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Review

Beyond Surgical Risk in Aortic Stenosis: The Emerging Role of Cardiac Damage Staging in Contemporary Decision-Making

Silvia Romiti[1,2,*], Ernesto Greco[1], Sara Iuliano[2], Giuseppe Sepolvere[3], Eduardo Vitagliano[2], Andrea Spadafora[2], Antonio De Bellis[2], Mattia Vinciguerra[1]

[1]Department of Health and Life Sciences, European University of Rome, 00163 Rome, Italy
[2]Department of Cardiology and Cardiac Surgery, Casa di Cura San Michele, 81024 Maddaloni, Italy
[3]Department of Anesthesia and Cardiac Surgery Intensive Care Unit, Casa di Cura San Michele, 81024 Maddaloni, Italy
*Correspondence: silvia.romiti@unier.it (Silvia Romiti)

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Abstract

Aortic stenosis (AS) is the most prevalent valvular heart disease in developed countries, with an increased burden due to population aging. Current indications for aortic valve replacement (AVR) are primarily based on symptom status, valve disease severity, procedural risk, age, life expectancy, and anatomical features. However, increasing evidence suggests that the prognostic impact of AS extends beyond valvular obstruction alone. Chronic pressure overload promotes a progressive cascade of structural, functional, and hemodynamic abnormalities involving the left ventricle, left atrium, pulmonary circulation, and right ventricle, collectively termed extra-valvular cardiac damage. Over the past decade, several staging systems have been proposed to characterize the extent of cardiac damage associated with AS. These classifications consistently show that adverse outcomes increase with advancing stages of cardiac involvement, even among asymptomatic patients and those with moderate AS. Importantly, recent evidence suggests that the extent of cardiac damage associated with AS provides additional prognostic value, especially right ventricular involvement, after both surgical aortic valve replacement (SAVR) and transcatheter aortic valve implantation (TAVI). This review aims to summarize the pathophysiological basis, staging classifications, and prognostic implications of cardiac damage in AS, with particular emphasis on its potential role in contemporary clinical decision-making. Although current evidence does not support the use of cardiac damage staging as an independent criterion for selecting between SAVR and TAVI, it may provide incremental prognostic information, contribute to risk stratification, and help identify patients who may benefit from earlier intervention before advanced and potentially irreversible cardiac remodeling develops.

Keywords: aortic stenosis; cardiac damage staging; transcatheter aortic valve implantation; surgical aortic valve replacement; risk stratification; cardiac remodeling; prognosis

1. Introduction

Aortic stenosis (AS) is the most common valvular heart disease in Western countries, and represents a growing clinical and public health challenge due to population aging [1]. The epidemiological burden of AS is expected to increase further over the coming decades as improvements in quality of life and scientific and technological innovations have extended life expectancy [2,3]. Regardless of its underlying etiology, AS is characterized by progressive obstruction of left ventricular (LV) outflow, leading to chronic pressure overload, LV remodeling, and, if untreated, eventually heart failure (HF) and premature death [4,5]. No pharmacological therapy has demonstrated sufficient efficacy to prevent or significantly delay disease progression, and current international guidelines do not recommend medical treatment as an alternative to valve intervention [6,7]. Although patients may remain asymptomatic for several years, symptom onset marks a major turning point in the natural history of the disease and is associated with a substantial worsening in prognosis [1,8]. Once severe AS becomes symptomatic, survival decreases markedly in the absence of aortic valve replacement (AVR) [9]. Mortality after diagnosis of severe AS remains high despite improvements in management strategies, reaching approximately 36% at 3 years and 49% at 5 years [10]. Among patients managed conservatively without AVR, mortality is even higher, exceeding 50% within 3 years after diagnosis [10]. Currently, AVR remains the only effective treatment for severe symptomatic AS. Although both surgical aortic valve replacement (SAVR) and transcatheter aortic valve implantation (TAVI) have substantially improved clinical outcomes, a relevant proportion of patients remain untreated or are referred for intervention too late, highlighting the need for earlier recognition, accurate risk stratification, and timely intervention [10,11,12].

Over the past decade, the progressive expansion of TAVI indications from high-risk and inoperable patients to those aged ≥70 has profoundly reshaped the therapeutic landscape of AS management. Current guidelines are mainly based on surgical risk assessment, age, life expectancy, anatomical considerations, and procedural feasibility [7]. However, this approach may not fully reflect

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the complexity of AS pathophysiology and its impact on the myocardium and the cardiovascular system as a whole. Indeed, although AVR effectively relieves mechanical obstruction, increasing evidence suggests that correcting the valvular lesion alone may be insufficient, particularly when associated myocardial and extra-valvular cardiac damage is present [13]. Long-standing pressure overload leads to LV hypertrophy, myocardial fibrosis, myocyte degeneration, LV dysfunction, atrial remodeling, and pulmonary hypertension (PH). These changes may persist even after successful SAVR or TAVI and significantly influence long-term prognosis [14]. In this context, recent studies have highlighted the prognostic importance of staging cardiac damage beyond the aortic valve (AV) [15,16]. Several investigations have demonstrated that the extent of extra-valvular cardiac involvement is strongly associated with adverse outcomes following both SAVR and TAVI, suggesting that staging cardiac damage may provide not only prognostic information but also support clinical decision-making and the timing of intervention [17,18,19]. This review aims to provide an overview of the emerging role of prognostic staging in AS, focusing on its potential integration into contemporary decision-making strategies beyond conventional risk and valvular severity assessment.

