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STATE-OF-THE-ART REVIEW

Aortic Valve Disease, Transcatheter Aortic Valve Replacement, and the Heart Failure Patient

A State-of-the-Art Review

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HIGHLIGHTS

- AVR is recommended in severe AS with symptoms or LV dysfunction.
- TAVR enables new insights into the management of AS in diverse patient populations.
- Ongoing trials investigate the benefit of GDMT after TAVR to address residual risk postprocedure.
- Cardiac damage staging identifies TAVR candidates for early AS intervention in vulnerable patients.

ABSTRACT

Concomitant aortic stenosis (AS) in heart failure (HF) is associated with high rates of mortality and morbidity. Current guidelines recommend aortic valve replacement in patients with severe symptomatic AS and asymptomatic AS with left ventricular ejection fraction <50% and during other cardiac surgeries. Transcatheter aortic valve replacement (TAVR) has now allowed for the treatment of severe AS in previously inoperable or high-surgical-risk patients. Leveraging multimodality imaging techniques is increasingly recognized for reinforcing the rationale for intervening early, thus mitigating the risk of ongoing progression to advanced HF. There are increasing data in favor of TAVR in diverse clinical scenarios, particularly asymptomatic AS and moderate AS. Limited information is, however, available regarding the advantages of HF medical therapy before and after intervention. This review aims to comprehensively examine the phenotypes of AS in the context of HF progression, while exploring the evolving role of TAVR in specific populations. (J Am Coll Cardiol HF 2023;11:1070–1083) © 2023 by the American College of Cardiology Foundation.

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The co-occurrence of heart failure (HF) and aortic stenosis (AS) represents a challenging clinical scenario, as these conditions exhibit a bidirectional causal relationship. HF develops in patients with AS due to a combination of increased afterload and compensatory cardiac remodeling, which poses a high risk of mortality. Although cardiac output can be initially maintained despite increased forward impedance, subsequent left ventricular (LV) hypertrophy caused by pressure overload results in impaired diastolic filling and ultimately reduced stroke volume. Conversely, patients with preexisting HF may develop progressive AS. The outcomes of these patients may not be similar to those with isolated valvular disease. Coexistence of coronary artery disease further impacts outcomes.

Advances in cardiac imaging and the broad availability of transcatheter aortic valve replacement (TAVR) technology has ushered in an era of improved outcomes in patients with AS who have previously been deemed either high surgical risk or inoperable. The significance of extravalvular damage in the progression of AS, starting from the initial stages of LV hypertrophy and dysfunction, to left atrial damage, pulmonary hypertension, and eventually right ventricular dysfunction, has raised discussions regarding the optimal management for patients with asymptomatic AS or symptomatic moderate AS, including early aortic valve replacement (AVR) vs medical therapy. We review the contemporary data and ongoing advances in the management of HF patients with AS.

PATIENT SELECTION: IDENTIFYING THE RIGHT TAVR CANDIDATE

CURRENT INDICATIONS OF TAVR. The 2020 ACC/AHA (American College of Cardiology/American Heart Association) guidelines recommend AVR as a Class I indication for patients with severe symptomatic AS and severe asymptomatic AS with left ventricular ejection fraction (LVEF) <50% (**Figure 1**).[1] With significant mortality benefits at 1 year when compared with standard medical therapy including balloon valvuloplasty, TAVR has become a reliable treatment option for patients who were previously deemed inoperable.[1-3] Numerous landmark trials in high-risk patients (mean STS [Society of Thoracic Surgeons] scores ranging from 7% to 11%) and subsequently in intermediate- and low-risk patients (mean STS scores ranging from 2.9% to 5.8%) all showed similar mortality rates between SAVR and TAVR. Notably, in their meta-analysis, Siontis et al[4] showed superiority at 2 years in all-cause mortality and stroke with TAVR when compared with SAVR across all surgical risk groups.

Due to lack of long-term (>7-8 years) data with TAVR in large numbers of low- to intermediate-risk patients, SAVR is still the preferred intervention for patients younger than 65 years of age or those with ≥20-year life expectancy.[1] To address the concern for TAVR valve durability, Pibarot et al[5] showed similar rates of structural valve deterioration at 5 years with third generation SAPIEN 3 balloon-expandible valve (Edwards Lifesciences) when compared with SAVR. Moreover, 8-year follow-up results of NOTION (The Nordic Aortic Valve Intervention Trial) showed higher structural valve deterioration rate with SAVR when compared with TAVR (28.3% vs 13.9%; $P = 0.0017$).[6] Short- to medium-term outcomes of the lower-risk trials (especially with newer-generation TAVR valves) have been promising (PARTNER-3 [Placement of Aortic Transcatheter Valves 3] 2-year data, and recently published 3-year Evolut low-risk data), but the need for extended data including valve-in-valve TAVR and overall durability remains.

CARDIAC DAMAGE STAGING. Current guidelines classify AS based on echocardiographic findings, invasive hemodynamic findings, symptoms, and presence of LV dysfunction. The current criteria for severe AS (a mean gradient >40 mm Hg, maximum aortic jet velocity >4.0 m/s, and aortic valve area <1.0 cm^2) harbor certain limitations. First, these values, used both for echocardiographic and catheterization data, can differ due to the pressure recovery phenomenon. Second, according to the Gorlin formula (when calculated with a normal flow rate), a mean gradient of 40 mm Hg corresponds to an aortic area of 0.8 cm^2, while an aortic valve area of 1 cm^2 leads to a mean gradient between 30 and 35 mm Hg, hence the dilemma when the calculated aortic valve area is between 0.8 and 1.0 cm^2. Third, a Doppler velocity index cut point of 0.25 correlates with a mean gradient of 50 mm Hg and an aortic valve area of 0.8 cm^2. Given the discrepancy between the criteria used to define severe AS and these measures, 0.30 is thought to be a more appropriate cutoff.[7,8] Finally, severely reduced arterial compliance along with uncontrolled hypertension can also alter the hemodynamic measurements during the assessment of AS.[9]

Once deemed severe, AS is further staged based on HF symptoms, LVEF, and surgical risk. Généreux

