) evidence from the contemporary trials on the role of TAVR in patients with severe AS and HF, and (6) future directions and research.

Pathophysiology of HF in patients with severe AS

AS results in reduction in stroke volume and increase in left ventricle (LV) pressure. As the stenosis progresses, the pressure gradient across the aortic valve during ejection increases. The magnitude of the trans-valvular pressure gradient is determined by the severity of stenosis and the flow rate across the valve. The pressure overload is initially compensated by the development of concentric hypertrophy to maintain normal wall stress, preserving systolic function. However, the degree of hypertrophy is only weakly related to the severity of valve obstruction [4, 5]. Moreover, the hypertrophic response is modulated by multiple other contributors of increased afterload such as hypertension and increased arterial stiffness, which is commonly found in this patient population due to the association with advanced age, atherosclerosis, and diabetes.

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Progression of hypertrophy leads to a non-compliant stiff LV with reduction in the diastolic function and elevation of LV end-diastolic pressure. Several physiological, pathological, and genetic factors modulate the degree of hypertrophy [6, 7]. Increased afterload and LV hypertrophy increase myocardial oxygen demand in severe AS. In some patients, hypertrophy fails to compensate for the increased afterload resulting in reduction in cardiac output and manifesting clinically as HF. In addition, other structural changes such as left atrial enlargement due to elevated LV filling pressures, mitral annular calcification, and/or mitral regurgitation ensues. Alterations in coronary blood flow reserve and impaired subendocardial blood flow are found due to increased hypertrophy and elevated diastolic filling pressures. The transition from adaptive changes such as hypertrophy to LV dysfunction and cardiac damage, in general, marks the tipping point that heralds a rapid trajectory of symptoms, adverse events, and a poor prognosis. Recently, a new staging classification has been proposed based on the extent of anatomical and functional cardiac damage associated with AS (Fig. 1) [8].

As per current guidelines, ‘classical’ low-flow low-gradient AS is defined as an aortic valve area (AVA) $< 1.0 \text{ cm}^2$, a mean gradient $< 40 \text{ mmHg}$, and an LV ejection fraction (LVEF) $< 50\%$. In these patients, the low-flow state is predominantly due to LV systolic dysfunction, which may be related to the presence of severe AS and ensuing LV afterload mismatch and/or to the presence of concomitant ischemic cardiomyopathy. The main diagnostic challenge in patients with low-gradient severe AS with low LVEF is to distinguish true-severe from pseudo-severe AS. In the former, elevated gradients due to dobutamine not only signify true nature of AS but also reflect significant myocardial reserve which has been associated with favorable prognosis [9]. Although the transvalvular pressure gradient is highly flow-dependent, a low-flow state does not necessarily imply the presence of low gradient and some patients with severe AS may have low flow and still a high gradient (mean gradient $> 40 \text{ mmHg}$). Moreover, patients with same degree of AS and systolic HF have gradients that can range from high gradients to low flow gradients. The pathophysiological basis for such hemodynamic variations is not completely understood. However, in patients with AS with high-gradient physiology, usually the valve constitutes the primary problem whereas low-gradient AS represents a systemic disease with valvular, vascular, and myocardial components, resulting in a slower progression of transvalvular gradient, but worse prognosis [10].

Multimodality imaging in assessment of left ventricle function in aortic stenosis

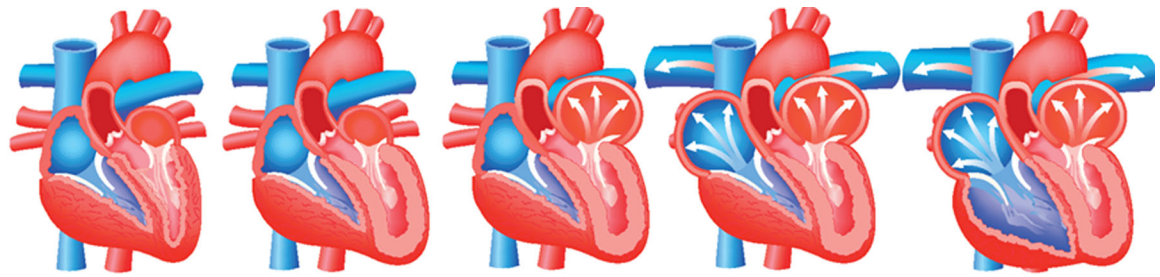
An accurate assessment of LV function is warranted in all patients with AS. The identification of early signs of