2. Current Decision-Making: Limits of Risk-Based Models

According to the latest guidelines, the indication for AVR, whether SAVR or TAVI, is primarily based on the severity of valvular obstruction, as assessed by echocardiographic parameters, and on the presence of symptoms. In selected asymptomatic patients, intervention should be considered in the presence of LV systolic dysfunction or other features associated with an increased risk of adverse outcomes. The choice of treatment is based on an integrated Heart Team evaluation that considers patient age, comorbidities, frailty, life expectancy, anatomical suitability, and procedural feasibility to select the most appropriate therapeutic strategy between SAVR and TAVI [6,7]. Among the factors influencing therapeutic choice, age remains a major determinant, with TAVI generally recommended in older patients, particularly those aged ≥70 years. In contrast, SAVR is more frequently considered in younger individuals with longer life expectancy. Anatomical suitability also plays a pivotal role, including valve morphology, vascular access, extent and distribution of calcification, coronary anatomy, and the presence of bicuspid or tricuspid AV disease [7]. In parallel, operative risk assessment continues to rely predominantly on validated surgical risk models, mainly the Society of Thoracic Surgeons predicted risk of mortality (STS-PROM) score and the European system for cardiac operative risk evaluation score (EuroSCORE II) [20,21,22]. However, despite their widespread use, these risk models present important limitations. Both STS and EuroSCORE II were primarily developed to estimate perioperative mortality and procedural complications in cardiac surgery and, therefore, mainly reflect procedural risk rather than the overall biological and prognostic burden of the disease [23,24]. Importantly, these metrics do not adequately account for the extent of all cardiac damage secondary to long-standing AS. Consequently, these risk-based models may fail to capture disease stage and long-term prognosis. However, increasing evidence suggests that patients with similar operative risk may have substantially different outcomes according to the degree of extra-valvular cardiac involvement [13]. This limitation has generated growing interest in staging systems capable of integrating not only valvular severity and procedural risk, but also the progressive cardiac damage associated with AS, potentially improving prognostic stratification and therapeutic decision-making beyond conventional risk scores.

3. Pathophysiology of Advanced AS

The main pathophysiological consequence of AS is the progressive increase in the pressure gradient between the LV and the aorta, resulting in chronic elevation of LV afterload [25]. Initially, the LV adapts through concentric hypertrophic remodeling, which reduces wall stress and preserves systolic performance despite increasing pressure overload [1,26]. Persistent pressure overload progressively transforms this adaptive response into a maladaptive process characterized by oxygen supply–demand mismatch, myocyte loss, fibroblast activation, and progressive extracellular matrix expansion [27,28,29]. Fibrosis initially develops as diffuse interstitial fibrosis, which is partially reversible, and later progresses to replacement fibrosis, characterized by irreversible loss of functional myocardium. These processes progressively impair ventricular mechanics and myocardial function, contributing to both systolic and diastolic dysfunction [29,30,31]. In diastolic dysfunction, which represents the early manifestation of this remodeling, hypertrophy and fibrosis reduce ventricular compliance and impair relaxation, resulting in elevated LV filling pressures despite a preserved ejection fraction. Consequently, symptoms and exercise intolerance may develop before overt systolic dysfunction owing to impaired hemodynamic reserve. Progressive elevation of LV filling pressures extends cardiac damage beyond the LV. Increased left atrial (LA) pressure promotes atrial enlargement, contractile dysfunction, and atrial fibrillation (AF), while ventricular remodeling contributes to functional mitral regurgitation (MR) [32,33]. Chronic elevation of left-sided pressures also involves the pulmonary circulation, where pulmonary vascular remodeling could amplify PH beyond passive congestion [34]. The resulting increase in right ventricular (RV) afterload promotes RV remodeling, systolic dysfunction, and functional tricuspid regurgitation (TR) [35,36]. Although cardiac damage is commonly described as progressing from LV remodeling to pulmonary and right-sided involvement, this evolution ap-

pears to be non-uniform [35,36]. The extent and pattern of extra-valvular cardiac damage likely reflect the interaction among chronic pressure overload, myocardial reserve, ventricular interdependence, adaptive capacity, and the timing of valve intervention [37].

4. Cardiac Damage Beyond the Valve: Staging Classification

The hemodynamic and myocardial changes induced by chronic pressure overload in AS are not confined to the LV but progressively involve multiple extra-valvular cardiac structures, as previously discussed. The recognition that cardiac remodeling influences outcomes led to the development of staging systems to provide a more integrated assessment of disease severity [14]. The first widely adopted framework was proposed by Généreux et al. [35], who introduced an echocardiographic classification of AS based on the anatomical extension of cardiac damage. Patients were categorized into five stages according to the most advanced stage identified. In this model, Stage 0 corresponds to isolated valvular disease without detectable extra-valvular involvement. Stage 1 includes LV damage, represented by ventricular hypertrophy and abnormalities of systolic or diastolic function. Stage 2 identifies extension toward the LA and mitral valve (MV), including atrial enlargement, AF, and MR. Stage 3 reflects involvement of the pulmonary circulation and tricuspid valve (TV), while Stage 4 corresponds to RV dysfunction. This classification showed that higher stage was associated with progressively worse outcomes after AVR and suggested that disease severity is also influenced by the amount of cardiac remodeling already present at the time of intervention. Subsequent studies explored whether the same concept could be captured through different approaches. Using invasive hemodynamic measurements, Maeder et al. [38] proposed a staging model based on catheterization-derived variables. Rather than relying on structural abnormalities, this approach described progression through increasing LV and LA filling pressures, pulmonary vascular involvement, and right-sided pressure overload. The findings of Maeder et al. [38] supported the observation that pulmonary and right-sided hemodynamic abnormalities identify patients with a less favorable prognosis. The relevance of advanced right-sided involvement was further discussed in later analyses focusing on the interaction between the RV and pulmonary circulation [37,39,40]. These studies showed that PH and RV dysfunction are not simply markers of disease duration but may provide additional prognostic information independently of conventional left-sided parameters.

To improve discrimination among advanced stages, Okuno et al. [41] refined the original staging model by further subdividing pulmonary and right-sided involvement. Pulmonary stages were stratified by PH severity, and right-sided stages incorporated the coexistence of low-flow state and RV dysfunction. This modification was based on the observation that patients with apparently similar degrees of advanced remodeling may experience different clinical outcomes. Subsequently, Gutierrez-Ortiz et al. [42] shifted attention from structural abnormalities to earlier indicators of myocardial dysfunction. Their classification introduced left ventricular global longitudinal strain (LV-GLS) as a marker of subclinical LV impairment and right ventricular–arterial coupling (RVAc) as an indicator of advanced right-sided involvement.

