Structural Heart 6 (2022) 100089

Articles and Issues Available at ScienceDirect

Structural Heart

journal homepage: www.structuralheartjournal.org

Review Article

Left Ventricular Systolic Dysfunction in Aortic Stenosis: Pathophysiology, Diagnosis, Management, and Future Directions

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ARTICLE INFO

Article history:
Submitted 10 May 2022
Revised 3 August 2022
Accepted 8 August 2022
Available online 15 September 2022

Keywords:
Aortic stenosis
Aortic valve replacement
Late gadolinium enhancement
Strain echocardiography
Systolic dysfunction

ABSTRACT

Degenerative calcific aortic stenosis (AS) is the most common valvular heart disease and often co-exists with left ventricular (LV) systolic dysfunction at the time of diagnosis. Impaired LV systolic function has been associated with worse outcomes in the setting of AS, even after successful aortic valve replacement (AVR). Myocyte apoptosis and myocardial fibrosis are the 2 key mechanisms responsible for the transition from the initial adaptation phase of LV hypertrophy to the phase of heart failure with reduced ejection fraction. Novel advanced imaging methods, based on echocardiography and cardiac magnetic resonance imaging, can detect LV dysfunction and remodeling at an early and reversible stage, with important implications for the optimal timing of AVR especially in patients with asymptomatic severe AS. Furthermore, the advent of transcatheter AVR as a first-line treatment for AS with excellent procedural outcomes, and evidence that even moderate AS portends worse prognosis in heart failure with reduced ejection fraction patients, has raised the question of early valve intervention in this patient population. With this review, we describe the pathophysiology and outcomes of LV systolic dysfunction in the setting of AS, present imaging predictors of LV recovery after AVR, and discuss future directions in the treatment of AS extending beyond the traditional indications defined in the current guidelines.

ABBREVIATIONS

ARB, angiotensin receptor blockers; AS, aortic stenosis; AV, aortic valve; AVR, aortic valve replacement; CMR, cardiac magnetic resonance; ECV, extracellular volume; EF, ejection fraction; GLS, global longitudinal strain; HF, heart failure; HFrEF, heart failure with reduced ejection fraction; hsTnI, high-sensitivity troponin I; LFLG, low-flow low-gradient; LGE, late gadolinium enhancement; LV, left ventricle/left ventricular; LVEF, left ventricular ejection fraction; LVH, left ventricular hypertrophy; LVMi, left ventricular mass index; RAS, renin-angiotensin system; SAVR, surgical aortic valve replacement; TAVR, transcatheter aortic valve replacement.

Introduction

Degenerative aortic stenosis (AS) affects 2% to 4% of patients older than 65 years.[1,2] As the incidence of heart failure (HF) with reduced ejection fraction (HFrEF) increases with age, the AS often co-exists with left ventricular (LV) systolic dysfunction. Approximately one-third of patients who are diagnosed with severe AS have LV systolic dysfunction, defined as LV ejection fraction (LVEF) less than 50%.[3–5]

Aortic valve replacement (AVR), transcatheter or surgical, is the definitive treatment of severe AS; however, the presence of reduced LV systolic function at baseline may significantly affect prognosis and outcomes after the intervention. The most recent American College of Cardiology/American Heart Association guidelines for the management of valvular heart disease recommend AVR for symptomatic patients with severe AS and asymptomatic patients with severe AS and LVEF <50%.[6]

Although surgical AVR (SAVR) for severe AS is overall associated with survival benefit and morbidity reduction irrespective of baseline LV function, patients with systolic dysfunction have increased midterm and long-term mortality compared to patients with normal LV systolic function.[7]

In the recent years, transcatheter AVR (TAVR) has been established as an effective and less invasive first-line therapy for severe AS across all surgical risk categories.

