Cardiovascular Ultrasound

REVIEW

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Moderate aortic stenosis: diagnostic pitfalls and the role of multimodality imaging in risk stratification and clinical management

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Abstract

Background Moderate aortic stenosis (AS) has traditionally been considered a transitional and relatively benign stage of valvular disease. Yet, contemporary evidence shows that it is associated with substantial morbidity and mortality even before progression to severe AS.

Main body of the abstract This paper synthesizes current evidence on the limitations of standard echocardiography, highlights the role of advanced imaging and artificial intelligence, and outlines evolving strategies for risk stratification and clinical management. Multimodality imaging provides a more accurate assessment of disease severity beyond conventional echocardiographic parameters: computed tomography aortic valve calcium scoring, cardiac magnetic resonance, and 18 F-sodium fluoride positron emission tomography reveal early myocardial injury and identify rapid progressors. AI further enhances reproducibility and supports the development of emerging prognostic models. A staging approach that integrates ventricular, atrial, and right-sided involvement correlates more closely with clinical outcomes than valve metrics alone, enabling a more comprehensive characterization of disease burden. Although guideline-directed surveillance remains the standard strategy for most patients, selected high-risk individuals, particularly those with adverse remodeling, elevated biomarkers, or recurrent heart failure admissions, may benefit from earlier intervention.

Short conclusion While waiting for the results of ongoing randomized trials cardiologist should implement all the imaging multimodality tools available in order to individuate patients in which an earlier treatment of moderate AS will more probably improve long-term outcomes.

Keywords Moderate Aortic Stenosis, Multimodality imaging, Advanced echocardiography, Strain imaging, CT calcium scoring, Cardiac magnetic resonance, ^18F-NaF PET, Artificial intelligence, Risk stratification

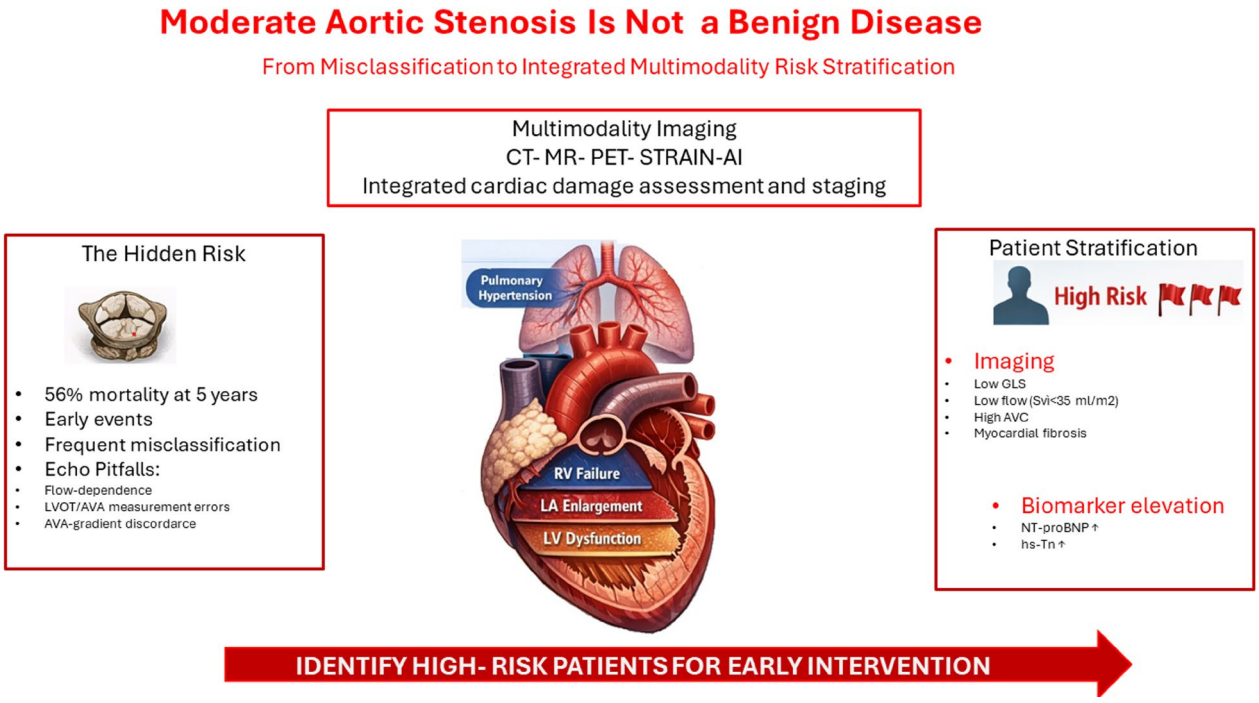
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Graphical Abstract