In this model, deterioration of ventricular–vascular interaction emerged as a relevant marker of outcome, supporting the idea that functional abnormalities may become clinically relevant before advanced structural remodeling becomes evident. Recently, Tomaselli et al. [15] extended this functional approach by integrating multi-chamber myocardial deformation analysis. The model by Tomaselli et al. [15] incorporated measures of LV, LA, and RV strain and proposed a staging system based on progressive impairment of myocardial mechanics. An important observation emerging from this work was that patients with evidence of impaired RV deformation showed poorer outcomes than those with preserved RV mechanics, despite similar degrees of structural involvement. This finding further supports the hypothesis that deterioration of RV performance represents an advanced stage of disease progression. Recently, attempts have been made to expand classification systems beyond structural and functional staging. In this context, Généreux et al. [43] proposed a framework based on patterns of clinical presentation, introducing the concepts of "Stable Valve Syndrome, Progressive Valve Syndrome, and Acute Valve Syndrome". Unlike previous staging models, this classification does not aim to quantify cardiac damage but to describe different clinical trajectories of AS progression. The rationale is that disease evolution may not always occur gradually and that some patients may present with rapid clinical deterioration despite apparently stable previous status. The main characteristics, strengths, and limitations of the currently available staging models are summarized in Table 1 (Ref. [15,35,38,41,42,43]).

Although different staging systems have been proposed, most are based on the concept that cardiac damage progressively extends from the LV to the pulmonary circulation and the right heart structures (Fig. 1).

5. Prognostic Impact of Extra-Valvular Cardiac Involvement

Staging of extra-valvular cardiac damage has expanded the assessment of AS beyond valve severity to include the consequences of chronic pressure overload on the cardiovascular system. Although conventional echocardiographic parameters, symptom status, and left ventricular ejection fraction (LVEF) remain central to clinical evaluation, these parameters do not fully explain the different outcomes observed among patients with similar AS severity [13,44].

Table 1. Main staging systems for cardiac damage assessment in aortic stenosis.

Staging system	Main parameters	Key features	Strengths	Limitations
Généreux et al. [35]	Echocardiographic structural and functional abnormalities involving the LV, LA/MV, pulmonary circulation/TV, and RV	Five-stage hierarchical model (Stages 0–4) based on the anatomical extension of cardiac damage	Most widely adopted and externally validated staging system; simple and clinically applicable	Primarily based on conventional echocardiographic parameters; limited assessment of subclinical myocardial dysfunction
Maeder et al. [38]	Invasive hemodynamic measurements obtained during cardiac catheterization	Staging based on progressive increases in filling pressures, pulmonary vascular involvement, and right-sided hemodynamic burden	Direct physiological assessment of disease severity	Invasive approach limits routine clinical applicability
Okuno et al. [41]	Modified Généreux classification incorporating severity of pulmonary hypertension and right-sided involvement	Refined characterization of advanced stages of cardiac damage	Improved discrimination among patients with advanced disease	More complex classification; limited external validation
Gutierrez-Ortiz et al. [42]	Left ventricular global longitudinal strain (LV-GLS) and right ventricular–arterial coupling (RVAc)	Functional staging focused on early myocardial dysfunction and ventricular–vascular interaction	Detects subclinical abnormalities before overt structural remodeling	Requires advanced echocardiographic analysis; limited availability in some centers
Tomaselli et al. [15]	Multi-chamber myocardial deformation analysis (LV, LA, and RV strain)	Staging based on progressive impairment of myocardial mechanics	Comprehensive functional assessment of cardiac damage	Novel classification with limited clinical experience and validation
Généreux et al. [43]	Clinical presentation patterns	Classification into stable valve syndrome, progressive valve syndrome, and acute valve syndrome	Incorporates clinical trajectories and disease presentation	Does not directly quantify structural or functional cardiac damage

LA, left atrium; LV, left ventricle; RV, right ventricle; MV, mitral valve; TV, tricuspid valve; LV-GLS, left ventricular global longitudinal strain; RVAc, right ventricular–arterial coupling.

Growing evidence shows that extra-valvular cardiac damage provides prognostic information beyond AS severity. The main studies are summarized in Table 2 (Ref. [16,35,45,46,47,48,49]).

The original staging model proposed by Généreux et al. [35] and its subsequent modifications [41,42,50] have been validated across multiple cohorts, leading to the introduction of a hierarchical framework in which the progression of cardiac remodeling from the left heart to pulmonary and right-sided involvement is associated with progressively worse clinical outcomes [45,51]. As summarized in Table 2, cardiac damage is highly prevalent across the spectrum of AS. Bennett et al. [45], in a systematic review and meta-analysis of a total of 18 studies and more than 20,000 patients included, reported cardiac damage in 76% of patients with symptomatic severe AS and in 88% of those with asymptomatic moderate-to-severe AS. Stage 2, according to the Généreux staging model [35], was the most frequently reported; meanwhile, mortality progressively increased with advancing cardiac damage, reaching 36.1% in stage 4 among symptomatic severe AS and 51.2% in stages 3–4 among asymptomatic moderate-to-severe AS [45]. Parada-Barcia et al. [46] also showed that, in an older high-risk TAVI population, pre-procedural cardiac damage staging predicted HF hospitalization and all-cause mortality. Patients with severe cardiac damage, defined by right-heart involvement, had the poorest prognosis, with 42% mortality during a mean follow-up of 2.26 ± 0.90 years and significantly more HF hospitalizations than the other groups. Similarly, Espinoza Romero et al. [16] evaluated a preoperative echocardiographic staging classification in a population undergoing SAVR and demonstrated that patients classified as stage 3 according to their modified Généreux classification (right-sided involvement of extra-valvular cardiac damage) experienced markedly worse outcomes despite relatively low conventional surgical risk scores. In addition, lower mean transaortic gradients, potentially reflecting low-flow, low-gradient physiology, were linked to poorer prognosis [16]. In this group, long-term all-cause mortality reached 40.3%, while the composite endpoint of mortality and cardiovascular readmissions occurred in 77.3% of patients. Collectively, these findings suggest that the extent of extra-valvular cardiac damage identifies a subgroup of patients at particularly high