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https://doi.org/10.1016/j.shj.2022.100089
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In the high-risk surgical population of the Placement of Transcatheter Aortic Valves (PARTNER) trial (31.9% of the patients had LVEF <50%), all-cause mortality was similar between the groups of reduced and preserved LVEF at 30 days and 1 year after AVR. Approximately one-third of patients with baseline systolic LV dysfunction did not demonstrate improvement in LVEF (defined as absolute increase ≥10%) 30 days after TAVR.[8,9] Absence of LVEF improvement was associated with 3-fold increase in 1-year mortality after TAVR.[3] In contrast, in the intermediate-risk PARTNER 2 trial (28% had LVEF <50% at baseline), patients with reduced LVEF had a higher all-cause and cardiovascular mortality at 2 years than patients with normal baseline LV function. Baseline LVEF was an independent predictor of 2-year cardiovascular mortality after TAVR.[4]

Furthermore, retrospective data have shown that, even in patients with moderate AS, the presence of LV systolic dysfunction is associated with significant mortality and HF hospitalization rates.[10] In a recent propensity-matched analysis, patients with LVEF <50% and moderate AS had higher all-cause mortality and HF hospitalization rates at 3 years than patients with LV dysfunction alone. A small subgroup of those patients who underwent AVR, and especially TAVR, had improved clinical outcomes and survival during follow-up.[11]

Overall, these findings suggest that baseline LV systolic dysfunction may adversely affect prognosis across the spectrum of AS severity. Detection of LV dysfunction at an early stage, followed by appropriate valve intervention, even in cases of nonsevere AS, may significantly improve patient outcomes.

Pathophysiology of LV Dysfunction in Aortic Stenosis

AS represents an increased afterload state for the LV. The increase in wall stress induces remodeling at the myocyte and extracellular matrix levels. This pressure overload state may remain clinically silent for years, until the AS becomes severe and the LV fails to compensate for the afterload mismatch and maintain adequate cardiac output, leading to development of symptoms. The LVEF reduction in patients with AS may be initially due to afterload/contractility mismatch. The increased afterload causes an increased stroke work and reduction in stroke volume despite preserved or even increased contractility during the early stages. As the disease progresses, irreversible myocardial damage and interstitial fibrosis occur, leading to LV systolic dysfunction and further decline in LVEF, if the AS is left untreated.[12]

Conversely, real-time pressure-volume loop analysis during TAVR has shown an acute increase in LVEF after valve replacement and LV unloading. A decrease in end-diastolic and end-systolic pressure results in reduced afterload and systolic work stress, which is reflected by decreased stroke work and total mechanical energy generated by the LV.[13] These immediate changes may be attenuated by certain procedural steps, such as rapid ventricular pacing, which causes LV stunning and transient dilatation.[14]

The initial response to the development of AS and increased afterload at the cellular level is myocyte hypertrophy, leading to concentric LV remodeling and increase in wall thickness, in an effort to normalize the wall stress (according to Laplace's Law) and maintain LV systolic function and cardiac output.[15] While the concentric myocardial hypertrophy is adaptive, a clear association between increasing degrees of hypertrophy/myocardial mass and adverse cardiovascular events and mortality has been shown.[16] As the AS progresses over time, the LV wall stress and end-diastolic pressure continue to increase, and eventually the LV contractile function declines. Ultimately, the patient transitions from the hypertrophy phase to HF with development of symptoms.

Two key processes driving LV decompensation and the transition from hypertrophy to HF are progressive myocyte apoptosis and reactive myocardial fibrosis.[17,18] Apoptosis occurs as a direct response to biomechanical stress secondary to increased afterload and indirectly due to supply-demand ischemia of the myocardium as a result of hypertrophy, fibrosis, and diminished capillary density, leading to impaired coronary flow reserve.[19] Increased circulating cytokine levels, such as tumor necrosis factor-A and its soluble receptors, have been described in animal and human models of cardiac pressure overload, with important implications in the process of myocyte apoptosis and LV decompensation.[20,21]

