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Cardiac remodelling in aortic stenosis

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ABSTRACT

Aortic stenosis (AS) imposes a chronic, progressive pressure overload on the left ventricle. The myocardium responds through a sequence of mechanical and biological processes that initially preserve wall stress and cardiac output but eventually become maladaptive, leading to fibrosis, loss of contractile reserve and clinical heart failure. Integrating myocardial fibrosis assessment and staging frameworks into clinical decision-making may support earlier valve replacement, even before conventional triggers such as symptoms or reduced ejection fraction, to prevent irreversible myocardial damage in patients with severe/significant AS. Advances in imaging biomarkers – including cardiac magnetic resonance-derived late gadolinium enhancement, extracellular volume quantification and strain analysis – allow for more personalized risk stratification and may help identify which patients with asymptomatic severe AS stand to benefit most from earlier intervention. Beyond the valve procedure itself, adjunctive pharmacological strategies, such as antifibrotic therapies, renin–angiotensin system blockade, neprilysin inhibition and metabolic modulators, are being explored to address persistent fibrotic and metabolic remodelling that valve replacement alone cannot reverse. Equally important is the optimal treatment of concomitant cardiovascular comorbidities such as hypertension, coronary artery disease and atrial fibrillation, which may aggravate myocardial remodelling and blunt the benefits of valve replacement if left untreated.

1. Abbreviations

AS	aortic stenosis
AVR	aortic valve replacement
LGE	late gadolinium enhancement
TGF-β	transforming growth factor-β

2. Background

Aortic stenosis (AS) imposes a chronic, progressive pressure overload on the left ventricle. The myocardium responds through a sequence of mechanical and biological processes that initially preserve wall stress and cardiac output but eventually become maladaptive, leading to fibrosis, loss of contractile reserve and clinical heart failure. Cardiac remodelling determines patient outcomes and could be used to refine intervention timing. Recent advances in understanding molecular pathways, imaging characterization and sex-specific patterns have improved clinical management of patients with AS.

3. Pathophysiology of cardiac remodelling in AS

3.1. Wall stress and the LaPlace principle: where mechanical stimulus originates

Left ventricular (LV) wall stress is determined fundamentally by intracavitary pressure, chamber radius and wall thickness (i.e. the LaPlace law):

$$wall\ \ stress = \frac{pressure \times LV\ \ radius}{2 \times wall\ \ thickness}$$

In AS, chronic elevation of systolic LV pressure increases circumferential wall stress; hypertrophic thickening initially normalizes stress by reducing radius/wall thickness ratio. However, geometric simplifications in the classical LaPlace formulation miss regional variations in stress caused by myocardial geometry, fibre architecture and heterogeneous loading. Finite-element and patient-specific modelling show that subendocardial regions and basal segments frequently bear the highest stress burden in AS, explaining the propensity for subendocardial ischaemia and regionally accentuated remodelling [1,2]. These complex patterns of intramural stress distribution are functionally important because

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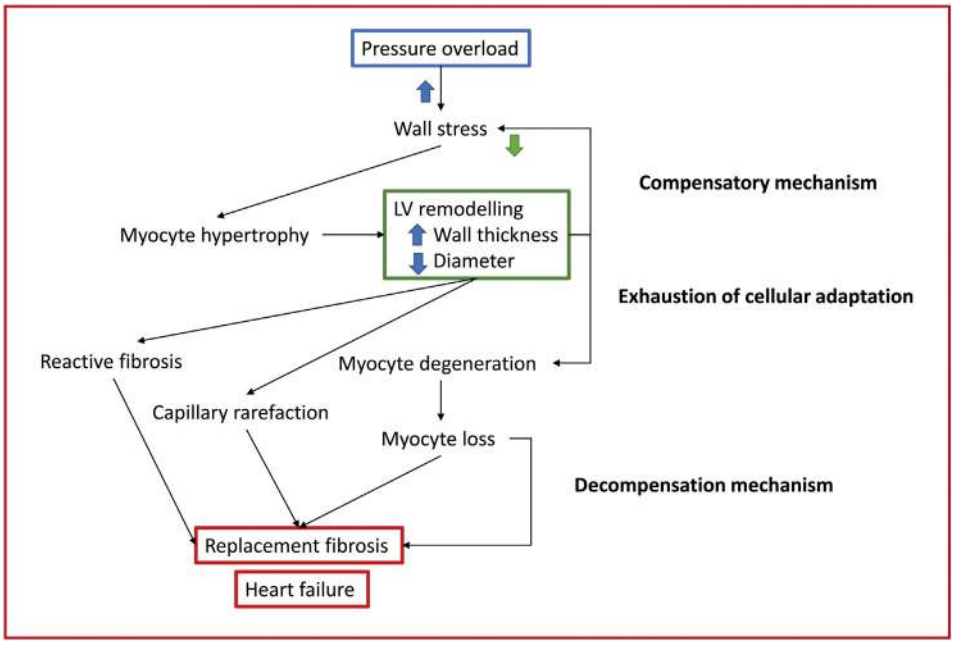