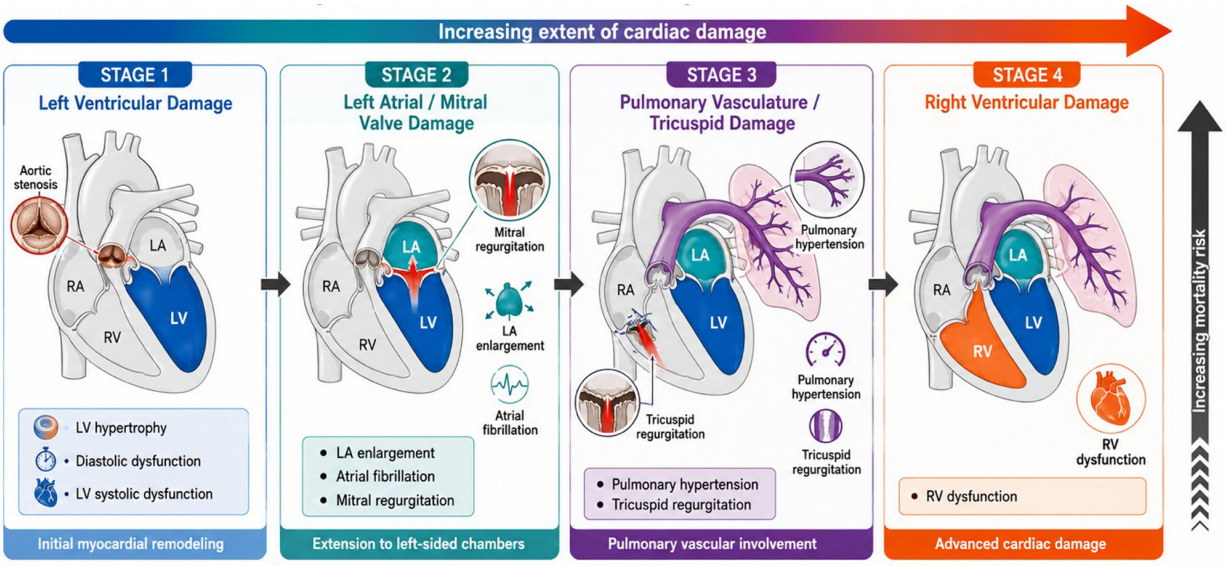


Fig. 1. Progressive extension of cardiac damage in AS. Chronic pressure overload from AS promotes a progressive cascade of structural and functional abnormalities that extends from the left ventricle (Stage 1) to the left atrium and mitral valve (Stage 2), pulmonary vasculature and tricuspid valve (Stage 3), and finally the right ventricle (Stage 4). Increasing stages of cardiac damage have consistently been associated with progressively worse clinical outcomes after both SAVR and TAVI. AS, aortic stenosis; LA, left atrium; LV, left ventricle/ventricular; RA, right atrium; RV, right ventricle/ventricular; SAVR, surgical aortic valve replacement; TAVI, transcatheter aortic valve implantation.

risk despite apparently favorable conventional risk stratification.

Functional TR, RV dysfunction, reduced tricuspid annular plane systolic excursion (TAPSE), and impaired RVAc have consistently emerged as markers of advanced disease and adverse outcomes [16,17,45,47], suggesting that pulmonary vascular and right-heart involvement reflect reduced cardiac reserve and a lower likelihood of complete recovery after intervention, irrespective of the treatment strategy. Consistent with this hypothesis, Harmon et al. [48] reported that, even in patients with moderate AS, staging of extra-valvular cardiac damage provides relevant prognostic information. Advanced cardiac damage (Stages 3–4, defined by pulmonary vascular, tricuspid, and RV involvement) was associated with the worst clinical outcomes. Specifically, patients in these stages had the highest incidence of the composite endpoint of all-cause death and HF hospitalization, reaching 254.8 events per 1000 person-years, compared with 51.6, 99.9, and 94.3 events per 1000 person-years in Stages 0, 1, and 2, respectively. In survival analyses, Stages 3 and 4 were associated with the highest risk of adverse outcomes (hazard ratio (HR) 4.43, 95% confidence interval (CI) 2.78–7.08), and this association remained significant after multivariable adjustment (HR 3.40, 95% CI 1.59–7.26). The authors also evaluated the evolution of cardiac damage over time in patients undergoing AVR, including both SAVR and TAVI. Notably, cardiac damage progressively accumulated while patients awaited intervention, and reverse remodeling after AVR was only partial. Similarly, Jacob et al. [49] showed that the absence of symptoms does not exclude advanced cardiac remodeling and that SAVR does not necessarily reverse established cardiac damage. Although some improvement was observed after treatment, many patients remained in advanced stages, suggesting that extra-valvular remodeling may not be completely reversible once established. These findings highlight the need for tools that identify myocardial dysfunction before irreversible cardiac remodeling develops. In this context, multimodality imaging has emerged as a complementary approach that identifies different stages of ventricular decompensation and improves both severity assessment and risk stratification. Reduced stroke volume index (SVi) $\leq$35 mL/m^2, conventionally assessed by Doppler echocardiography and potentially refined by three-dimensional echocardiography, reflects early hemodynamic impairment, whereas global longitudinal strain (GLS) and cardiac magnetic resonance tissue characterization through late gadolinium enhancement (LGE) and extracellular volume (ECV) identify progressive myocardial dysfunction and fibrosis [7,31,52]. Within this multimodality framework, stress echocardiography (SE) can provide functional information beyond resting imaging and improve identification of patients who may benefit from earlier intervention, particularly in selected clinical scenarios. Consistent with the most recent European Society of Cardiology/European Association for Cardio-Thoracic Surgery (ESC/EACTS) Guidelines, SE is recommended in patients with low-flow low-gradient AS to assess LV contractile re-

Table 2. Principal studies evaluating the prognostic impact of extra-valvular cardiac damage staging in AS.