ABBREVIATIONS AND ACRONYMS

AI = aortic insufficiency

AS = aortic stenosis

AVR = aortic valve replacement

HF = heart failure

LFLG = low flow, low gradient

LV = left ventricular

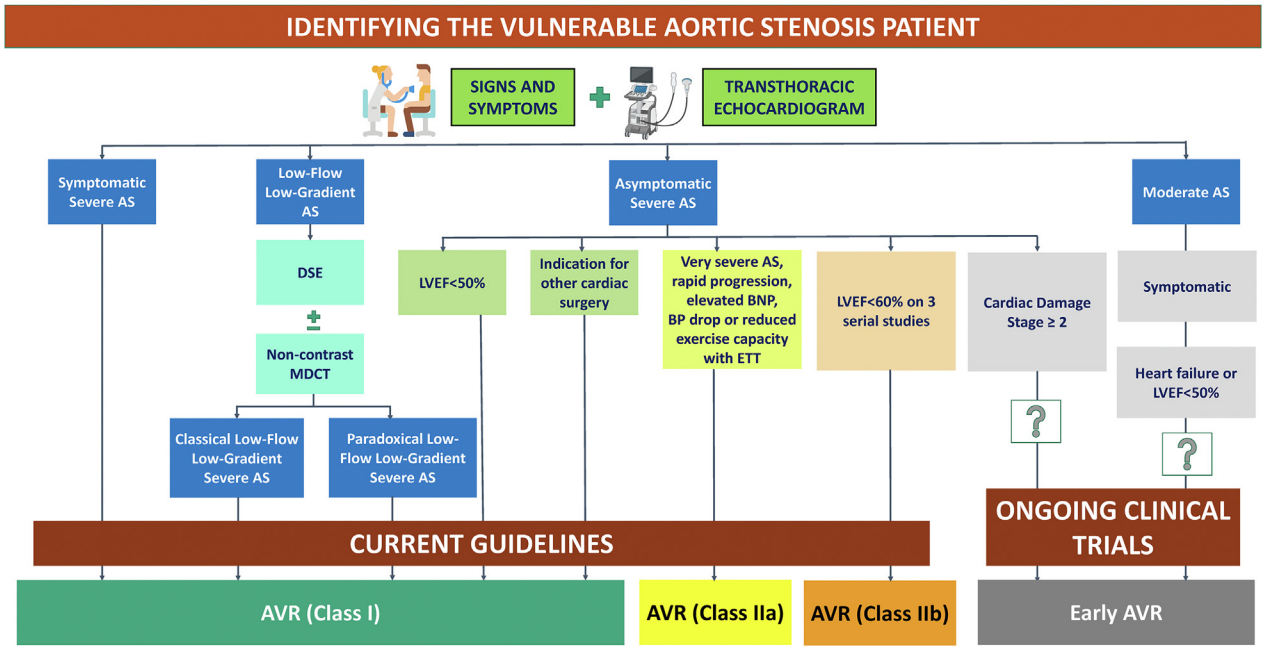
LVEF = left ventricular ejection fraction

SAVR = surgical aortic valve replacement

STS = Society of Thoracic Surgeons

TAVR = transcatheter aortic valve replacement

FIGURE 1 Diagnostic Considerations in Evaluating Heart Failure Patients With AS

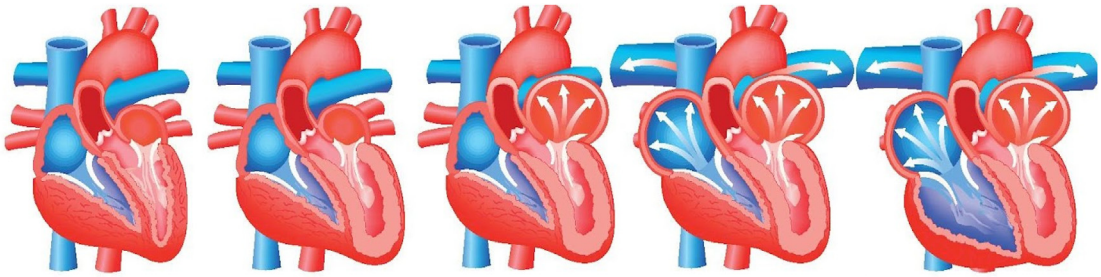


Staging classification of aortic stenosis (AS) based on the extent of cardiac damage. The data for the bar graph were derived from Généreux et al.[10] AVR = aortic valve replacement; BNP = B-type natriuretic peptide; BP = blood pressure; DSE = dobutamine stress echocardiography; ETT = exercise treadmill test; LVEF = left ventricular ejection fraction; MDCT = multidetector computed tomography.

et al[10] classified cardiac damage into 5 stages with a more extensive echocardiography-based evaluation of degrees of cardiac remodeling and evidence of backward failure as reflected by valvular regurgitation, atrial fibrillation, and/or right ventricular dysfunction (Figure 2). Mortality increases by approximately 45% incrementally with each stage of cardiac damage. Furthermore, these stages are independently associated with cardiovascular death and rehospitalization at 1-year follow-up after AVR and is one of the strongest mortality predictors, independent of STS score.[10] Improvement of the baseline stage after TAVR was also associated with substantial improvement in Kansas City Cardiomyopathy Questionnaire Overall Summary Score (+26.8 [95% CI: 24.2-29.4]; $P < 0.0001$) when compared with those without change or with deterioration. Therefore, baseline cardiac damage should be considered in the overall evaluation process. Because 50% of patients in stage 4 remained at the same stage and 28.2% of patients in this stage died 2 years post-TAVR, there is ongoing debate as to whether AVR should be performed earlier in patients with significant cardiac damage despite being asymptomatic or when AS is still in the moderate range.[11,12]

MYOCARDIAL FIBROSIS AS AN INDICATOR OF THE VULNERABLE HF PATIENT WITH AS. Observed in one-third of patients undergoing AVR, the presence of myocardial fibrosis is associated with long-term adverse outcomes and inversely correlates with improvement of LV function and symptoms after AVR. Global longitudinal strain, severe LV hypertrophy, and myocardial fibrosis are indices of increased risk in patients with asymptomatic severe AS.[13] Cardiac magnetic resonance is a reliable method for quantifying myocardial fibrosis, while global longitudinal strain can be used as a widely available alternative for evaluating these patients.[14,15] Multimodality imaging may therefore facilitate identification of patients who would benefit from AVR prior to irreversible structural damage. The ongoing EVOLVED (Early Valve Replacement Guided by Biomarkers of Left Ventricular Decompensation in Asymptomatic Patients with Severe Aortic Stenosis) trial is testing this hypothesis (Table 1).[16]

FIGURE 2 Cardiac Stratification of AS Based on the Extent of Cardiac Damage



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/m² (Male) >95 g/m² (Female)	Indexed left atrial volume >34mL/m²	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		

Staging classification of aortic stenosis based on the extent of cardiac damage. Reproduced with permission from Généreux et al.[10] LA = left atrium; LV = left ventricular; RV = right ventricular; other abbreviation as in Figure 1.