As a response to increased myocyte apoptosis and wall stress, myofibroblasts infiltrate the myocardium leading to increased expression of collagen type I, III, and IV genes and other transcripts involved in collagen synthesis.[17] Additionally, increased expression of tissue matrix metalloproteinase inhibitors has been observed in patients with AS, compared to normal subjects.[22] This imbalance in extracellular matrix synthesis and degradation ultimately leads to interstitial fibrosis, which is reflected in cardiac magnetic resonance (CMR) imaging findings. Extracellular volume (ECV) expansion (diffuse fibrosis), detected by T1, and mid-wall late gadolinium enhancement (LGE) (replacement fibrosis) are more pronounced in patients with AS. While ECV expansion has been described in the initial stages of this process, replacement fibrosis is considered the final and irreversible stage of LV remodeling in AS. These findings are associated with diastolic dysfunction and longitudinal systolic dysfunction, leading to LV decompensation and transition from adaptive hypertrophy to HF in patients with AS (Figure 1).[23]

LV Systolic Function Assessment and Predictors of Recovery After AVR

Echocardiography

LV function assessment is a key component in the evaluation of patients with severe AS and determining the timing of AVR. Echocardiography is the initial diagnostic test, as it enables assessment of LVEF, regional wall thickness, and LV mass, thus allowing classification of LV geometry into normal, concentric remodeling, concentric hypertrophy, and eccentric hypertrophy. Global longitudinal strain (GLS) is another marker of LV systolic function, which can detect LV dysfunction even in the presence of preserved LVEF and may be a better predictor of myocardial recovery after AVR.[24,25] In a cohort of 395 patients with severe AS and preserved LVEF, about 75% of the patients were found to have depressed GLS.[26]

Several echocardiographic features may be predictive of LV recovery after AVR. Baseline LVEF ≤35% has been described as the strongest independent predictor of LV recovery after TAVR although associated with overall higher 1-year mortality.[5] The presence of regional wall motion abnormalities consistent with a prior myocardial infarction are predictive of poor LV recovery.[9]

Baseline GLS greater than −13.3% was found to predict GLS normalization after TAVR. Expectedly, circumferential, rotational, and torsional mechanics were increased in severe AS with preserved ejection fraction (EF) and decreased in the low-EF group, with improvement after TAVR.[27] In low-flow low-gradient (LFLG) AS patients, GLS improved but did not normalize, suggesting a degree of irreversible adverse remodeling and myocardial damage.[26,28] In LFLG AS, GLS was a stronger predictor of LV recovery after TAVR than LVEF.[22]

Additionally, the role of LV mass index (LVMi) regression in LVEF recovery has been highlighted among patients in the PARTNER I, II, and S3 trials and registries. Despite no difference in baseline LVEF, patients with greater LVMi regression after AVR had higher LVEF at 1-year follow-up. Importantly, among patients with moderate or severe LV hypertrophy (LVH) treated with TAVR, greater LVMi regression at 1 year was also associated with lower mortality and hospitalization rates at 5 years, emphasizing the prognostic significance of LVMi.[29]

Other echocardiographic parameters, such as right ventricular dysfunction, bicuspid aortic valve (AV) anatomy, mean AV gradient, and postprocedural aortic regurgitation, have been linked to LV function recovery and are summarized in Table 1.[9,27,30,31]