Fig. 1. Pathophysiological mechanisms from compensatory cardiac remodelling to heart failure decompensation in AS. This schema shows the progression from compensatory cardiac remodelling to decompensation and heart failure. Pressure overload leads to increased wall stress, triggering myocyte hypertrophy and LV remodelling with increased wall thickness and altered diameter as compensatory mechanisms. When cellular adaptation becomes exhausted, myocyte degeneration occurs, leading to myocyte loss, reactive fibrosis and capillary rarefaction. These decompensation mechanisms result in replacement fibrosis and ultimately progress to heart failure. AS: aortic stenosis; LV: left ventricular.

local mechanical load is a proximate trigger for mechanotransduction pathways in cardiomyocytes and fibroblasts.

3.2. Compensatory mechanisms: hypertrophic remodelling to normalize wall stress

In response to chronically increased afterload, the left ventricle undergoes concentric hypertrophy characterized by increased cardiomyocyte cross-sectional area, increased wall thickness and relative preservation of cavity size: a pattern that reduces wall stress and maintains systolic performance for prolonged periods (Fig. 1). This adaptive hypertrophy is driven by several overlapping signalling cascades activated by mechanical stretch, neurohormonal stimuli (angiotensin II, catecholamines), growth factors and metabolic cues. Key intracellular mediators include PI3K/Akt signalling (physiologic and early adaptive hypertrophy) and downstream activation of mTORC1, which promotes protein synthesis and myocyte growth via S6K1 and 4E-BP1 [3]. MAPK/ERK and calcineurin-NFAT pathways also participate, and their relative activation contributes to whether hypertrophy retains a compensated phenotype or progresses towards maladaptation [4].

Metabolic reprogramming accompanies structural remodelling: hypertrophied myocardium shifts substrate use from fatty acids towards greater glucose reliance, with relative energetic inefficiency and impaired mitochondrial function observed as disease progresses. Autophagy and proteostasis pathways are altered during sustained pressure overload, contributing to cardiomyocyte dysfunction when compensatory processes can no longer match demand [5].

3.3. Hypertrophy and progressive fibrosis: from reactive interstitial fibrosis to focal replacement scars

While hypertrophy initially normalizes wall stress, persistent mechanical and paracrine injury (ischaemia, oxidative stress, neurohormonal signalling) triggers activation of cardiac fibroblasts and extracellular matrix remodelling. Two broad forms of fibrosis are relevant in AS: (1) diffuse reactive interstitial and perivascular fibrosis (increased collagen deposition between myocytes) and (2) focal replacement fibrosis (scar) resulting from cardiomyocyte loss and local necrosis/apoptosis (Fig. 1). Mechanistically, transforming growth factor-β (TGF-β) is a central profibrotic cytokine in pressure overload: binding to its receptors leads to Smad2/3 phosphorylation and nuclear transcriptional programmes that upregulate collagen I/III and matricellular proteins, promote fibroblast-to-myofibroblast transition (α-smooth muscle actin expression) and increase cross-linking enzymes (e.g. lysyl oxidase), thereby stiffening the myocardium [6,7]. Matrix metalloproteinases and their inhibitors (tissue inhibitors of metalloproteinases) undergo dynamic dysregulation during disease: early increases in certain matrix metalloproteinase activities may accompany matrix turnover, while later tissue inhibitors of metalloproteinases dominance favours collagen accumulation and stiffness [8].