ventricular dysfunction is particularly important in asymptomatic patients with severe AS.

Echocardiography remains the initial imaging modality for the diagnosis of AS and assessment of LVEF. Echocardiographic evaluation should include aortic valve morphology, cause, and severity of AS (Doppler assessment of left ventricular outflow tract and valve gradient), LV function (including stroke volume, LVEF, and diastolic function), left atrial pressure, and pulmonary arterial pressure. Systolic blood pressure should be optimized for accurate assessment of hemodynamic parameters. Often overlooked, hypertension may contribute to increase LV afterload and may interfere with the Doppler assessment of AS [11]. Nitroprusside challenge test has been shown to reclassify 25% of low-gradient severe AS to moderate AS [12]. Severe AS is associated with an abnormal LV remodeling pattern manifested as altered LV mass index and relative wall thickness. 3D echocardiography not only allows for better estimation of AS severity but also permits accurate measurement of LV stroke volume and EF.

Stress echocardiography is useful to unmask symptoms, confirm stenosis severity, and to identify patients at high risk of cardiovascular events. In patients with reduced LVEF, a low-dose (up to $20 \mu\text{g/kg/min}$) dobutamine stress echocardiography is useful to differentiate true- versus pseudo-severe AS. However, in patients with inadequate increase in stroke volume ($< 20\%$) and no significant changes in mean gradient and aortic valve area (AVA), the severity of AS remains indeterminate [13]. An absence of increase in stroke volume with dobutamine stress echocardiography suggests inadequate LV contractile reserve and has been associated with worse prognosis after SAVR [14]. Interestingly, the utility of contractile reserve has not been found in patients undergoing TAVR. In a recent study from the TOPAS-TAVI registry involving 287 patients with symptomatic low-flow, low-gradient severe AS who had an LVEF $\leq 40\%$, there was no difference in 1-year mortality between patients with versus without contractile reserve. Moreover, contractile reserve was also not associated with post-procedure improvement of LVEF in this cohort [15].

Strain imaging with speckle tracking echocardiography has emerged as a useful test to assess LV myocardial deformation and LV contractility. In AS, LVEF may remain preserved for a long time despite reduced myocardial contractility owing to preload reserve [16] or changes in LV geometry [17]. Global longitudinal strain can detect latent LV systolic dysfunction which can be useful to identify high-risk cohorts. Global longitudinal strain has been shown to be associated with severity of AS [18], systolic and diastolic hemodynamic indices [19], extent of myocardial fibrosis (scarring) assessed with cardiac magnetic resonance imaging [20], and cardiovascular or all-cause mortality [21, 22]. Moreover, stress strain imaging during dobutamine or exercise echocardiography may provide incremental prognostic value beyond resting strain measures [21, 23].



Stages/Criteria	Stage 0	Stage 1	Stage 2	Stage 3	Stage 4
	No Cardiac Damage	LV Damage	LA or Mitral Damage	Pulmonary Vasculature or Tricuspid Damage	RV Damage
Echocardiogram		Increased LV Mass Index >115 g/m ² (Male) >95 g/m ² (Female)	Indexed left atrial volume >34 mL/m ²	Systolic Pulmonary hypertension ≥60 mmHg	Moderate-Severe right ventricular dysfunction
		E/e' >14	Moderate-Severe mitral regurgitation	Moderate-Severe tricuspid regurgitation	
		LV Ejection Fraction <50%	Atrial Fibrillation		