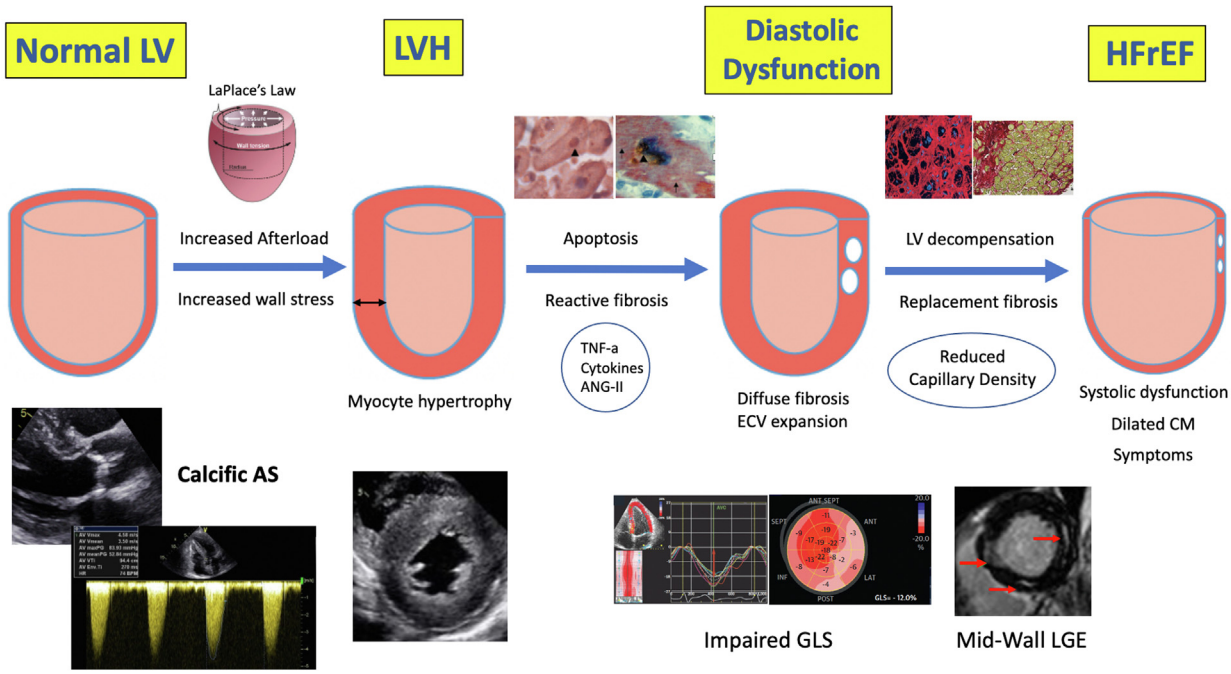


Figure 1. The progression from left ventricular hypertrophy to heart failure with reduced ejection fraction in patients with severe aortic stenosis. Abbreviations: ANG-II, angiotensin II; AS, aortic stenosis; CM, cardiomyopathy; ECV, extracellular volume; GLS, global longitudinal strain; HFrEF, heart failure with reduced ejection fraction; LGE, late gadolinium enhancement; LV, left ventricle/ventricular; LVH, left ventricular hypertrophy; TNF-a, tumor necrosis factor-a.

Dobutamine Stress Echocardiography

Several studies have assessed the prognostic role of contractile/flow reserve in patients with LFLG severe AS by using dobutamine stress echocardiography. Although lack of contractile reserve was associated with higher operative mortality after SAVR in a small patient cohort, the presence or absence of contractile reserve did not predict LV recovery over time.[32,33] In a larger patient cohort of LFLG severe AS and reduced EF, contractile flow reserve by dobutamine stress echocardiography was not predictive of survival. AVR (surgical or transcatheter) was associated with better survival independent of flow reserve.[34]

Cardiac Magnetic Resonance

CMR is the current gold standard for noninvasive assessment of systolic function and LV geometry, with the advantage of tissue characterization. T1-weighted images with LGE are helpful in detecting focal fibrosis (scar) that may represent irreversible myocardial damage,[23,35] while T2-weighted images can detect increased water content within the myocardium, which represents inflammation or edema.[36] The degree of myocardial fibrosis correlates with impaired longitudinal systolic function, increased LV cavity dimensions, and reduced LVEF. A dose-dependent relationship has been described between the amount of mid-wall LGE and adverse cardiovascular events and mortality.[23] Additionally, CMR can facilitate the diagnosis of concomitant transthyretin amyloid cardiomyopathy, a treatable infiltrative disease that is common in older adults referred for severe AS evaluation.[37,38] Further evaluation of myocardial tissue properties, through T2 relaxation time, may also provide prognostic information regarding LV recovery potential. In a study of patients with severe AS, T2 values above 70.2 milliseconds were associated with more pronounced reverse LV remodeling after TAVR, while patients with initial low T2 did not have significant improvement in LV end-diastolic volumes or LVEF.[36]