LOW-GRADIENT AS. Low-flow, low-gradient (LFLG) AS is defined as aortic valve area <1.0 cm^2 with a mean gradient <40 mm Hg in the setting of stroke volume index <35 mL/m^2. Eleid et al[17] showed a significant increase in mortality rates with stroke volume index <43 mL/m^2 followed by an incremental impact in mortality that became much more significant with stroke volume index below 35 mL/m^2. Interestingly, sex-specific cutoff values (<32 mL/m^2 and <40 mL/m^2 in women and men, respectively) have been suggested for prognostication.[18] Low flow can also be defined based on the mean transvalvular flow rate with a cutoff of <210 mL/s.[19]

Low-dose dobutamine stress echocardiography can identify HF patients with severe AS, as defined by mean gradient >40 mm Hg with aortic valve area <1 cm^2 at any dobutamine dose.[1] Discordant grading of LFLG AS with low LVEF was reported in 50% of patients in the TOPAS registry. In patients with LFLG with reduced or normal LVEF, aortic valve calcification score assessment with an Agatston score threshold cutoff of 1,300 for women and 2,000 for men is recommended when the diagnosis of severe AS is unclear.[20]

Low flow is an independent risk factor for increased mortality in patients with AS.[21] Whether or not lack of contractile reserve (failure to achieve >20% increase in actual stroke volume during dobutamine stress echocardiography in these patients with LFLG is associated with adverse outcomes remains unclear. In patients with LFLG and LVEF ≤40% who did not demonstrate contractile reserve, SAVR was shown to improve survival when compared with conservative therapy at 5 years (54% vs 13%; $P = 0.001$) despite an operative mortality of 22%.[22] In contrast, the TOPAS-TAVI registry showed favorable outcomes in patients with classical LFLG AS who underwent TAVR, with better survival rates of 96.1% at 30 days and 67.7% at 2-year follow-up. Following TAVR, the mean increase in LVEF was 8.3% and positively correlated with lower baseline LVEF and stroke volume index. Interestingly, no significant association was reported between contractile flow reserve and clinical outcomes.[23]

Differentiation of paradoxical LFLG from moderate AS remains challenging to date. While paradoxical LFLG AS is associated with worse prognosis than severe AS with high gradients, similar outcomes were shown in both groups following TAVR.[24,25] Furthermore, these patients have a greater improvement in stroke volume index along with significant N-terminal pro-B-type natriuretic peptide (NT-proBNP) reduction and symptom relief when compared with high-gradient AS after AVR.[26]

Current guidelines recommend AVR as a Class I indication for classical LFLG AS and paradoxical LFLG

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TABLE 1 Summary of Ongoing Randomized Controlled Trials in AS

AS Category	Randomized Controlled Trial	Research Objective	Inclusion Criteria
Asymptomatic severe AS	EVOLVED	Evaluate the benefit of early AVR in patients with at-risk asymptomatic severe AS based on midmyocardial fibrosis	• Asymptomatic severe AS • Age ≥18 y
Asymptomatic severe AS	EARLY TAVR	Evaluate the safety and effectiveness of the Edwards SAPIEN 3/SAPIEN 3 Ultra THV compared with clinical surveillance in asymptomatic patients with severe, calcific AS	• Asymptomatic severe AS • 65 y of age or older • LVEF ≥50% • STS risk score ≤10
Asymptomatic severe AS	EASY - AS	Determine whether early AVR results in better clinical outcomes and cost-effectiveness than expectant management in asymptomatic patients with severe AS	• Asymptomatic severe AS • Age >18 y • Clinician feels that either ongoing surveillance or early AVR is appropriate • Suitable for AVR
Moderate AS	EXPAND TAVR II Pivotal (NCT05149755)	Obtain safety and effectiveness data to support indication expansion for the Medtronic TAVR System to include patients with moderate, symptomatic AS	• Moderate AS • NYHA functional class ≥II and symptoms of AS • LVEF >20% • HF event; NT-proBNP ≥600 pg/mL; GLS ≤15%; E/e′ ≥14.0
Moderate AS	PROGRESS (NCT04889872)	Establish the safety and effectiveness of the Edwards SAPIEN 3/SAPIEN 3 Ultra Transcatheter Heart Valve in subjects with moderate, calcific aortic stenosis	• Moderate AS • Age ≥65 y • Symptoms or evidence of cardiac damage/dysfunction
Symptomatic severe AS and small aortic annulus	SMART	Generate clinical evidence on valve safety and performance of SE vs BE TAVR in subjects with a small aortic annulus and symptomatic severe native AS	• Symptomatic severe AS • Candidate for TAVR • Predicted risk of operative mortality <15% • Small aortic annulus by MDCT • Appropriate anatomy for both BE and SE TAVR • Anatomy suitable for transfemoral vessel access
Symptomatic severe AS	BEST	Evaluate the impact of THV design (SE vs BE) on the risk of all-cause mortality at 90 d and 1 y	• Symptomatic severe AS • Eligible for both BE and SE TAVR • Feasible via percutaneous transfemoral approach
Symptomatic severe AS (female population)	RHEIA	Evaluate the safety and efficacy of TAVR as compared with SAVR in females with severe symptomatic AS	• Females with severe AS (high- and low-gradient AS) • NYHA functional class ≥II or limited exercise capacity, abnormal BP response, or arrhythmia on ETT • Age ≥18 y
Pharmacotherapy post-TAVR for severe AS	RASTAVI (NCT03201185)	Demonstrate that ramipril after transcatheter aortic valve replacement has benefits in terms of prognosis, cardiovascular events, and ventricular remodeling (MRI)	• Underwent TAVR due to severe AS
Pharmacotherapy post-TAVR for severe AS	DapaTAVI (NCT04696185)	Analyze the benefits of dapagliflozin treatment in patients with severe aortic stenosis discharged after TAVR	• Underwent TAVR due to severe AS • Prior HF admission and 1 of the following: LVEF ≤40% DM GFR 25-75 mL/min/1.73 m^2
Pharmacotherapy in mild or moderate AS	A Multicenter Trial Assessing the Impact of Lp(a) Lowering with Pelacarsen on the Progression of Calcific AS	Evaluate the efficacy and safety of Pelacarsen administered subcutaneously once monthly compared with placebo in slowing the progression of calcific AS	• Male or female >50 y • Lp(a) ≥125 nmol/L • Mild or moderate AS