Fig. 1 Staging classification of aortic stenosis based on the extent of cardiac damage. Adapted from Genereux P et al. Staging classification of aortic stenosis based on the extent of cardiac damage. *Eur Heart J*. 2017

Cardiac magnetic resonance imaging not only provides accurate assessment of stroke volume and LVEF but can also detect myocardial replacement fibrosis in patients with severe AS. Fibrosis patterns such as mid wall and infarct-like scarring (subendocardial or transmural) were associated with an eight-fold and six-fold increase in all-cause mortality, respectively [24]. Myocardial fibrosis is a marker of more advanced structural damage; however, further work is required before magnetic resonance imaging is recommended routinely in these patients.

Biomarkers in AS and HF

Biomarkers can play an important role in risk stratification of asymptomatic patients. Both B-type natriuretic peptide (BNP) and NT-proBNP are released in response to ventricular and atrial stretch and their diagnostic and prognostic value in patients with HF is well established. Furthermore, BNP is the only biomarker that has been acknowledged as a prognostic marker in patients with AS. The European Society Cardiology/European Association for Cardio-Thoracic Surgery guidelines recommend that AVR may be considered in patients with asymptomatic severe AS and markedly elevated levels of natriuretic peptides in the absence of an alternative explanation (class IIb) [25]. Multiple studies have shown strong association of BNP and NT-proBNP with symptoms, severity of AS, and post-procedure outcomes. A report from the PARTNER trial involving 1097 patients who underwent transfemoral TAVR showed that baseline BNP as well as elevated 30-day BNP was associated with increased mortality at 1 year [26]. Table 1 lists major reports that have primarily studied the association of BNP and/or NT-proBNP

with outcomes in patients who underwent TAVR [26–33]. Baseline troponin levels have also been shown to be associated with worse outcomes in AS, irrespective of management strategies [34, 35]. Several other inflammatory biomarkers have been studied; however, majority are still in investigational stage and lack any conclusive evidence for additional value.

Impact of other valvular heart diseases

Aortic regurgitation can coexist with severe AS and causes combined pressure and volume overload on the LV. The combination also portends worse outcomes compared to isolated severe AS [36]; however, prospective studies have shown similar 30-day and 2-year outcomes in patients undergoing TAVR for mixed aortic valve disease versus isolated severe AS [37]. Mitral regurgitation (MR) is commonly associated with severe AS. In patients with severe AS and LV dysfunction, the etiology of MR can vary from primary to mixed etiology. Functional MR can be a maladaptive consequence of severe AS and may be a marker of underlying LV dysfunction [38]. In such patients, LVEF can be overestimated since MR enhances ejection fraction and can mask subclinical myocardial dysfunction [39]. Significant (moderate-to-severe) MR is found to be present in about 15% of patients undergoing TAVR [40]. Severe MR is recognized as an independent predictor of short- and long-term survival in patients undergoing TAVR. In a meta-analysis of eight prospective studies of patients undergoing TAVR, moderate-to-severe MR was associated with 1.5-fold increase in 30-day mortality and 1.3-fold increase in 1-year mortality [41]. The impact on MR following TAVR is controversial and not well defined. In this meta-analysis, about one-quarter of patients had improvement in

Table 1 Studies evaluating the prognostic significance of B-type natriuretic peptide in patients undergoing TAVR