Table 1
Predictors of LV recovery after AVR

Modality	Predicts recovery	Predicts lack of recovery
ECG	• Left ventricular hypertrophy	• Left bundle brunch block
Echo	• AV gradient $\geq$ 40 mm Hg • GLS $<$ 13.3%	• LVEF $<$ 35% • Regional wall motion abnormalities suggesting prior myocardial infarction • RV dysfunction • Bicuspid valve morphology • Moderate/severe AR or new mild AR
CMR	• T2 relaxation time (highest quartile)	• Late gadolinium enhancement • T2 relaxation time (lowest quartile)
CT		• Expanded extracellular volume
Nonimaging modalities	• BNP reduction	• Cytokines (hepatocyte growth factor)

AR, aortic regurgitation; AV, aortic valve; AVR, aortic valve replacement; BNP, B-type natriuretic peptide; CMR, cardiac magnetic resonance; CT, computed tomography; ECG, electrocardiography; GLS, global longitudinal strain; LV, left ventricle/ventricular; LVEF, left ventricular ejection fraction; RV, right ventricular.

Computed Tomography

ECV derivation from computed tomography may predict early recovery of LV systolic function after AVR. Increased ECV has been associated with decreased LVEF recovery after TAVR in patients with impaired LV systolic function at baseline. With each percent increase in ECV over 30%, there was an 11% reduction in the likelihood of early LVEF recovery. Extracellular expansion and replacement fibrosis are considered to represent an advanced stage of LV dysfunction. An expanded ECV could also suggest cardiac amyloidosis which is associated with poor LV recovery.[39]

Electrocardiography

LVH, as detected on electrocardiography, has been associated with lower incidence of adverse clinical outcomes (all-cause death, major adverse cardiovascular events, and rehospitalization).[40] Signs of hypertrophy represent viable myocardium and may be associated with greater reverse remodeling and LV function recovery after TAVR. Conversely, the

absence of LVH could be related to extensive myocardial fibrosis or the presence of amyloidosis.[40,41] Left bundle branch block before or after TAVR correlates with a lower rate of reverse LV remodeling, as is right ventricular pacing.[42]

Nonimaging Modalities

Reduction of B-type natriuretic peptide levels after TAVR has been associated with reverse LV remodeling, decrease in LV end-diastolic volume index, and improvement in GLS and LV contractility over time.[43] Certain cytokines have also been linked to LV recovery after AVR although their clinical utility is limited. Elevated hepatocyte growth factor levels have been associated with reduced LV recovery.[44] Table 1 summarizes the predictors of LV function recovery after AVR.

The Role of Medical Therapy in Degenerative Aortic Stenosis

The current paradigm of monitoring asymptomatic patients with progressive AS with serial echocardiograms, followed by AVR once severe AS is established and symptoms arise, does not delineate a specific role for HF medical therapy. As put forward in a recent viewpoint from Lindman and Lindenfeld, there has been no role for pharmacologic therapy to specifically treat or prevent AS and its known myocardial consequences.[45]

Observational data support a potential role for the renin-angiotensin system (RAS) blockade therapy in patients with AS before and after AVR, given its association with reverse LV remodeling, reduction of hypertrophy and fibrosis, and overall clinical and mortality benefit in the HF population.[46–49] Proposed mechanisms for increased survival associated with RAS blockade after AVR include cardioprotection (i.e., atherosclerotic plaque stabilization) and regression of myocardial fibrosis.[50,51] Although increased angiotensin-converting enzyme 2 levels have been associated with increased valvular calcification, LV mass, LV end-diastolic volume, and higher mortality in patients with AS, data on the role of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers (ARBs) in slowing the progression of calcific AS have been inconclusive.[52–54]