Study	Population	Staging system	Clinical setting	Main endpoint	Principal findings	Clinical message
Généreux et al. [35]	Patients with AS	Original cardiac damage staging (Stages 0–4)	AS	Prognostic stratification	Increasing stage was associated with progressively worse outcomes	Cardiac damage provides prognostic value beyond AS severity
Bennett et al. [45]	Systematic review and meta-analysis (18 studies, >20,000 patients)	Généreux staging	Symptomatic severe AS; asymptomatic moderate-to-severe AS; post-AVR	CV and ACM	Cardiac damage was highly prevalent across the AS spectrum. Mortality increased progressively across stages	Increasing cardiac damage stage is associated with worse prognosis
Parada-Barcia et al. [46]	High-risk patients undergoing TAVI	Simplified Généreux classification (mild, moderate, severe)	TAVI	HF hospitalization and ACM	Right-sided cardiac damage was associated with the highest mortality and HF hospitalization rates	Right-sided cardiac damage confers higher risk after TAVI
Espinoza Romero et al. [16]	Patients undergoing SAVR	Modified Généreux classification	SAVR	Long-term ACM and CV readmissions	Right-sided cardiac damage was associated with the highest mortality despite relatively low surgical risk scores. Lower transaortic gradients were associated with worse prognosis	Cardiac damage staging improves risk stratification beyond conventional surgical scores
Román et al. [47]	Patients undergoing TAVI and SAVR	Multiple staging systems, including Gutiérrez-Ortiz classification	TAVI vs. SAVR	One-year ACM	TAVI patients had more advanced cardiac damage than SAVR patients. Right-sided cardiac damage independently predicted one-year mortality	Right-sided cardiac damage is associated with higher mortality
Harmon et al. [48]	Patients with moderate AS	Généreux staging	Moderate AS	ACM and HF hospitalization	Advanced cardiac damage independently predicted adverse outcomes. Reverse remodeling after AVR was only partial	Cardiac damage has prognostic value even in moderate AS
Jacob et al. [49]	Patients undergoing SAVR	Cardiac damage staging	SAVR	Evolution of cardiac damage after surgery	Absence of symptoms did not exclude advanced cardiac remodeling. Cardiac damage was incompletely reversible after SAVR	Timely treatment is needed before advanced remodeling develops

AS, aortic stenosis; AVR, aortic valve replacement; SAVR, surgical aortic valve replacement; TAVI, transcatheter aortic valve implantation; ACM, all-cause mortality; HF, heart failure; CV, cardiovascular.

serve and distinguish true severe from pseudo-severe stenosis, as well as in the evaluation of asymptomatic patients when clinical status and resting echocardiographic findings are discordant [7]. In addition to these established indications, recent evidence has proposed a broader role for SE in the comprehensive functional assessment of AS-related cardiac damage, particularly through the ABCDEG approach [53]. This multiparametric evaluation, by integrating the assessment of myocardial ischemia, pulmonary congestion, LV contractile reserve, coronary microvascular function, autonomic reserve, stress-induced transvalvular hemodynamics, may allow a more complete characterization of the clinical phenotype and may improve risk stratification before advanced structural cardiac damage becomes

evident. A recent systematic review further reported the prognostic relevance of several stress-derived parameters not only in severe asymptomatic AS but also in moderate AS. Among these, exercise-induced increases in mean transvalvular gradient, elevated E/e′ ratio, exercise-induced PH, and reduced exercise capacity emerged as the most reproducible predictors of adverse clinical outcomes [54].

6. SAVR Versus TAVI: Current Evidence and the Role of Cardiac Damage

The growing recognition that the extent of extra-valvular cardiac involvement influences prognosis in AS raises an important question: should patients with varying degrees of cardiac damage be expected to derive similar benefit from SAVR and TAVI? Over the past decade, randomized trials and large observational studies have progressively expanded indications for TAVI from inoperable and high-risk patients to intermediate- and low-risk populations, demonstrating outcomes comparable to SAVR across selected groups [7]. However, most pivotal trials that established equivalence between treatment strategies were primarily designed around procedural risk, symptom burden, and valve-related variables. In contrast, the extent of pre-existing cardiac damage was not incorporated into patient allocation or treatment algorithms [7,55,56]. Thus, current evidence supporting procedural selection remains largely independent of the biological stage of myocardial remodeling. Emerging evidence suggests that patients undergoing TAVI and SAVR may not arrive at intervention with comparable degrees of extra-valvular involvement [17,47,57]. In real-world cohorts, patients treated with TAVI are generally older, present with a greater burden of comorbidities, and frequently exhibit more advanced structural and hemodynamic abnormalities at baseline than those treated with SAVR [47]. Several mechanisms may contribute to this observation. First, interpreting symptoms in older patients is often challenging. Functional limitation, frailty, chronic pulmonary disease, reduced exercise capacity, and pre-existing HF may obscure the onset of AS-related symptoms and delay referral, even as cardiac remodeling progresses. Second, symptom-based surveillance strategies may be less sensitive in older populations because declining functional status is frequently attributed to age or comorbid disease rather than to progressive valvular burden. Together, these factors may favor the accumulation of extra-valvular cardiac damage before treatment is ultimately performed.