Study	Year	Patients	Study participants	Result summary
Kefer et al.	2010	58	Severe AS at high-risk (logistic EuroSCORE > 20% or STS score > 10%) or had a contra-indication for surgery	BNP levels (baseline value and change at 24 h) were independent predictors of 30-day survival
Lopez-Otero et al.	2013	85	Severe AS who were non-operable or surgically high-risk patients (Logistic EuroSCORE > 20%)	Pro-BNP levels 24-h prior to the procedure is predictive of 30-day and long-term mortality
Gotzmann et al.	2014	226	Severe AS at high surgical risk	BNP > 475 pg/mL was predictive of long-term all-cause and cardiovascular mortality. BNP level > 328 pg/mL at 30 days post TAVR was associated with all-cause mortality
O'Sullivan et al.	2015	340	Severe AS who were non-operable or surgically high-risk patients	High BNP \geq 596 pg/mL had a significantly higher incidence of 30-day all-cause and cardiac mortality, and cerebrovascular events
O'Neill et al.	2015	1097	Severe AS patients from cohort A and B of PARTNER trial	Increase in BNP at 30 days post TAVR was associated with 1-year mortality
Koskinas et al.	2015		Severe AS	High baseline BNP (\geq 591 pg/mL) had increased risk of 2-year all-cause and cardiovascular mortality
Abramowitz et al.	2015	780	Severe AS	High baseline BNP (\geq 453 pg/mL) was associated with 30-day and 3-year all-cause mortality
Mizutani et al.	2017	1094	Severe AS from OCEAN-TAVI registry	BNP level at discharge > 202 pg/mL had best risk stratification and was associated with 2-year all-cause mortality and heart failure hospitalization

MR, whereas in three-quarter of patients, MR was either unchanged (in majority) or worsened.

Functional or 'secondary' tricuspid regurgitation is frequently seen in late stages of severe AS secondary to elevated pulmonary pressure leading to right ventricular dilation and distortion of the tricuspid valvular apparatus [42]. Tricuspid regurgitation is also a marker of advanced HF and is associated with poor outcomes in patients undergoing TAVR. In PARTNER II trial analysis involving 524 TAVR patients, 27% of patients had moderate or severe TR at baseline, with only ~ 1/3rd showing improvement in TR at 1-year follow-up. In contrast, among 1-year survivors with no or mild TR at baseline, about 1/5th had progression to moderate or severe TR at 1-year follow-up. Severe TR was associated with 3.2-fold and moderate TR was associated with 1.6-fold increase in 1-year mortality [43]. In the TOPAS (true or pseudo-severe aortic stenosis) registry among the 211 patients with low-flow, low-gradient severe AS and LVEF < 40%, moderate/severe TR was associated with 1.9-fold increase in 30-day all-cause and cardiovascular mortality [44].

TAVR vs SAVR in HF

As outlined earlier, overt or subclinical HF is associated with increased mortality and morbidity in patients with severe AS

and increases the risk of peri-operative mortality in patients undergoing SAVR. Patients with LV dysfunction, in combination with advanced age and other co-morbidities which accompany HF, have high Society of Thoracic Surgeons (STS) risk and European System for Cardiac Operative Risk Evaluation (EuroSCORE) scores, predicting high mortality and morbidity with SAVR. TAVR has revolutionized the management of severe AS with comparable outcomes to SAVR in intermediate-, high-, and prohibitive-risk patients. However, TAVR in patients with HF with reduced LVEF needs closer scrutiny.

Randomized controlled trial data

Randomized trials conducted thus far have enrolled a substantial proportion of patients with severe AS and reduced LVEF (Fig. 2a). The pivotal PARTNER trial cohort A compared the efficacy of TAVR in high-risk patients with severe AS. A dedicated analysis according to LV dysfunction groups provided valuable insights [45]. Of the 203 patients with LVEF \leq 50%, all-cause mortality and cardiac mortality were comparable between TAVR and SAVR at 30 days, 1 year, and 2 years. On 1-year follow-up, in patients with LV dysfunction, mean LVEF increased from 36 ± 9 to $49 \pm 11\%$ ($p < 0.0001$) after TAVR and from 38 ± 8 to $50 \pm 11\%$ after SAVR ($p < 0.0001$). Failure to improve LVEF by 30 days was associated