AS = aortic stenosis; AVR = aortic valve replacement; BE = balloon expandable; BEST = Balloon-Expandable vs Self-Expanding Transcatheter Heart Valve; BP = blood pressure; DapaTAVI = Dapagliflozin After Transcatheter Aortic Valve Implantation; DM = diabetes mellitus; EARLY TAVR = Evaluation of TAVR Compared to Surveillance for Patients with Asymptomatic Severe Aortic Stenosis; EASY - AS = The Early Valve Replacement in Severe Asymptomatic Aortic Stenosis Study; ETT = exercise treadmill test; EVOLVED = Early Valve Replacement Guided by Biomarkers of Left Ventricular Decompensation in Asymptomatic Patients with Severe Aortic Stenosis trial; GFR = glomerular filtration rate; GDMT = guideline-directed medical therapy; GLS = global longitudinal strain; HF = heart failure; Lp(a) = lipoprotein(a); LVEF = left ventricular ejection fraction; MDCT = multidetector computed tomography; MRI = magnetic resonance imaging; NT-proBNP = N-terminal pro–B-type natriuretic peptide; PROGRESS = Management of Moderate Aortic Stenosis by Clinical Surveillance or TAVR; RASTAVI = Renin-angiotensin System Blockade Benefits in Clinical Evolution and Ventricular Remodeling After Transcatheter Aortic Valve Implantation; RHEIA = Randomized Research in Women All Comers With Aortic Stenosis; SE = self-expanding; SAVR = surgical aortic valve replacement; SMART = Small Annuli Randomized to Evolut™ or Sapien™ Trial; STS = Society of Thoracic Surgeons; TAVR = transcatheter aortic valve replacement; THV = transcatheter heart valve.

AS if it is thought to be the underlying cause of symptoms but do not specify the choice of intervention (Figure 1). Classical LFLG AS can be considered as severe AS with HF with reduced ejection fraction, whereas paradoxical LFLG AS can be considered as AS with HF with preserved ejection fraction. Considering higher incidence of other comorbidities in these vulnerable HF patients, TAVR may be a safer option, but further trials comparing outcomes in SAVR with TAVR are needed in this population.

Normal-flow, low-gradient AS with preserved EF is common and represents a heterogeneous group of patients that may present with HF. This phenomenon has now been included in the ESC/EACTS (European Society of Cardiology/European Association for Cardio-Thoracic Surgery) guidelines for the management of valvular heart diseases as a distinct category for the first time. In normal-flow, low-gradient patients, it is crucial to verify the accuracy of measurements; calculate the transvalvular flow rate, as it can lead to low gradients despite normal stroke volume; carefully assess the presence of symptoms; and use other modalities such as dobutamine stress echocardiography and multidetector computed tomography to determine the severity of AS.[27,28] To date, 2 meta-analyses revealed that normal-flow, low-gradient AS is associated with worse outcomes that significantly improved with AVR.[29,30] Considering the heterogeneity of this group along with limited data, a multidisciplinary multiparametric approach is needed to determine the benefit from AVR.

MODERATE AS. Moderate AS is associated with higher mortality risk than no or mild AS but is only marginally lower than severe AS.[31] Patients with HF and LV dysfunction with moderate AS are at higher risk of death when compared with those with normal LVEF (16.5 vs 4.2 per 100 person-years).[32] Moreover, in patients with LV dysfunction, moderate AS was associated with increased mortality and HF hospitalizations.[33] SAVR is currently recommended as a Class IIb indication in patients with moderate AS undergoing cardiac surgery for another indication (Figure 1).[1] In a small subset of patients, TAVR is associated with improved mortality in moderate AS with LV dysfunction, while this benefit is not seen in patients who underwent SAVR.[34] In the light of recent data showing increased mortality with moderate AS especially with factors such as impaired global longitudinal strain, elevated NT-proBNP, and extravalvular cardiac damage leading to worse outcomes, the interest in earlier intervention in this population is growing, especially given the favorable risk profile of TAVR in a wide spectrum of patients.[35-37] The results of ongoing trials will inform our decision making in these patients in the coming years (Table 1).

AORTIC INSUFFICIENCY. In patients between 70 and 83 years of age, approximately 2% have moderate or greater aortic insufficiency (AI).[38] Chronic AI can lead to adverse and, possibly, irreversible LV remodeling due to volume and pressure overload, regardless of symptoms. Cardiac magnetic resonance–based volumetric assessment has helped identify a LV end-systolic volume index of 45 mL/m^2 or greater and aortic regurgitant fraction of ≥32% as risk markers for mortality and incident HF in grade 3 to 4 AI patients with no or minimal symptoms.[39] The current treatment of choice for isolated AI is SAVR. TAVR is infrequently used in patients with isolated AI primarily due to challenges related to valve anchorage in the absence of significant native aortic valve calcification, frequent accompaniment of a dilated aortic root and ascending aorta, and increased stroke volume across the valve in systole. Postprocedural risks include valve malpositioning, embolization, and significant paravalvular leak. HF is common (23 ± 4%) in 10-year follow-up after AI diagnosis and is associated with excess subsequent mortality (10%-20% per year).[40,41] Up to 8% of patients with AI who meet criteria for surgical intervention do not undergo treatment.[42] Hence, there is a need for a feasible and safe transcatheter approach for those with severe AI and have a high-surgical-risk profile. Two dedicated transcatheter valves[43,44] are under investigation for severe AI (Table 1). Currently available TAVR devices have been used off label for the treatment of severe AI. Though a high 30-day all-cause mortality (9.5%) was noted in a recent meta-analysis of 911 patients undergoing TAVR for pure AI, the use of new-generation devices was associated with statistically significant higher success rates and lower rates of postprocedural complications when compared with early-generation devices.[45]

Observational studies have supported TAVR as a therapeutic option for AI after failed bioprosthetic surgical valves.[46] Outcomes of TAVR for isolated AI are overall worse when compared with TAVR for AS.[47] With careful patient selection incorporating preprocedural computed tomography imaging, use of rapid pacing during deployment to reduce stroke volume and valve motion and oversizing the device by 15% to 20%, TAVR with currently available devices may provide satisfactory outcomes in candidates unsuitable for surgery.[38] Randomized controlled trials are needed to establish TAVR as a safe and effective treatment option for isolated AI.