Roman and colleagues [17] showed that patients selected for TAVI had a greater burden of advanced cardiac damage, including lower LV systolic performance, larger LA dimensions, higher filling pressures, more frequent pulmonary vascular involvement, lower TAPSE values, and greater impairment of RVAc compared with SAVR populations. Importantly, the difference was not limited to age and appeared particularly driven by a higher prevalence of advanced right-heart involvement. These observations raise an important clinical consideration. If TAVI populations frequently present for treatment at more advanced stages of cardiac remodeling, comparisons of procedural outcomes may partly reflect differences in baseline disease biology rather than the intrinsic superiority of one intervention. Cardiac damage staging provides an additional perspective for interpreting these findings. Across several cohorts, increasing stage remained associated with progressively worse outcomes following both SAVR and TAVI, suggesting that the burden of cardiac remodeling influences prognosis independently of treatment modality [13,44,51]. Importantly, advanced stages, particularly those with pulmonary and right-heart involvement, retained prognostic significance even after adjustment for conventional surgical risk scores. These observations raise the possibility that, beyond procedural risk estimation alone, the extent of extra-valvular cardiac damage may inform treatment selection by identifying patients with a reduced likelihood of functional recovery despite technically successful intervention. In this context, some authors [16] have proposed that patients with advanced cardiac damage, particularly those with PH and/or RV involvement, may derive greater benefit from less invasive approaches. However, current evidence does not support the conclusion that one treatment strategy should be systematically preferred according to stage alone. Some observational studies suggested that increasing cardiac damage may have a more pronounced effect on peri-procedural outcomes after SAVR than in TAVI, leading to the hypothesis that less invasive approaches could partially attenuate the procedural burden in patients with advanced disease [57]. Nevertheless, these observations derive predominantly from retrospective analyses and administrative databases and remain vulnerable to residual confounding and indication bias. Therefore, these observations should not be interpreted as evidence that TAVI modifies the biological consequences of advanced remodeling.

Meanwhile, available data indicate that correction of valvular obstruction does not necessarily translate into complete reversal of cardiac damage, as previously discussed [58], although available evidence remains heterogeneous. Jacob et al. [49] showed that progression of cardiac damage may continue despite intervention, while Généreux et al. [14] demonstrated that post-procedural evolution of cardiac damage, including improvement, persistence, or worsening, carries independent prognostic implications after AVR [44,49]. Similarly, Zhou et al. [59] introduced the concept of dynamic cardiac damage, showing that early post-TAVI changes in stage were independently associated with long-term outcome and that residual cardiac damage remained clinically meaningful even after successful intervention [59]. These observations challenge the traditional assumption that valve replacement necessarily interrupts disease progression once hemodynamic obstruction has been relieved. An additional question concerns

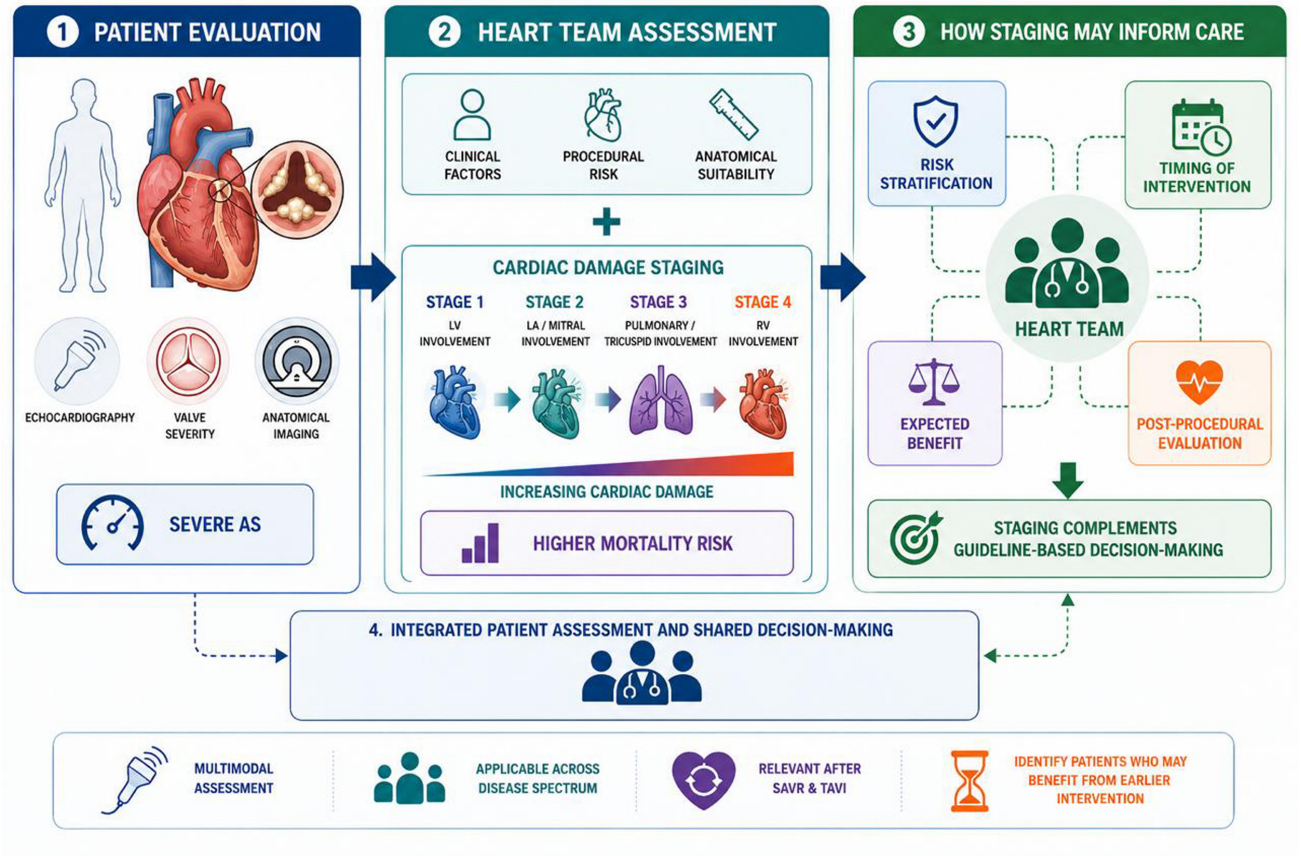


Fig. 2. Potential integration of cardiac damage staging into contemporary management of AS. Current decision-making in AS is based on an integrated assessment of symptoms, valve severity, procedural risk, age, frailty, and anatomical suitability. Cardiac damage staging may provide additional prognostic information by incorporating the extent of extra-valvular cardiac involvement into patient evaluation, thereby supporting Heart Team-based risk stratification, timing of intervention, estimation of expected benefit, and post-procedural assessment. AS, aortic stenosis; LV, left ventricle/ventricular; LA, left atrium; RV, right ventricle/ventricular; SAVR, surgical aortic valve replacement; TAVI, transcatheter aortic valve implantation.