Focal replacement fibrosis in AS is often subendocardial or patchy and reflects areas of chronic ischaemic injury or microinfarction due to supply-demand mismatch (see below). Clinically, replacement scars detected by late gadolinium enhancement (LGE) on cardiac magnetic resonance identify regions of irreversible injury and associate with worse post-aortic valve replacement (AVR) outcomes. In contrast, diffuse interstitial fibrosis, quantified by T_1 mapping/extracellular volume fraction, correlates with diastolic dysfunction and exercise intolerance. Quantitative studies have emphasized that both types of fibrosis accumulate gradually and that cross-linking (and resulting stiffness) increases disproportionately with disease duration and severity [9]. Thus, LGE and T_1 mapping serve as complementary imaging biomarkers that help distinguish irreversible scarring from potentially reversible diffuse fibrosis [10]. Emerging evidence also supports the use of T_2 mapping to detect areas of active inflammation or oedema, which may represent an early, reversible stage of myocardial injury [11]. However, further research is needed to validate this technique in AS [12].

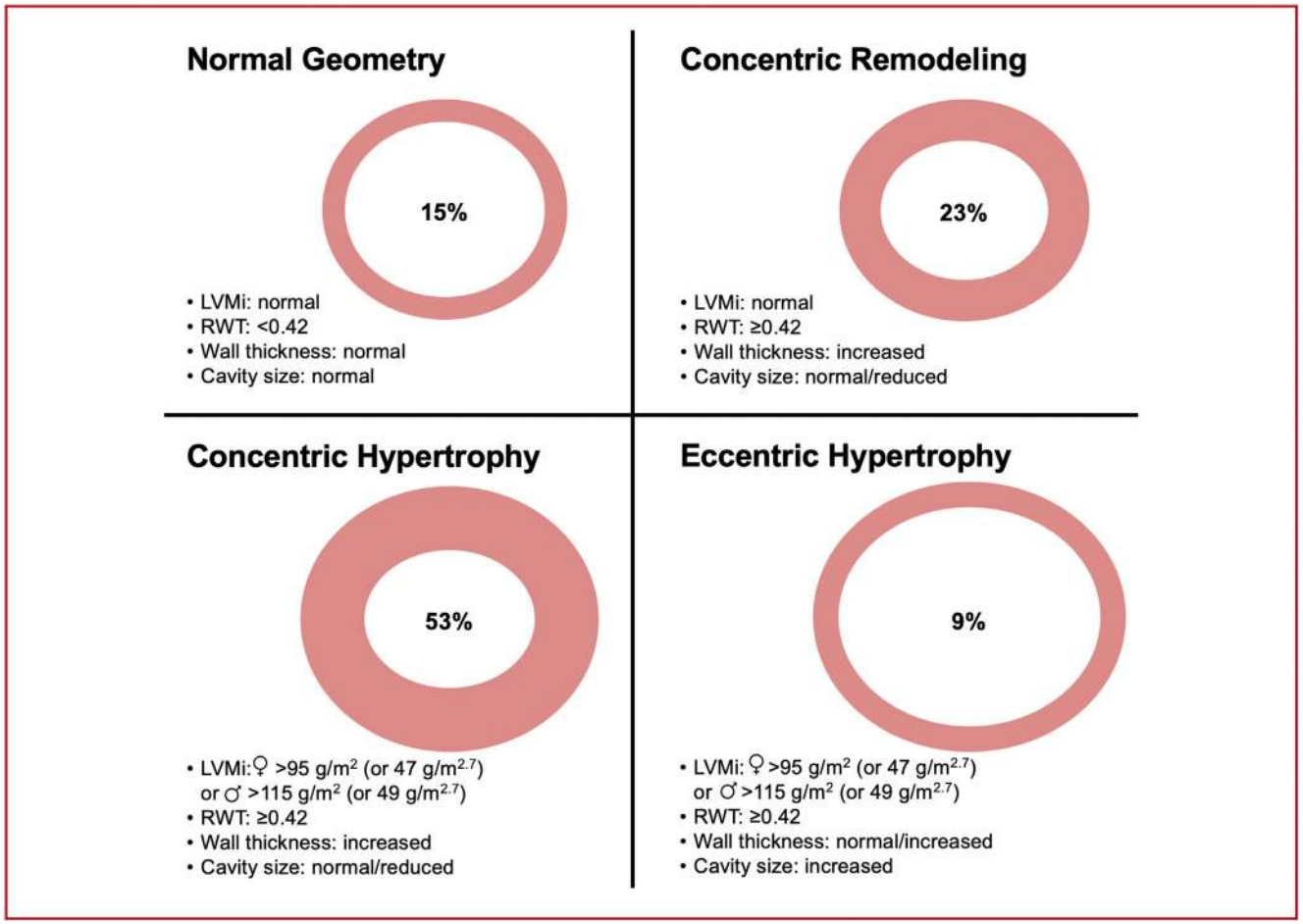


Fig. 2. Classification of LV remodelling pattern in AS. LV geometry and remodelling patterns in AS, adapted from Capoulade et al. [17]. The pink rings represent the LV wall, with percentages indicating relative wall thickness. AS: aortic stenosis; LV: left ventricular; LVMi: left ventricular mass index; RWT: relative wall thickness.