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OTHER DIAGNOSTIC AND THERAPEUTIC CONSIDERATIONS IN HF-AS PATIENTS

NATRIURETIC PEPTIDES. The presence of elevated natriuretic peptides may inform the degree of underlying myocardial stress or damage as it relates to HF. Pressure overload due to AS leads to increased LV wall stress, causing an elevation in natriuretic peptide levels.[48] Studies have shown that natriuretic peptides can be used to predict symptom onset in patients with asymptomatic severe AS.[49] The degree of LV hypertrophy also correlates with natriuretic peptide levels, a 2-fold higher LV mass index coinciding with a 6-fold increase in natriuretic peptide levels.[49] It can also serve as a useful prognostic marker to predict symptom response after TAVR. Low (<800 mg/L) and very high (>10,000 ng/L) NT-proBNP levels are associated with no symptomatic improvement at 1 year after TAVR, suggesting an alternative cause of HF symptoms or irreversible ventricular damage, respectively.[50]

Serial natriuretic peptide measurement may be useful for early detection of the maladaptive transition from compensated LV hypertrophy to LV decompensation.[49] Studies have shown that natriuretic peptides predict mortality in patients with AS before and after AVR. Clavel et al[51] showed that incremental elevations in B-type natriuretic peptide (BNP) ratio (BNP levels adjusted for age-specific normal levels) are inversely related to survival in patients with AS. In a study of 3,391 patients who underwent TAVR, elevated natriuretic peptide levels at discharge, 30 days, and 1 year after TAVR was noted to be independently associated with increased mortality and rehospitalizations.[52] Therefore, natriuretic peptides may serve as a surrogate marker to help identify patients with asymptomatic severe AS, those with moderate AS who may benefit from intervention, and TAVR recipients with paravalvular leak.[35]

BALLOON AORTIC VALVULOPLASTY. Prior to the TAVR era, balloon aortic valvuloplasty was an important tool in the management of AS patients with high to prohibitive risk for surgery. In the light of favorable outcomes of TAVR in these patients, the role of balloon aortic valvuloplasty has evolved.[2,3] Current guidelines recommend balloon aortic valvuloplasty as a bridge to TAVR or SAVR in critically ill patients.[1] In a prospective study, 100 patients with severe AS with a mean STS score of 11.4% who underwent balloon aortic valvuloplasty as a bridge to decision, definitive therapy, or palliation had 6% mortality at 30-day follow-up. Among those who had definitive therapy, the 1-year mortality rate was 11.1%. Notably, in patients who were not a candidate for definitive therapy after balloon aortic valvuloplasty, the mortality rate was 73.7%. Therefore, balloon aortic valvuloplasty may still be a useful tool in optimizing patients with a high-risk profile prior to definitive therapy and help to determine those who may symptomatically improve after TAVR.[53]

SPECIAL HF POPULATIONS WITH AS

CARDIAC AMYLOIDOSIS AND AS. Approximately 1 in 8 patients with AS referred for TAVR have concomitant cardiac amyloidosis.[54] Transthyretin amyloidosis is the most common cardiac amyloidosis associated with AS. Light chain cardiac amyloidosis, caused by light chain accumulation from plasma cell dyscrasia, is rarely seen in patients with AS.[55] A history of carpal tunnel syndrome, lumbar spinal stenosis, and disproportionate HF symptoms and elevated natriuretic peptide levels, along with conduction abnormalities and low voltage disproportionate to LV wall thickness and/or echocardiographic evidence of classic or paradoxical LFLG AS, should raise the suspicion of underlying transthyretin amyloidosis. Dobutamine stress echocardiography, often used to evaluate LFLG AS, may show inconclusive results due to an inability to augment stroke volume caused by underlying cardiomyopathy in transthyretin amyloidosis patients. Alternatively, quantification of aortic valve calcium burden with cardiac computed tomography to assess severity may be considered, though there are reports of subthreshold aortic calcium scores in patients with severe AS and cardiac amyloidosis.[55,56] Outcomes including mortality and functional status are poor after undergoing AVR in patients with AS and cardiac amyloidosis. Small but underpowered studies have suggested that outcomes may be better with TAVR when compared with SAVR. TAVR is both effective for symptom relief and safe in patients with cardiac amyloidosis.[57] Based on our experience, rapid pacing is poorly tolerated by cardiac amyloidosis patients, often resulting in hypotension and a greater need for inotropes or mechanical circulatory support following implantation. Special attention to valve choice and implantation technique can help minimize the need for rapid pacing. Conditions suggesting futility of AVR such as severely depressed LV function, severely reduced global longitudinal strain, restrictive pattern, multiple comorbidities, and frailty should be considered by the heart team.[58] Prevention of conduction and rhythm disorders, maintenance of a higher heart rate, anticoagulation in the presence of atrial arrhythmias,

diuretic use when appropriate, and discontinuation of beta-blockers and calcium-channel blockers are the key components of medical management in patients with cardiac amyloidosis.[55] Screening for cardiac amyloidosis in AS patients with "red flags" of cardiac amyloidosis will facilitate early institution of transthyretin-stabilizing therapy, tafamidis, thus delaying disease progression.