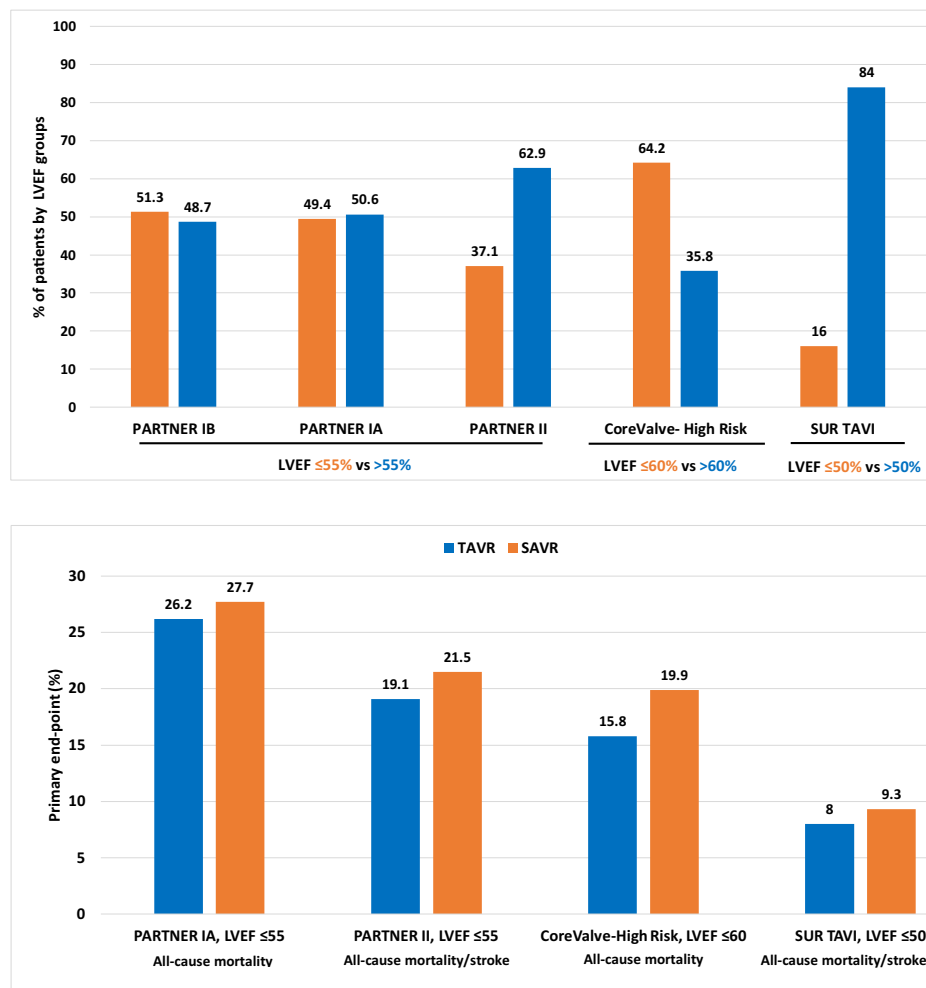


Fig. 2 **a** The proportion of patients with reduced and preserved left ventricular ejection in major TAVR trials, as defined in individual studies. **b** Comparison of primary end-point between TAVR vs SAVR in patients with reduced left ventricular ejection fraction among major trials

with poor 1-year all-cause and cardiac mortality after TAVR, but not SAVR [45].

Subgroup analysis of the US CoreValve trial using a self-expanding transcatheter aortic valve bioprosthesis in high-risk severe AS patients showed similar findings [46]. The primary outcome of all-cause mortality was similar after TAVR vs SAVR in patients with LVEF $\leq 60\%$ [46]. Thus far, in patients with reduced EF in all the randomized trials, TAVR has shown comparable outcomes to SAVR for the primary end-point of all-cause mortality or composite of all-cause mortality and stroke (Fig. 2b).