Given that LV mass regression is associated with significantly lower rates of hospitalization after SAVR and TAVR, there has been growing interest in the role of RAS inhibition in facilitating reverse LV remodeling and improved outcomes. The Ramipril in Aortic Stenosis (RIAS) trial evaluated the use of ramipril in patients with asymptomatic moderate or severe AS and showed significant reduction in LV mass in the ramipril group compared to placebo; however, it was not powered to assess differences in clinical outcomes.[55]

Another randomized study evaluated the effect of the ARB candesartan on the LV mass of patients who underwent SAVR for severe AS. The study showed significantly lower LVMi in patients treated with candesartan, as well as lower rates of atrial fibrillation.[56]

Several large observational studies have demonstrated the association of angiotensin-converting enzyme inhibitors/ARB utilization with mortality benefit and reduced hospitalization rates in the TAVR population.[57,58] These findings led to the design of a multicenter, open-label, randomized trial (RAS blockade After Transcatheter Aortic Valve Implantation [RASTAVI]) that is currently enrolling.[59]

With evolving treatment paradigms in HF across the LVEF spectrum, beyond the traditional RAS and beta blockade, there is growing interest in the extension of novel pharmacologic HF therapies to patients with AS. The potential benefits of newer agents, including sodium-glucose cotransporter 2 inhibitors, are currently under investigation. "Dapagliflozin after transcatheter aortic valve implantation" (DAPA TAVI; NCT04696185) is a prospective randomized trial, evaluating the effect of dapagliflozin on survival and HF hospitalization of patients with severe AS, LVEF $\leq$40%, and renal dysfunction undergoing TAVR.[60] This study is currently enrolling with estimated completion in 2023.

Future Directions

Staging of AS Severity Based on Cardiac Damage

Recognizing the prognostic significance of LV dysfunction in patients with AS undergoing AVR, Généreux et al.[61] suggested a new staging system for AS based on the extent of upstream cardiac changes and damage, utilizing data from the PARTNER 2A and 2B trials (1661 patients). More specifically, patients were categorized into 5 stages depending on the presence or absence of cardiac damage or dysfunction (myocardial and valvular), as detected by echocardiography prior to AVR (Figure 2). The study showed a consistent association between the extent of upstream cardiac damage prior to AVR and all-cause and cardiac mortality at 1 year after AVR (Figure 2).[61] Although this staging system requires further validation, its integration as a risk-stratification tool for patients with severe AS may facilitate an earlier intervention and help improve prognosis after AVR.

Moderate AS and LV Systolic Dysfunction

The observation that moderate AS is associated with significant mortality, HF hospitalization rates, and need for AVR in patients with HFrEF[10] supports the utility of an early AV intervention in this patient population.

In a retrospective study of patients with HFrEF and moderate AS, moderate AS was independently associated with almost a 3-fold increase in all-cause mortality compared to patients with HFrEF without AS. TAVR was associated with improved survival in this patient population compared to medical therapy and expectant management.[11] Furthermore, a retrospective analysis of a large patient cohort from the Duke Echocardiographic Database showed mortality benefits from AVR (with or without concomitant coronary artery bypass grafting) in patients with moderate AS and LV systolic dysfunction.[62] These findings suggest that the increased afterload imposed on the LV by moderate AS may negatively affect prognosis and outcomes in the HFrEF population, supporting the hypothesis for an early AV intervention.