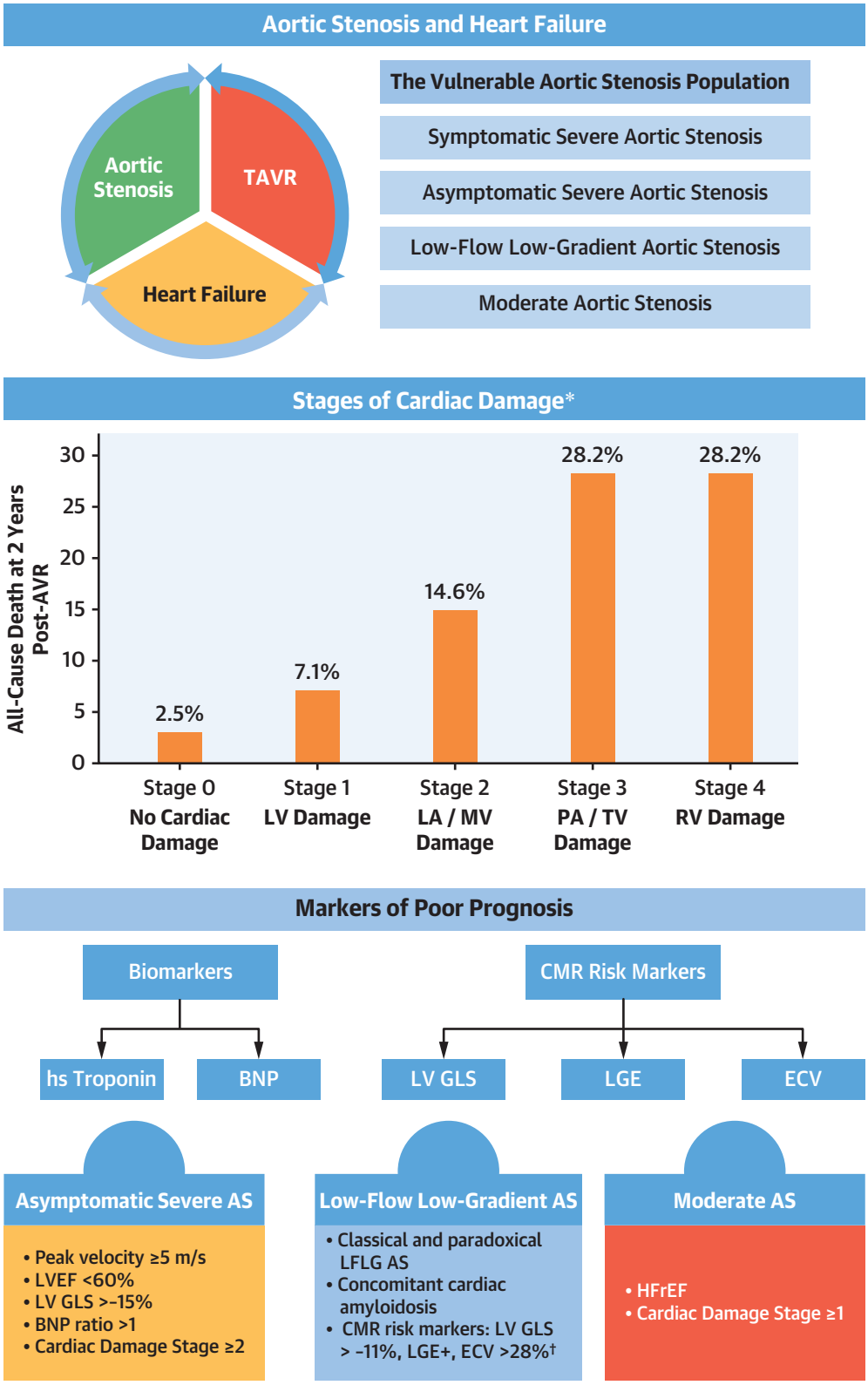
HYPERTROPHIC CARDIOMYOPATHY AND AS. AS with concomitant hypertrophic cardiomyopathy presents a unique challenge in management. TAVR in patients with hypertrophic cardiomyopathy can lead to an abrupt drop in afterload, resulting in dynamic subvalvular outflow obstruction and hemodynamic collapse. DiMeglio et al[59] showed higher occurrence of adverse cardiovascular events, in-hospital mortality, and cardiogenic shock in patients with hypertrophic cardiomyopathy who underwent TAVR when compared with those without hypertrophic cardiomyopathy. Notably, patients who survived the initial cardiogenic shock had favorable outcomes in the long term.[59] Invasive hemodynamic studies may be needed to delineate the severity of AS and degree of dynamic outflow obstruction. Surgical myectomy and SAVR should be primarily considered, as this offers definitive management of both levels of obstruction. In those with high surgical risk, an alternative approach of alcohol septal ablation followed by TAVR after reassessment of gradients in 2 to 3 months is recommended.[60] Our experience suggests that a reasonable approach may be to perform initial combined alcohol septal ablation and balloon aortic valvuloplasty to facilitate LV adaptation to afterload changes, followed by TAVR at a later stage.

BICUSPID AORTIC VALVE STENOSIS. Patients with bicuspid aortic valves with severe AS display marked LV remodeling translating into a higher incidence of postoperative HF admissions after AVR when compared with those with tricuspid aortic valves.[61] Though bicuspid valve stenosis patients have a lower LVEF when compared with those with tricuspid aortic valves prior to AVR, retrospective data suggest that survival outcomes post-AVR are similar in both groups. Identification of patients at risk (higher LV mass, lower LV global longitudinal strain) may help identify those patients who require intervention earlier before LV dysfunction ensues.[61] Bicuspid AS poses a unique technical challenge with respect to TAVR because of heavier calcification, often extending to the LV outflow tract and a noncircular annulus. In those with intermediate and high surgical risk, increased rates of paravalvular leak and stroke have been noted. Observational registry-based data have suggested that low-surgical-risk patients treated for bicuspid vs tricuspid AS with TAVR had no significant difference in mortality or stroke at 1 year. However, in the absence of randomized data, the utility of TAVR in this patient population remains unclear.[62]

TAVR WITH CONCOMITANT VALVULAR HEART DISEASES IN HF-AS PATIENTS. Mitral regurgitation is the most common valvular heart disease seen with HF-AS.[63] Its prevalence varies between 11.5% and 36.8% and is associated with increased mortality after AVR.[64] In a systematic review, approximately 50% of patients with at least moderate mitral regurgitation who underwent TAVR had improvement in mitral regurgitation severity. Functional mitral regurgitation, which accounts for ~50% of individuals with concomitant mitral regurgitation, is reported to improve after TAVR. The factors associated with improvement of mitral regurgitation are LV dysfunction, absence of atrial fibrillation, and pulmonary hypertension. In a registry investigating the outcomes of subsequent mitral valve interventions (predominantly transcatheter edge-to-edge mitral valve repair) in patients who had persistently significant mitral regurgitation after TAVR, 3-year mortality was 29%. Although not statistically significant, staged mitral valve intervention was associated with lower mortality compared with medical therapy (57.5% vs 30.8%; $P = 0.05$).[65,66] Widespread use of TAVR over the past decade without concurrent treatment of pre-existing significant mitral regurgitation raises the potential need for subsequent or simultaneous percutaneous treatment of mitral regurgitation. Concomitant TAVR and percutaneous mitral intervention can be considered in the absence of favorable characteristics such as reduced LVEF, functional mitral regurgitation, absence of atrial fibrillation, or pulmonary hypertension, given lower likelihood of improvement in the severity of mitral regurgitation.[64]