whether current guideline recommendations may contribute to delayed intervention in some patients. Contemporary guidelines [7] primarily rely on symptom status, severity of valve obstruction, LV systolic dysfunction, and procedural risk assessment. While these criteria remain supported by robust evidence, they do not systematically incorporate the extent of extra-valvular remodeling. This may become particularly relevant in elderly or multimorbid populations, where symptom recognition is often delayed, and structural damage may already be advanced by the time treatment thresholds are reached. A potential framework for integrating cardiac damage staging into contemporary management of AS is illustrated in Fig. 2.

7. Future Perspectives

The growing evidence supporting the prognostic relevance of staging cardiac damage raises important questions regarding its future role in the management of AS. However, several important clinical and research questions remain unresolved (Table 3).

The potential applications of current staging systems may extend beyond risk stratification and contribute to a more comprehensive assessment of disease progression and the timing of intervention. Several observations support this perspective. Cardiac damage appears to accumulate progressively throughout the natural history of AS and may already be present before symptom onset. Furthermore, increasing evidence suggests that reverse remodeling following AVR is often incomplete, particularly when advanced pulmonary vascular and right-sided cardiac involvement have already developed [13,14,48,49]. In addition, recent studies have shown that post-procedural changes in cardiac damage stage provide independent prognostic information, introducing the concept of dynamic cardiac damage assessment as a potential marker of treatment response and residual risk [13,59]. Therefore, future research may shift from simply identifying cardiac damage to understanding its temporal evolution. Interestingly, emerging evidence suggests that moderate AS is not a benign condition but is associated with substantially increased mortality com-

Table 3. Outstanding questions and future directions.

Outstanding question	Current evidence	Future priority
Which staging system should be adopted in routine practice?	Multiple structural, hemodynamic, and functional models exist, without universal consensus.	External validation and harmonization of staging criteria.
Should structural and functional imaging be integrated?	Emerging evidence suggests incremental value of myocardial deformation and RVAc.	Development of multimodality staging algorithms.
Can cardiac damage staging identify patients who benefit from earlier AVR?	Observational studies suggest benefit before advanced remodeling, but causality is unproven.	Prospective trials evaluating staging-guided intervention.
Is advanced cardiac damage reversible after SAVR or TAVI?	Reverse remodeling is variable and often incomplete.	Identification of reversible versus irreversible components of damage.
Can residual or dynamic cardiac damage guide follow-up?	Early studies suggest post-procedural staging has prognostic value.	Longitudinal studies incorporating serial imaging assessments.
Should cardiac damage staging be incorporated into future guidelines?	Evidence consistently supports prognostic value but remains observational.	Randomized evidence and standardized staging definitions.

RVAc, right ventricular–arterial coupling; AVR, aortic valve replacement; SAVR, surgical aortic valve replacement; TAVI, transcatheter aortic valve implantation.

pared with mild or no AS, with an even greater adverse prognostic impact in patients with LV systolic dysfunction [60,61]. A recent meta-analysis of more than 400,000 patients demonstrated that moderate AS is associated with a markedly increased risk of all-cause mortality and significant loss of life expectancy, challenging the traditional view of moderate AS as a relatively low-risk stage of disease [62]. These observations suggest that, in some patients, the biological progression of the disease may outpace its hemodynamic classification. Therefore, the presence of extra-valvular cardiac damage may identify individuals in whom myocardial remodeling and ventricular decompensation are already well established despite only moderate transvalvular obstruction. In this context, cardiac computed tomography (CCT) represents an important complementary imaging modality. While computed tomography-derived aortic valve calcium score (CT-AVC) is established for confirming AS severity in patients with low-flow low-gradient or discordant hemodynamic findings using sex-specific thresholds (>2000 Agatston units (AU) in men and >1200 AU in women), its accuracy may be reduced in low-calcium or fibrosis-predominant phenotypes [7]. CT-AVC has also shown incremental prognostic value across the spectrum of AS, including moderate disease, while emerging CCT applications may enable a more comprehensive assessment of extra-valvular cardiac damage through quantitative evaluation of ventricular function, myocardial deformation, and extracellular volume [63,64]. Therefore, integrating these complementary CT findings with cardiac damage staging may improve patient selection for closer surveillance or earlier intervention before irreversible remodeling develops. The growing interest in earlier intervention is reflected in recent clinical studies [65,66]. In a contemporary systematic review and meta-analysis of four randomized trials with a mean follow-up of 4.1 years, early AVR in asymptomatic severe AS significantly reduced HF hospitalizations and stroke compared with clinical surveillance. However, no significant reductions in all-cause or cardiovascular mortality were observed. Similarly, the TAVR UNLOAD trial [66] demonstrated that, among patients with moderate AS and HF with reduced ejection fraction, TAVI was safe and resulted in greater improvements in health status and quality of life, despite failing to meet its primary endpoint. Although these studies do not support routine intervention in moderate AS, they reinforce the concept that waiting for progression to conventionally defined severe stenosis may not represent the optimal strategy for all patients. Whether staging of cardiac damage can identify subgroups that derive greater benefit from earlier AVR remains an important unanswered question and a key focus of ongoing prospective trials. In this context, serial assessment of cardiac damage could help identify patients at risk of progressive myocardial deterioration despite apparently stable clinical status and may eventually help refine the timing of intervention before irreversible remodeling becomes established. Another area of interest could be integrating staging systems with emerging markers of myocardial injury and reserve. Advanced echocardiographic parameters, myocardial deformation imaging, cardiac magnetic resonance assessment of fibrosis, and circulating biomarkers may provide complementary information beyond conventional structural evaluation (Table 4) [54,67].