This hypothesis led to the design of the "Transcatheter Aortic Valve Replacement to Unload the Left Ventricle in Patients with Advanced Heart Failure" (TAVR UNLOAD; NCT02661451), which is an international randomized-controlled trial aiming to evaluate the safety and efficacy of transfemoral TAVR plus optimal HF therapy compared with optimal HF therapy alone in patients with moderate AS and LVEF <50%. This study is based on the rationale that TAVR may provide additional afterload reduction and thus improve prognosis and clinical outcomes in patients with moderate AS and LV dysfunction.[63]

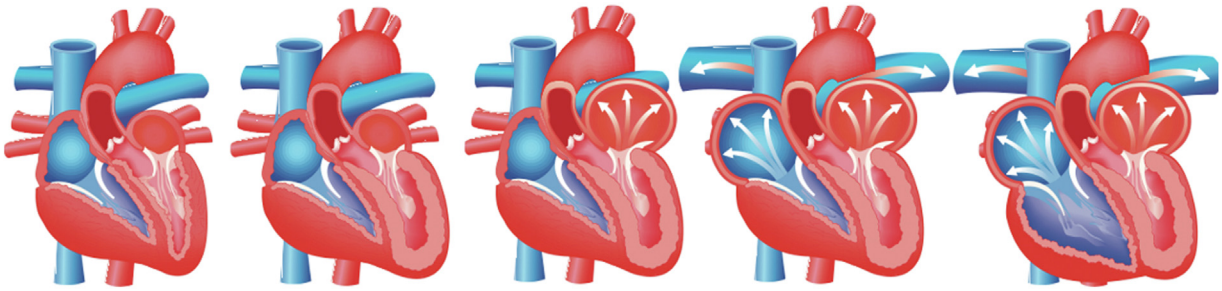
Asymptomatic Patients With Severe AS

Close monitoring and expectant management of asymptomatic patients with severe AS and preserved LVEF (defined currently as >50%) has been historically considered as a safe strategy without adverse effects on prognosis.

However, observational data suggest that the natural history of asymptomatic severe AS is not as benign as originally thought. Early SAVR has been associated with improved survival in this patient population compared to conservative/expectant management.[64,65]

Advancements in cardiac imaging leading to early detection of LV remodeling and dysfunction, that precede the reduction in LVEF and development of symptoms, have raised the question about possible early intervention in asymptomatic patients with severe AS and signs of early, and thus reversible, LV dysfunction.

As mentioned above, reduced LV GLS is an early and more sensitive marker of impaired contractile function, when LVEF is still preserved, that corresponds to the development of interstitial fibrosis. A recent individual participant data meta-analysis of asymptomatic patients with severe AS showed that GLS <14.7% was associated with a 2.5-fold



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
	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		

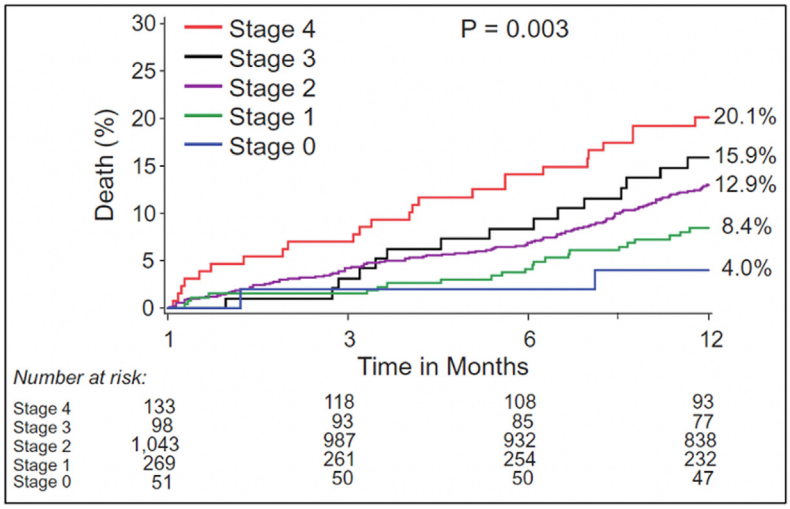


Figure 2. Staging of aortic stenosis based on the extent of upstream cardiac damage (top). One-year all-cause mortality after AVR among the different stages of cardiac damage (bottom). P. Généreux, et al., Staging classification of aortic stenosis based on the extent of cardiac damage, *European Heart Journal*, 2017. 38 (45); 3351-3358, by permission of Oxford University Press on behalf of the European Society of Cardiology.
Abbreviations: AVR, aortic valve replacement; LA, left atrium; LV, left ventricle/ventricular; RV, right ventricular.