Severe mitral stenosis is an independent risk factor for increased mortality and HF hospitalizations in patients with severe AS. It is reported in 2.7% of patients undergoing TAVR.[67] Treating mitral stenosis first in cases of concomitant AS and mitral stenosis requires caution, as it can result in severe pulmonary edema caused by the sudden increase in preload to an LV with a small cavity and low flow through a stenosed aortic valve.[64] Given the high long-term mortality, percutaneous interventions with or after TAVR can be considered in patients who are not deemed surgical candidates. Mitral balloon valvuloplasty is a

CENTRAL ILLUSTRATION AS, TAVR, and the Heart Failure Patient



Okumus N, et al. J Am Coll Cardiol HF. 2023;11(8):1070–1083.

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feasible option for rheumatic mitral stenosis. However, severe mitral annular calcification is the underlying etiology in the majority of mitral stenosis patients.[64] While case studies and early feasibility studies have reported transcatheter mitral valve implantation, larger studies are still needed.[68]

Significant tricuspid regurgitation is reported in 11% to 27% of patients undergoing TAVR.[64] Généreux et al[11] showed a mortality rate of 28.2% in stage 3 cardiac damage, which includes moderate-to-severe tricuspid regurgitation at the end of a 2-year follow-up period. In a meta-analysis of 9 studies, moderate-to-severe tricuspid regurgitation at baseline was associated with increased mortality after TAVR.[69] Notably, tricuspid regurgitation improved in 15% to 60% of cases after TAVR. The recently published TRILUMINATE Pivotal (Transcatheter Repair for Patients with Tricuspid Regurgitation) trial testing transcatheter edge-to-edge repair of the tricuspid valve showed symptomatic improvement in patients with severe tricuspid regurgitation.[70] Transcatheter repair may be an option for patients with severe tricuspid regurgitation who experience persistent symptoms after TAVR. Ongoing trials on percutaneous tricuspid valve interventions will provide crucial insights into mortality and symptom relief in this area.

CONSIDERATION OF TRANSPLANTATION/LVAD VS AVR IN HF-AS PATIENT. The coexistence of severe LV dysfunction with severe AS may pose a decisional dilemma between AVR vs heart transplantation. There are no one-to-one comparative studies addressing this question. Data suggest that in patients with severe AS, severe LV dysfunction, and coexisting coronary artery disease requiring 3 or more bypass grafts or with a prior history of a myocardial infarction, heart transplantation may be an appropriate consideration.[71] On the contrary, patients with severe AS, severe LV dysfunction, and no coronary artery disease have outcomes equal to or better than heart transplantation, and some of these patients may achieve LV recovery with SAVR.[71]

TAVR FOR AI POST-LVAD IMPLANTATION. In patients with advanced HF receiving LVAD implantation, 15% to 52% may develop AI over time.[72] Simultaneous decompression of the LV along with higher constant pressure above the AV leads to an increased transvalvular gradient, fusion of the commissures, and progressive AI. In patients with preexisting moderate or greater AI, intraoperative concomitant surgical repair is recommended at the time of LVAD implantation.[73] A INTERMACS (Aortic Insufficiency During Contemporary Left Ventricular Assist Device Support: Analysis of the INTERMACS Registry) registry analysis found that moderate to severe AI development in this population is linked to a high risk of deteriorating hemodynamics, rehospitalization, and mortality.[72] Initial management with guideline-directed medical therapy (GDMT) and LVAD speed adjustment may be attempted; however, surgical correction of more than mild AI with AV closure, repair, or bioprosthetic valve replacement may be needed eventually. Data from the National (Nationwide) Inpatient Sample data indicated that compared with SAVR, patients who underwent TAVR after LVAD implantation had significantly lower odds of experiencing in-patient mortality, stroke, transient ischemic attack, myocardial infarction, pacemaker implantation, need for open AV surgery, vascular complications, and cardiac tamponade.[74] The use of TAVR in these patients can be complicated with valve thrombosis, closure, embolization and recurrent cusp fusion.

PREVENTION AND OPTIMAL MEDICAL MANAGEMENT PRE-TAVR

The most frequent cause of hospitalization in the year after TAVR is unequivocally HF despite a significant reduction in hospitalization rates compared with before TAVR.[75] One-year post-TAVR, 39% of patients still experience poor outcomes despite decreasing rates of death and poor quality of life over time.[76] AS can drive and precipitate clinical HF due to cardiac remodeling and dysfunction, which may be irreversible even after AVR and contribute significantly to mortality and morbidity. A meta-analysis of 77,745 patients identified history of diabetes mellitus,

CENTRAL ILLUSTRATION Continued

*Reproduced data are from Généreux et al.[11] †Magnetic resonance imaging are data from Fukui M, Annabi MS, Rosa VEE, et al. Comprehensive myocardial characterization using cardiac magnetic resonance associates with outcomes in low gradient severe aortic stenosis. *Eur Heart J Cardiovasc Imaging*. 2022;24(1):46-58. AS = aortic stenosis; AVR = aortic valve replacement; BNP = B-type natriuretic peptide; CMR = cardiac magnetic resonance; ECV = extracellular volume; GLS = global longitudinal strain; HFrEF = heart failure with reduced ejection fraction; hs = high sensitivity; LA = left atrial; LFLG = low flow, low gradient; LGE = late gadolinium enhancement; LV = left ventricular; LVEF = left ventricular ejection fraction; MV = mitral valve; PA = pulmonary artery; RV = right ventricular; TAVR = transcatheter aortic valve replacement; TV = tricuspid valve.

chronic kidney disease, AF, chronic pulmonary disease, and a high STS score as risk factors for increased hospitalizations for HF after TAVR.[77] Aggressive risk management of comorbidities may improve post-TAVR outcomes. The degree of baseline LV hypertrophy is associated with increased 5-year risk of all-cause death, cardiovascular death and rehospitalization post-TAVR.[78]