Integrating multimodal imaging and biological markers could improve characterization of disease severity and enhance the ability of staging models to identify patients with limited potential for functional recovery after AVR [15,42,53,54]. However, several challenges remain before cardiac damage staging can be incorporated into routine clinical decision-making. Existing classifications differ substantially in terms of methodology, variables included, and definitions of advanced disease. Moreover, most available evidence derives from observational studies, retrospective analyses, or post hoc investigations. Large prospective studies specifically designed to evaluate staging-guided

Table 4. Multimodal imaging markers that support staging of cardiac damage and clinical decision-making.

Cardiac damage and imaging assessment	Key imaging markers	Prognostic significance	Potential clinical implication
LV damage	LVEF, GLS, SVi, LGE, ECV	Early myocardial dysfunction; HF; mortality	Earlier AVR; closer surveillance
LA and MV involvement	LAVI, moderate/severe MR	Progressive remodeling; adverse outcomes	Risk stratification; earlier AVR
Pulmonary vascular involvement	PASP	Advanced disease; post-AVR mortality	Identify advanced cardiac damage
RV and TV involvement	TAPSE, RVAc, RV dysfunction, RVLS, moderate/severe TR	Advanced cardiac damage; persistent mortality after AVR	Limited reverse remodeling; residual risk
Functional assessment	Stress echocardiography	Contractile reserve; exercise hemodynamics; deformation reserve	Individualized timing of intervention
Multimodality valve assessment	CT-AVC	Severity assessment; prognostic value	Integrated risk stratification

LV, left ventricle; LVEF, left ventricular ejection fraction; GLS, global longitudinal strain; SVi, stroke volume index; LGE, late gadolinium enhancement; ECV, extracellular volume; HF, heart failure; AVR, aortic valve replacement; LA, left atrium; MV, mitral valve; LAVI, left atrial volume index; AF, atrial fibrillation; MR, mitral regurgitation; PASP, pulmonary artery systolic pressure; RV, right ventricle; RVAc, right ventricular–arterial coupling; RVLS, right ventricular longitudinal strain; TV, tricuspid valve; TAPSE, tricuspid annular plane systolic excursion; TR, tricuspid regurgitation; CT-AVC, computed tomography-derived aortic valve calcium score.

management strategies remain limited. Moreover, whether future guidelines will incorporate cardiac damage staging remains uncertain. Several ongoing prospective clinical trials are expected to provide important insights into whether earlier AVR can modify the natural history of cardiac damage. In particular, randomized studies evaluating early AVR in asymptomatic severe AS (e.g., NCT04204915), as well as trials investigating intervention in patients with moderate AS and LV dysfunction or other high-risk phenotypes (e.g., NCT05310461; NCT04889872), may help determine whether cardiac damage staging can identify patients who derive greater benefit from earlier intervention before irreversible myocardial remodeling occurs. These studies may also clarify whether cardiac damage is merely a marker of disease severity or a modifiable therapeutic target that can be altered through timely AVR.

8. Conclusion

AS should no longer be considered exclusively a valvular disorder but rather a progressive disease involving the entire cardiovascular system. Growing evidence indicates that the extent of extra-valvular cardiac damage provides important prognostic information beyond conventional measures of valve severity and procedural risk.

Therefore, staging of cardiac damage should be viewed as a complementary tool that enriches patient characterization by integrating the cumulative consequences of chronic pressure overload into clinical assessment. However, current evidence does not support its use as a standalone criterion for intervention or for selecting between SAVR and TAVI. Rather, its principal value lies in improving risk stratification, supporting a personalized lifetime management strategy, and potentially identifying selected patients who may benefit from closer surveillance or earlier intervention. As the management of AS continues to evolve, cardiac damage staging will likely need to be integrated with both conventional echocardiographic parameters and dynamic markers of disease progression, including SE, advanced imaging, and circulating biomarkers, to define the optimal timing of intervention, preserve myocardial reserve, and prevent irreversible cardiac damage. Structural remodeling, hemodynamic abnormalities, myocardial dysfunction, ventricular–vascular interaction, and clinical presentation could provide complementary information rather than alternative interpretations of disease severity.

Abbreviations

AF, atrial fibrillation; AS, aortic stenosis; AVR, aortic valve replacement; CCT, cardiac computed tomography; CT-AVC, computed tomography-derived aortic valve calcium score; ECV, extracellular volume; LGE, late gadolinium enhancement; HF, heart failure; LA, left atrium/left atrial; LV, left ventricle/left ventricular; LV-GLS, left ventricular global longitudinal strain; LVEF, left ventricular ejection fraction; MR, mitral regurgitation; MV, mitral valve; PH, pulmonary hypertension; PASP, pulmonary artery systolic pressure; RV, right ventricle/right ventricular; RVAc, right ventricular–arterial coupling; RVLS, right ventricular longitudinal strain; SAVR, surgical aortic valve replacement; SE, stress echocardiography; STS-PROM, Society of Thoracic Surgeons Predicted Risk of Mortality; SVi, stroke volume index; TAVI, transcatheter aortic valve implantation; TAPSE, tricuspid annular plane systolic excursion; TR, tricuspid regurgitation; TV, tricuspid valve.

Author Contributions

All authors contributed significantly to this work and read and approved the final version of the manuscript. SR performed the literature research and wrote the manuscript; MV performed the design and conception of the study and wrote the manuscript; EG, SI, EV, AS, ADB, GS contributed substantially to the analysis and interpretation of the reviewed literature through critical scientific evaluation and revision of the manuscript for important intellectual content. All authors contributed to editorial changes in the manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

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Declaration of AI and AI-Assisted Technologies in the Writing Process

During the preparation of this work, the authors used ChatGPT version GPT-5.5 (OpenAI, San Francisco, CA, USA) in order to check spelling and grammar. After using this tool, the authors reviewed and edited the content as needed and took full responsibility for the content of the publication.

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