3.4. Coronary supply-demand mismatch and microvascular disease as amplifiers of fibrosis

Concomitant to hypertrophy and extracellular matrix changes, the myocardial capillary network often fails to expand proportionally with myocyte growth (capillary rarefaction) and microvascular dysfunction becomes prevalent in AS (Fig. 1) [13]. Reduced coronary reserve, impaired subendocardial perfusion during systole and increased extravascular compressive forces synergistically create chronic subendocardial ischaemia. This ischaemic milieu promotes myocyte death, replacement scarring and further fibrotic signalling via hypoxia-driven pathways and inflammation.

3.5. Transition to decompensation and heart failure

When compensatory mechanisms can no longer normalize wall stress or when fibrosis and microvascular disease reach a critical extent, the left ventricle transitions from compensated hypertrophy to decompensation. Hallmarks of this phase include progressive diastolic dysfunction (increasing stiffness and impaired relaxation), rising filling pressures, exercise intolerance and, eventually, systolic dysfunction with chamber dilation in some patients. The mechanisms driving decompensation are multifactorial and encompass all the previously presented phenomena: accumulated diffuse fibrosis that increases passive stiffness [14], replacement fibrosis that causes irreversible loss of contractility [15], microvascular rarefaction and impaired coronary flow reserve that limit oxygen delivery and increase susceptibility to ischaemia during stress, accelerating myocyte loss [16] (Fig. 1), and metabolic dysfunction reducing energetic reserve and promoting maladaptive remodelling and cell death [4].

The clinical implication is that measures of valve severity alone do not fully capture myocardial health or the risk of irreversible damage. Imaging biomarkers (LGE for focal scars; extracellular volume/T_1 mapping for diffuse fibrosis), biomarkers of extracellular matrix turnover and physiological measures of coronary microvascular function provide mechanistic insight into the timing of decompensation and might, therefore, refine indications and timing for valve intervention [15].

4. Patterns of LV remodelling and sex differences in LV remodelling associated with AS

In addition to the temporal mechanistic progression (from pressure overload to hypertrophy/fibrosis and finally decompensation), patterns of LV remodelling in AS show phenotypic variation. Interestingly, sex differences exist in how the myocardium remodels under AS.

4.1. Patterns of LV remodelling in AS

In addition to the normal geometry, three patterns have been described for LV remodelling, according to the LV mass and relative wall thickness ratio (Fig. 2).

The concentric remodelling refers to increased wall thickness ratio (i.e. thicker walls relative to cavity size) without a large

increase in total mass. This remodelling pattern is seen in approximately 25% of patients with AS [17].

The concentric hypertrophy is the canonical adaptive pattern in AS. It presents an increased LV wall thickness and an increased mass, with a preserved or reduced chamber volume. Approximately 50% of patients with severe AS present a concentric hypertrophy [17].

The eccentric hypertrophy is less common in AS (approximately 5–10% of patients). It is represented by an increased mass and a chamber dilatation, relative wall thickness being less increased [17].

An asymmetric remodelling, often with hypertrophy and septal-predominant wall thickening, has also been also reported in imaging cohorts. Approximately 20–50% of patients with hypertrophy show some asymmetric wall thickening [18].

These patterns have prognostic implications: concentric hypertrophy is associated with worse outcomes than normal geometry or purely concentric remodelling, especially in women [17]. Adverse dilated patterns that are often associated with reduced LV ejection fraction are a signal for more advanced disease and poor prognostic.

4.2. Sex differences in LV remodelling and fibrosis in AS

Multiple studies have shown that men and women differ in how their ventricles remodel and accumulate fibrosis in AS, even when valve severity is similar. Women with AS more often have normal geometry or concentric remodelling/hypertrophy with smaller cavity sizes and lower LV mass indices [19]. However, women display relatively greater diffuse fibrosis (increased extracellular volume) compared to men for a similar AS severity [19]. Men, in contrast, tend to develop greater hypertrophy, more focal scar formation and earlier signs of systolic dysfunction [20].