increase in mortality.[66] Impaired GLS is also frequently detected among patients with moderate AS and has been associated with worse prognosis and higher mortality even after subsequent AVR.[67]

In the same context, the development of high-sensitivity assays for the detection of cardiac biomarkers of myocyte injury and death, such as high-sensitivity troponin I (hsTnI), has led to studies investigating the role of such biomarkers in prognosis of asymptomatic patients with severe AS. Plasma hsTnI concentrations have been shown to correlate with an advanced hypertrophic response (LV mass) and replacement fibrosis (mid-wall LGE) and are associated with higher cardiovascular mortality and AVR, independent of the burden of coronary artery disease.[68]

The accumulating evidence that subclinical LV dysfunction, myocyte apoptosis, and interstitial fibrosis in asymptomatic patients with severe AS are associated with adverse outcomes and increased mortality, the challenges in accurate determination of symptom status particularly in sedentary elderly patients, along with the low periprocedural morbidity and mortality of AVR in contemporary practice (especially TAVR), led to the design of 2 clinical trials that focus on early intervention.

The "Early Valve Replacement Guided by Biomarkers of LV Decompensation in Asymptomatic Patients With Severe AS" (EVOLVED; NCT03094143) trial is a multicenter randomized-controlled trial investigating whether objective markers of early LV decompensation can be used to optimize the timing of AVR. Asymptomatic patients with severe AS, normal LVEF, elevated hsTnI levels, and evidence of mid-wall myocardial fibrosis by CMR will be randomized to early AVR (TAVR or SAVR) or the standard watchful waiting approach. The primary endpoint will be the composite of all-cause mortality or unplanned hospitalization related to AS during the follow-up period.[69]

A more broadly inclusive trial is the "Evaluation of Transcatheter Aortic Valve Replacement Compared to Surveillance for Patients With Asymptomatic Severe Aortic Stenosis" (EARLY TAVR; NCT03042104). This is a prospective, randomized-controlled, multicenter study that aims to investigate the role of TAVR in asymptomatic patients with severe AS and preserved LV function, without requiring objective data of structural or functional LV decompensation. The trial protocol mandates the use of exercise testing in most patients, which should be normal before randomization. The primary endpoint will be the composite of all-cause mortality, stroke, and unplanned cardiovascular hospitalization at 2 years.[70]

LVEF Threshold

The threshold that has been traditionally used for the definition of systolic LV dysfunction and indication for intervention in patients with severe AS is 50%. Data from the Heart Valve Clinic International Database (HAVEC registry) showed that asymptomatic patients with severe AS and LVEF between 50% and 59% had worse outcomes and experienced more HF-related deaths than those with LVEF >60%, even after successful AVR.[71] This finding may support the re-evaluation and possible adjustment of the optimal LVEF cutoff to define dysfunction and consider AVR in patients with asymptomatic severe AS.

Conclusion

LV systolic dysfunction is associated with worse outcomes in patients with AS, even after successful AVR. Advanced methods of assessing myocardial function and structure, such as echocardiographic GLS, CMR assessment of the extracellular matrix, measurement of high-sensitivity biomarkers of myocyte injury and apoptosis, and the addition of the stage of cardiac damage as a covariable, may lead to better risk stratification, optimization of the timing of AVR, and improvement in patient outcomes. The optimal timing of AVR in asymptomatic patients with severe AS and the potential benefit of treating moderate AS in HFrEF are currently under investigation in randomized trials.

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Funding

The authors have no funding to report.

Disclosure statement

Dr Trejeeve Martyn receives research support from Ionis Therapeutics and is an advisor to Recora Health. The other authors have no conflicts to declare.

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