The availability of disease-modifying GDMT in HF including inhibitors of sodium-glucose cotransporter-2 as well as the renin-angiotensin-aldosterone system and beta-adrenergic system may help address this residual risk by augmenting LV reverse remodeling and recovery prior to AVR.[79] In the OCEAN-TAVI registry, institution of preprocedural beta-blockers was associated with a lower 2-year cardiovascular mortality in patients with a history of coronary artery bypass grafting, peripheral arterial disease, BNP ≥400 pg/mL, and postprocedural LVEF <50%.[80] A higher risk of cardiovascular death and HF hospitalization is noted in patients with a pulmonary capillary wedge pressure of >12 mm Hg following TAVR.[81] This supports adequate fluid management with diuretic agents prior to intervention. However, the use of pre-TAVR loop diuretic agents is associated with a trend toward worse 1-year mortality and is considered a marker of high-risk, frail patients with advanced LV remodeling.[82]

PERIPROCEDURAL CONSIDERATIONS

AS AND CARDIOGENIC SHOCK. Patients with AS presenting in cardiogenic shock pose a clinical challenge, as there are no large prospective trials on this subject. Use of sodium nitroprusside has shown an improved hemodynamic profile in a small study.[83] In an observational study, intra-aortic balloon pump was shown to improve the hemodynamic profile including central venous pressure, systemic vascular resistance, and cardiac index.[84] Successful use of other mechanical support devices such as TandemHeart (LivaNova), Impella (Abiomed), and venoarterial extracorporeal membrane oxygenation have also been reported in case series.[85-87] While these treatment strategies are important during initial management of cardiogenic shock with severe AS, the crucial step is the treatment of the fixed obstruction. With increasing expertise and its widespread use, TAVR has become a feasible option for AS cardiogenic shock in recent years. In a large registry-based study, TAVR in AS with cardiogenic shock had significantly higher 30-day mortality when compared with TAVR in stable high-risk patients with severe AS. The degree of shock (determined based on inotrope or mechanical support devices requirement) is independently associated with mortality.[88] In addition, emergent TAVR is associated with higher rates of acute kidney injury and new dialysis when compared with elective TAVR. Notably, the balloon-expandible valve was associated with better outcomes compared with the self-expandible valve in emergent TAVR. While TAVR is emerging as an effective and safe option in patients with cardiogenic shock, it is important to consider its cost-effectiveness in light of high mortality rates. As an alternative, rescue balloon aortic valvuloplasty may be a reasonable alternative when it is bridged to SAVR or TAVR.[89]

POSTPROCEDURAL CONSIDERATIONS

HF POST-TAVR AND GDMT. As mentioned previously, 1-year rates of HF readmissions are high (between 13.6% and 24.1%) after TAVR.[90] Nearly one-fifth of patients are readmitted early (<30 days) after discharge.[91] Long-term mortality rates are significantly elevated by a 2-fold factor in cases of multiple and late readmissions (>30 days after the procedure).[90] An analysis of the Nationwide Readmissions Database revealed an excess of $12,928 in cost of care for each 30-day HF readmission after TAVR when compared with those who did not get readmitted.[92] This highlights the importance of identification of high-risk patients and close outpatient follow-up in the post-TAVR clinic with the goal of optimizing volume status and initiation/continuation of appropriate GDMT. A model of early follow-up within 7 days, well adopted by HF clinics currently, can be extended to this high-risk population. Patients treated with renin-angiotensin-aldosterone system inhibitors following TAVR have regression of LV volumes and hypertrophy and reduction in 3-year cardiovascular mortality.[93] The 2020 ACC/AMA guidelines support a Class 2b recommendation for initiation of renin-angiotensin-aldosterone system inhibitors in patients who have undergone TAVR.[1] The RASTAVI (Renin-angiotensin System Blockade Benefits in Clinical Evolution and Ventricular Remodeling After Transcatheter Aortic Valve Implantation; NCT03201185) trial on the use of renin-angiotensin-aldosterone system inhibitors following TAVR and the DapaTAVI (Dapagliflozin After Transcatheter Aortic Valve Implantation; NCT04696185) trial on dapagliflozin in patients undergoing TAVR at high risk for HF hospitalization are ongoing trials in this space (**Table 1**).[94] There is also a high prevalence of elevated postprocedure filling pressures following TAVR warranting appropriate diuretic escalation, consequently reducing future HF events.[81]

PARAVALVULAR LEAK AND HF. Though the incidence of paravalvular leak after TAVR has significantly declined with preoperative planning with computed tomography imaging, improved devices, and operator proficiency, the prevalence remains ~3.4%.[95] Early identification of acute paravalvular leak immediately after valve deployment or more than mild chronic paravalvular leak is imperative to avoid complications including HF and hemolysis. The presence of moderate-to-severe paravalvular leak after SAVR or TAVR is an independent prognostic marker for mortality and HF hospitalizations.[95] The 2020 ACC/AHA guidelines support surgical repair of paravalvular leak as a Class I recommendation.[1] It is reasonable to opt for percutaneous repair in patients with intractable hemolysis or clinical HF, prohibitive surgical risk, and suitable anatomy for catheter-based repair.[1] Techniques including valve-in-valve TAVR, balloon postdilation, and utilization of occluder devices like the AMPLATZER vascular plug (Abbott Vascular) can be employed depending on the clinical scenario.[96] Successful paravalvular leak closure is associated with improved clinical outcomes including NYHA functional class and cardiovascular mortality.[97]

CONCLUSIONS

The presence of concomitant AS and HF is associated with high rates of mortality and morbidity, and the availability of TAVR has advanced therapeutic options for this highly vulnerable and often undertreated population. A heart team model, incorporating HF specialists within the structural team, offers valuable expertise both before and, importantly, after TAVR. It recognizes that TAVR is often just the beginning of HF management, emphasizing the need for a seamless transition to HF clinical care including optimizing GDMT, volume management, and consideration of additional therapies. Leveraging multimodality imaging techniques and circulating biomarkers to detect extravalvular cardiac damage allows early corrections to mitigate disease progression to advanced HF (**Central Illustration**). Several ongoing clinical trials will help inform best practices in managing these patients, particularly with regard to HF pharmacotherapy after TAVR. Integrating emerging technologies may further help to improve diagnosis and management of patients with AS prior to the initiation of LV remodeling and prevent HF.

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