These differences imply that women may decompensate, not via dilatation and reduced ejection fraction, but rather via stiffness, impaired filling and elevated filling pressures. In men, decompensation more often includes loss of contractile units, dilatation and overt systolic impairment. Recognising these sex-specific remodelling trajectories may help to refine the timing of intervention, by identifying patients (particularly women) who are at risk of irreversible fibrosis even before classic markers of systolic dysfunction emerge [21].

4.3. Integration of the sex differences into the mechanistic continuum

These remodelling patterns and sex differences intersect with the mechanistic phases described earlier. Women tend to maintain a more 'adaptive' geometry for longer, characterized by concentric remodelling with relatively less hypertrophy. While initially protective, this adaptation often results in a higher wall-thickness-to-radius ratio, smaller ventricular cavities, impaired compliance and a greater propensity to develop symptoms earlier, particularly diastolic symptoms. In addition, women frequently accumulate diffuse interstitial fibrosis at an earlier stage of AS, reflected by increased extracellular volume that appears disproportionate to the degree of hypertrophy, thereby contributing to stiffness even in the presence of preserved ejection fraction. In contrast, men more often progress toward overt hypertrophy, focal replacement fibrosis and chamber dilatation consistent with eccentric remodelling, ultimately predisposing them to earlier systolic dysfunction. The higher absolute burden of fibrosis and LV mass in men, compounded by metabolic and microvascular mismatch, may accelerate decompensation once adaptive responses are exhausted. Importantly, these distinct patterns of remodelling carry prognostic value: concentric hypertrophy – especially when accompanied by myocardial fibrosis and the initial stages of dilation/disease [19] – portends worse outcomes compared with either normal geometry or isolated concentric remodelling. Moreover, reverse remodelling after AVR (surgical or transcatheter) also demonstrates sex-specific features, with women showing greater relative regression of wall thickness and relative wall thickness, whereas men experience larger absolute reductions in LV mass but potentially less improvement in fibrosis burden depending on the timing of intervention [22].

5. Cardiac damage staging in AS and risk stratification

The impact of AS on the myocardium and other cardiac structures is now increasingly understood as a continuum of damage that extends beyond valve narrowing alone. Several groups have proposed staging systems that integrate structural and functional sequelae of AS to better predict outcomes and guide timing of intervention [23].

5.1. Rationale for staging

Traditional evaluation of AS has focused solely on AS severity, especially valve area and transvalvular gradients/velocity. However, these parameters do not fully capture the degree of disease, as myocardial injury or the broader systemic effects of long-standing pressure overload are not considered. Patients with similar valve haemodynamics may have very different prognoses depending on the extent of fibrosis, chamber remodelling, atrial and right ventricular involvement, and pulmonary hypertension. Cardiac staging frameworks aim to systematize these downstream consequences into a progressive scale.

5.2. Comprehensive staging of cardiac damage

Originally, the staging system was developed in pre-transcatheter intervention patients (Fig. 3) [24]:

- stage 0: isolated valve disease, no cardiac damage;
- stage 1: LV damage: LV hypertrophy, elevated filling pressure or reduced ejection fraction;
- stage 2: left atrial or mitral valve damage: left atrial enlargement, atrial fibrillation or significant mitral valve regurgitation;
- stage 3: pulmonary vasculature or tricuspid valve damage: systolic pulmonary hypertension or significant tricuspid valve regurgitation;
- stage 4: right ventricular damage: right ventricular significant dysfunction.

More recent echocardiographic staging frameworks emphasize quantifiable markers of each step: LV global longitudinal strain or stroke volume index [25,26].

5.3. Prognostic value

Cardiac staging carries clear prognostic value, as higher stages consistently confer an incremental risk of adverse outcomes, with progressively worse survival observed with or without transcatheter/surgical AVR [24,25]. This underscores a key clinical implication: the paradigm is shifting from an exclusive focus on valve lesion severity to a more comprehensive evaluation of damage across the ventricular-atrial-pulmonary-right ventricular axis. By highlighting that the extent of myocardial and extracardiac involvement, rather than valve obstruction alone, drives prognosis, staging reinforces the central role of the myocardium in determining outcomes. Incorporating cardiac staging into routine assessment may therefore re-stratify patient's risk, particularly in