Registry data

Several registry studies have evaluated the efficacy of TAVR in patients with HF and reduced ejection fraction. In a study of 162 patients with LVEF $< 35\%$ from the Italian National Institute of Health Observational Multicenter registry, there was no significant difference between TAVR and SAVR for 30-day mortality and incidence of periprocedural acute

myocardial infarction, stroke, and renal dysfunction [47]. However, TAVR was associated with significantly higher postprocedural permanent pacemaker implantation while more periprocedural transfusions were noted in SAVR [47]. Using data from the STS/Transcatheter Valve Therapy Registry (TVT) Registry, Brennan et al. analyzed 9464 propensity-matched intermediate- and high-risk patients who underwent TAVR or SAVR [48]. In the overall cohort, there was no difference in 1-year mortality and stroke between the two modalities. Subgroup analysis by LVEF showed similar outcomes among LVEF groups of < 35 , 35 to 49, and $\geq 50\%$ [48].

TAVR in severe AS and HF

Patients with severe AS and HF are being increasingly managed with TAVR. According to the recent TVT Registry report using data from 42,988 procedures from 2011 to 2015, patients with LVEF $< 45\%$ constitute 25% of all TAVR cases [49]. In addition to ejection fraction, several other

Fig. 3 Appropriate Use Criteria for the treatment of patients with severe symptomatic aortic stenosis and mitral valve disease (a) or tricuspid valve disease (b). Adapted from Bonow et al., ACC/AATS/AHA/ASE/EACTS/HVS/SCA/SCAI/SCCT/SCMR/STS 2017 Appropriate Use Criteria for the treatment of patients with severe aortic stenosis, JACC, 2017. A = appropriate; AS = aortic stenosis; BAV = balloon aortic valvuloplasty; LVOT = left ventricular outflow tract; M = may be appropriate; MBV = mitral balloon valvuloplasty; MR = mitral regurgitation; MS = mitral stenosis; PBMV = percutaneous balloon mitral valvuloplasty; R = rarely appropriate; SAVR = surgical aortic valve replacement; TAVR = transcatheter aortic valve replacement; TR = tricuspid regurgitation

a

Indication	Appropriate Use Median Score (1-9)					
	BAV (as Bridge to Decision)	TAVR alone	TAVR + PBMV	TAVR + MitraClip	SAVR alone	SAVR + Other Valve or Ascending Aortic Surgery or Myectomy
Symptomatic AS and Mitral Valve Disease						
<ul style="list-style-type: none"> Severe symptomatic AS Severe primary MR High surgical risk 	M (4)	M (4)		M (6)	R (3)	A (7)
<ul style="list-style-type: none"> Severe symptomatic AS Severe primary MR Intermediate surgical risk 	R (2)	R (3)		R (3)	R (3)	A (8)
<ul style="list-style-type: none"> Severe symptomatic AS Severe primary MR Low surgical risk 	R (1)	R (1)		R (2)	R (2)	A (9)
<ul style="list-style-type: none"> Severe symptomatic AS Severe secondary MR High surgical risk 	M (4)	M (5)		M (5)	M (4)	A (7)
<ul style="list-style-type: none"> Severe symptomatic AS Severe secondary MR Intermediate surgical risk 	R (3)	M (4)		M (4)	R (3)	A (8)
<ul style="list-style-type: none"> Severe symptomatic AS Severe secondary MR Low surgical risk 	R (1)	R (1)		R (2)	R (3)	A (9)
<ul style="list-style-type: none"> Severe symptomatic AS Severe rheumatic MS (no absolute contraindications to MBV) High surgical risk 	M (4)	M (4)	A (7)		R (3)	A (7)
<ul style="list-style-type: none"> Severe symptomatic AS Severe calcific MS or severe rheumatic MS (with absolute contraindications to MBV) with extensive mitral annular calcification High surgical risk 	M (4)	M (5)	R (2)		R (3)	A (7)

b

Indication	Appropriate Use Median Score (1-9)					
	BAV (as Bridge to Decision)	TAVR alone	TAVR + PBMV	TAVR + MitraClip	SAVR alone	SAVR + Other Valve or Ascending Aortic Surgery or Myectomy
Symptomatic AS and Tricuspid Valve Disease						
<ul style="list-style-type: none"> Severe symptomatic AS Severe secondary TR Dilated right ventricle and/or tricuspid valve annulus ≥40 mm Minimal to no right ventricular dysfunction Minimal pulmonary hypertension Intermediate surgical risk 	R (2)	M (5)			R (3)	A (8)
<ul style="list-style-type: none"> Severe symptomatic AS Severe secondary TR Dilated right ventricle and/or tricuspid valve annulus ≥40 mm Moderate to severe right ventricular dysfunction Minimal pulmonary hypertension Intermediate surgical risk 	R (2)	M (5)			R (3)	A (7)
<ul style="list-style-type: none"> Severe symptomatic AS Severe secondary TR Dilated right ventricle and/or tricuspid valve annulus ≥40 mm Moderate to severe right ventricular dysfunction Severe pulmonary hypertension High surgical risk 	M (4)	A (7)			R (2)	M (5)

A = Appropriate; AS = aortic stenosis; BAV = balloon aortic valvuloplasty; M = May Be Appropriate; MBV = mitral balloon valvuloplasty; MR = mitral regurgitation; MS = mitral stenosis; PBMV = percutaneous balloon mitral valvuloplasty; R = Rarely Appropriate; SAVR = surgical aortic valve replacement; TAVR = transcatheter aortic valve replacement; TR = tricuspid regurgitation

hemodynamic indices are evaluated in patients undergoing TAVR to aid in prognosis and risk stratification. Analysis of 11,292 patients from the TVT Registry showed that severe LV dysfunction (LVEF < 30%) was associated with higher rates of mortality (29.3 vs. 21.9%, *p* < 0.001) and recurrent HF (19.3 vs. 12.8%, *p* < 0.001) at 1 year compared with preserved LVEF [50]. However, after adjustment for clinical factors, low aortic valve gradient was found to be associated with worse outcomes, whereas the effect of LVEF was no longer significant [50]. In a recent single-center study of 340 patients with TAVR, low stroke volume index ≤ 35 mL/m² was associated with increased 1-year mortality (21.9 vs 7.4%; *p* = 0.0002) and HF (20.8 vs 5.3%; *p* = 0.011) [51]. After adjustment for

clinical factors, patients with low flow had increased mortality and HF, whereas neither low gradient nor low LVEF were associated with worse outcomes [51]. These studies underline the importance of flow-gradient parameters, particularly in patients with severe AS and HF. Low flow in patients with HF can be secondary to LV contractile dysfunction; however, it may also be due to high afterload with restrictive physiology, pronounced concentric hypertrophy, and reduced LV compliance and filling.

Valve-in-valve TAVR has also emerged as an alternative, less invasive treatment for patients with degenerated bioprostheses who are at prohibitive or high risk for repeat surgery. A significant proportion of these patients have LV dysfunction and HF. In the prospective, multicenter

PARTNER (Placement of Aortic Transcatheter Valves) 2 valve-in-valve registry of 365 patients (mean STS score $9.1 \pm 4.7\%$), ~22% patients had LVEF < 40% [52]. The valve-in-valve TAVR showed 1-year mortality of 14.4% and low rates of stroke, rehospitalization, and pacemaker implantation. Post-TAVR, core laboratory echocardiographic data showed that the mean LVEF increased from 50.6% at baseline to 54.2% at 1 year [52]. In a prospective, multicenter CoreValve U.S. Expanded Use Study, enrolling 233 patients with symptomatic surgical valve failure (mean STS score $9.0 \pm 6.7\%$), self-expanding TAVR showed 1-year mortality of 14.6% [53]. In this high-risk cohort, almost all patients had congestive HF (97.4%).