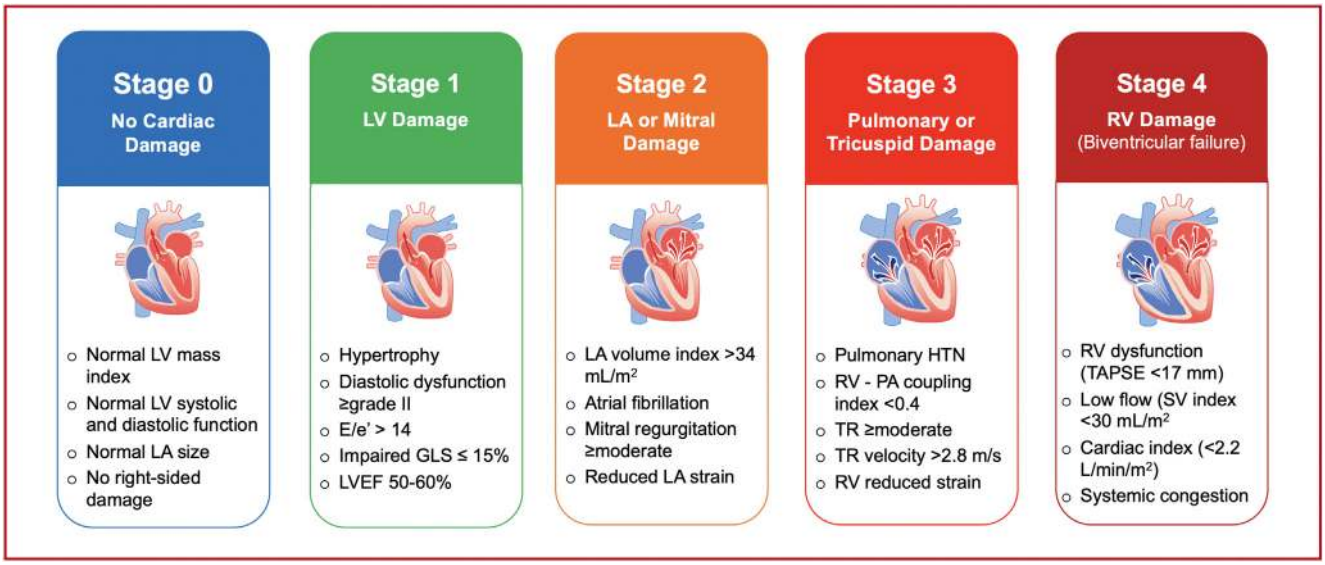


Fig. 3. Cardiac damage staging scheme in AS. This figure shows the classification system of cardiac damage in AS, adapted from Tastet et al. [25]. AS: aortic stenosis; GLS: global longitudinal strain; HTN: hypertension; LA: left atrial; LV: left ventricular; LVEF: left ventricular ejection fraction; RV: right ventricular; PA: pulmonary artery; SV: stroke volume; TAPSE: tricuspid annular plane systolic excursion; TR: tricuspid regurgitation.

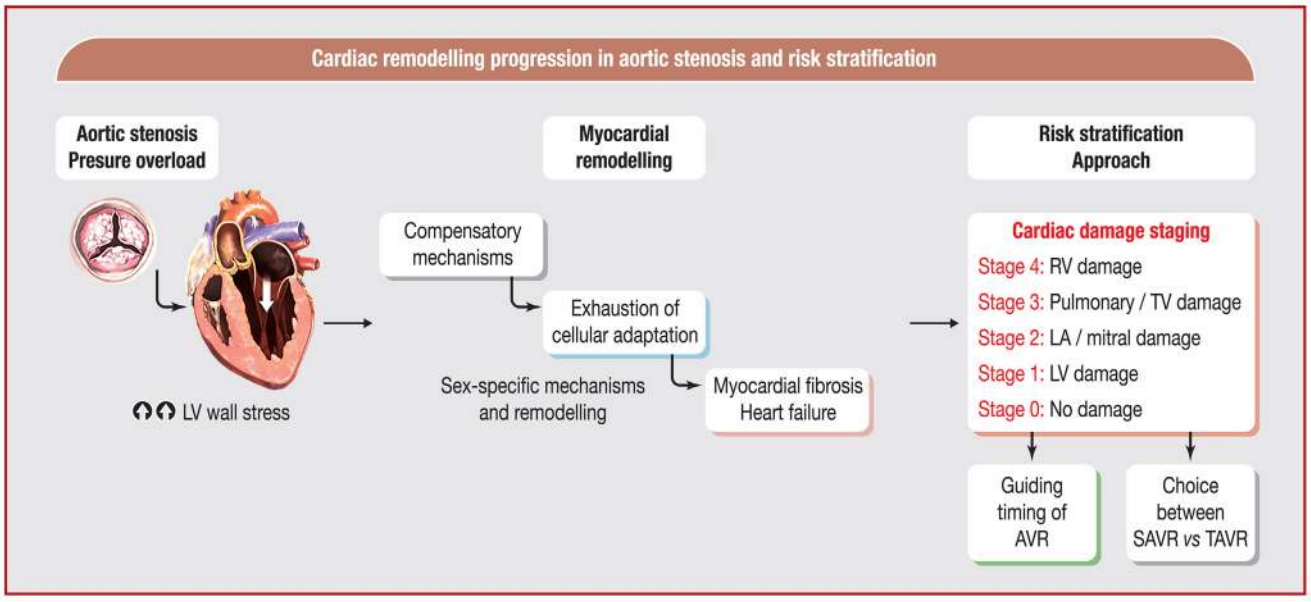
asymptomatic severe AS, where early recognition of advancing stage could prevent irreversible remodelling and improve long-term results.