TAVR in severe AS and other valve disorders

As discussed earlier, concomitant severe valvular disorders, particularly MR and TR, pose significant challenges in management of severe AS and heart failure. While surgical option has the advantage of correcting MR and/or TR during SAVR, such patients also possess higher peri-operative risks for mortality and morbidity. In patients with severe AS and MR, it is important to differentiate primary from secondary MR since the latter may improve with correction of the AS, whereas the former will not. For instance, a patient with functional MR associated with depressed LV ejection fraction and dilated cardiomyopathy will most likely show an improvement in MR after TAVR, especially in absence of concomitant restrictive physiology and pulmonary arterial hypertension. Several transcatheter mitral valve repair technologies have emerged for treating MR in patients at high or prohibitive surgical risk. If severe MR fails to improve post-TAVR, transcatheter mitral valve repair/replacement may be considered in selected patients. In patients who may likely require concomitant TAVR and transcatheter mitral valve intervention, usually TAVR is performed earlier, although there have been few case reports where combined aortic and mitral interventions were performed in single setting [54]. It is important to note that at the moment, prognostic data of the emerging combined approach are insufficient and conflicting and larger trials are needed before it can be recommended for routine consideration. The recently published Appropriate Use Criteria for the treatment of patients with severe AS provides some guidance on selection of management strategies in patients with severe AS and concomitant valve diseases (Fig. 3) [55].

TAVR in acute HF

Acute HF complicating severe AS represents one of the highest-risk group of patients. A recent report from the Japanese CURRENT AS registry enrolling 3813 consecutive

severe AS patients studied the effect of acute HF on short- and long-term clinical outcomes of severe AS [56]. The 5-year all-cause mortality and HF hospitalization rates in no HF, chronic HF, and acute HF groups were 37.1, 41.8, and 61.8% ($p < 0.001$) and 20.7, 33.8, and 52.3% ($p < 0.001$), respectively. Even in the initial AVR stratum, acute HF was associated with 1.6 times higher risk in 5-year mortality compared to no HF and, 1.5 times compared to chronic HF patients [56].

The utility of balloon aortic valvuloplasty (BAV) in patients with severe AS and HF with severely reduced EF or hemodynamic compromise has been reported and has a class IIb recommendation in the 2017 ACC/AHA guidelines for management of valvular heart diseases [57]. However, sudden aortic insufficiency after BAV can be lethal in patients with decompensated HF, and TAVR can be a more definitive option in such cases with comparable risks. There has been a gradual increase in urgent TAVR procedures. According to recent TVT registry data, of the 42,988 procedures, 3764 (8.8%) were classified as urgent TAVR cases [49]. In a single-center study of 410 consecutive patients undergoing TAVR, 21 (6.6%) had urgent TAVR for acute HF. In this study, 30-day mortality was 3.7% which was comparable to elective or semi-elective TAVR cases [58]. In another single-center study of 771 patients, 27 (3.5%) underwent emergent TAVR for acutely decompensated aortic stenosis with cardiogenic shock. The 30-day mortality was 33.3%, significantly higher than in electively treated patients (7.7%, $p < 0.0001$) [59].

Future directions and research

Available data suggests that TAVR is a favorable alternative to SAVR in patients with severe AS and HF. The TAVR UNLOAD trial is an international, multicenter trial that will evaluate the efficacy and safety of TAVR in patients with moderate AS (defined as mean transaortic gradient ≥ 20 and < 40 mmHg and an aortic valve area > 1.0 and ≤ 1.5 cm² at rest or after dobutamine stress echocardiography) and HF on top of optimal HF therapy [60]. The results of this trial will further our understanding of role of TAVR in patients with AS and HF. TAVR has been used for very specific indications such as new-onset aortic regurgitation in patients with advanced HF treated by left ventricular assist devices [61]. The role of TAVR in patients with paradoxical low-flow, low-gradient severe AS is unclear. These patients have similar outcomes compared to high-gradient severe AS, but worse compared to normal-flow, low-gradient severe AS [62]. Further research on the utility of TAVR in this subset of AS patients is needed.

AS aortic stenosis, BNP B-type natriuretic peptide, TAVR transcatheter aortic valve replacement

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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