5.4. Limitations of cardiac staging

A growing body of evidence indicates that cardiac damage in patients with AS is often present even at mild stages of valve obstruction and is strongly influenced by comorbid conditions rather than by the severity of the valve lesion alone. Indeed, in patients with mild AS (peak aortic velocity 2–3 m/s), only approximately 20% have no detectable cardiac damage (stage 0), the remaining 80% exhibit damage across stages 1–4, with over half already in stage 2 or higher [27]. Importantly, the extent of cardiac damage does not correlate with increasing valve velocity, but does increase with the number and severity of comorbidities such as hypertension, ischaemic heart disease, kidney disease and chronic lung disease [27]. These findings underscore that relying exclusively on valvular parameters (e.g. gradients or valve area) or on staging based on cardiac damage may mislead the timing of intervention. Thus, cardiac staging is very useful prognostically but cannot be the sole criterion for therapeutic decision-making; clinical context, AS severity, comorbidities and markers of myocardial injury or dysfunction must also inform the timing of valve intervention.

6. Therapeutic implications and future perspectives

In conclusion, integrating myocardial fibrosis assessment and staging frameworks into clinical decision-making may support earlier valve replacement, even before conventional triggers such as symptoms or reduced ejection fraction, to prevent irreversible myocardial damage in patients with severe/significant AS. Advances in imaging biomarkers – including cardiac magnetic resonance-derived LGE, extracellular volume quantification and strain analysis – allow for more personalized risk stratification and may help to identify which patients with asymptomatic severe AS stand to benefit most from earlier intervention. Beyond the valve procedure itself, adjunctive pharmacological strategy – such as antifibrotic therapies, renin–angiotensin system blockade, neprilysin inhibition and metabolic modulators – are being explored to address persistent fibrotic and metabolic remodelling that valve replacement alone cannot reverse. Equally important is the optimal treatment of concomitant cardiovascular comorbidities such as hypertension, coronary artery disease and atrial fibrillation, which may aggravate myocardial remodelling and blunt the benefits of valve replacement if left untreated. Finally, patients who already present at higher stages at the time of valve intervention warrant intensified surveillance, as residual fibrosis, pulmonary hypertension and limited potential for reverse remodelling continue to shape long-term outcomes (Central Illustration).



Central Illustration. Cardiac remodelling progression in AS and risk stratification. Cardiac remodelling in AS progresses from chronic pressure overload to compensatory hypertrophy, diffuse and focal fibrosis, microvascular dysfunction and ultimately heart failure decompensation. Sex-specific mechanisms are common, with women showing more concentric LV remodelling and diffuse fibrosis, while men present overt hypertrophy and replacement scarring. The cardiac damage staging concept (stages 0–4) integrates myocardial and extracardiac sequelae, providing a comprehensive prognosis and guiding intervention timing. AS: aortic stenosis; AVR: aortic valve replacement; LA: left atrial; LV: left ventricular; RV: right ventricular; SAVR: surgical aortic valve replacement; TAVR: transcatheter aortic valve replacement; TV: tricuspid valve.

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