Introduction

Aortic stenosis (AS) is the most common valvular heart disease in developed countries, with both incidence and prevalence rising steeply with age [1]. Current European guidelines define moderate AS by an aortic valve area (AVA) of 1.0–1.5 cm^2 (indexed AVA 0.60–0.85 cm^2/m^2), a peak jet velocity (Vmax) of 3.0–3.9 m/s, and/or a transvalvular mean gradient (MG) of 20–39 mmHg under normal-flow conditions [2]. Table 1 summarizes the American Society of Echocardiography (ASE) / European Association of Cardiovascular Imaging (EACVI) echocardiographic thresholds for grading moderate AS and, importantly, highlights the main technical limitations of each parameter—an essential step given the frequent discordance between valve area and gradients in real-world practice.

Registry data suggest that moderate AS accounts for 30–45% of clinically relevant AS in elderly cohorts [3–5]. Traditionally considered an intermediate stage toward severe disease, moderate AS is increasingly recognized as a heterogeneous and clinically meaningful entity. Longitudinal studies reveal that many patients progress to severe AS within a few years. Yet, adverse outcomes such as heart failure (HF) hospitalization and mortality can also occur without apparent echocardiographic progression [6, 7]. The clinical staging system proposed by Généreux et al., distinguishing stable, progressive, and acute valve syndromes, highlights that some patients present with acute decompensation, bypassing mild symptoms, and experience markedly higher mortality and HF hospitalization rates following aortic valve replacement (AVR) [7]. Risk in moderate AS is not dictated solely by valvular hemodynamics. Comorbidities, particularly chronic kidney disease, contribute to myocardial remodeling and dysfunction [8].

Furthermore, emerging parameters, such as a reduced transaortic flow rate (FR < 218 mL/s), have demonstrated prognostic value [6]. Conventional Doppler indices remain central to diagnosis (Fig. 1). However, they are insufficient to fully capture the interplay among valvular obstruction, ventricular–arterial coupling, and systemic comorbidity burden. Consequently, an integrated assessment is required. Imaging modalities can be complemented by biomarker profiling and advanced hemodynamic measures, including FR and valvular-arterial impedance, offering a more nuanced view of disease activity [9]. This review aims to integrate emerging evidence to support a multimodal, imaging clinical framework that refines risk stratification, optimizes intervention timing, and personalizes management in moderate AS, a stage frequently underestimated yet carrying significant clinical risk.

Table 1 Classification of moderate aortic stenosis through multimodality imaging

Parameter	Moderate AS cut-off (ASE/EACVI)	How it is measured	Main limitations	What to do if discordant
Vmax	3.0–3.9 m/s	CW Doppler from multiple windows	Angle dependence; underestimation if windows not systematically interrogated	→ Reacquire from apical + right parasternal + suprasternal + Pedoff before any reclassification
Mean Gradient (MG)	20–39 mmHg	Derived from Bernoulli equation	Strongly flow-dependent; affected by pressure recovery and small aortic roots	→ Check flow status (SVi, FR) and consider pressure recovery if small root
AVA (continuity equation)	1.0–1.5 cm^2 (indexed 0.60–0.85 cm^2/m^2)	LVOT diameter + LVOT VTI + AV VTI	Highly sensitive to LVOT diameter; assumes circular LVOT	→ Verify LVOT measurement; consider CT-AVA if doubt persists
DVI	0.25–0.50	Ratio LVOT VTI / AV VTI	Still flow-dependent; unreliable in arrhythmias or very low flow	→ If DVI < 0.25 with moderate gradients, evaluate low-flow physiology
Stroke Volume Index (SVi)	Normal ≥ 35 mL/m^2	Echo volumetry or Doppler	Load-dependent	→ If < 35, evaluate low-flow AS
Flow Rate (FR)	Normal ≥ 218 mL/s	SV / ejection time	Less widely used; needs careful timing	→ If < 218 mL/s, treat as *concealed low-flow*
AT/ET ratio	Typically > 0.35 normal	CW Doppler contour	Influenced by HR and loading	→ Low AT/ET supports higher hemodynamic burden

AS Aortic stenosis, *AVA* Aortic valve area, *AVC* Aortic valve calcium, *CMR* Cardiac magnetic resonance, *CT* Computed tomography, *CW* Continuous-wave Doppler, *ECV* Extracellular volume, *FR* Transaortic flow rate, *LGE* Late gadolinium enhancement, *LV* Left ventricle, *LVOT* Left ventricular outflow tract, *MG* Mean transvalvular gradient, *PET* Positron emission tomography, *PW* Pulsed-wave Doppler, *SVi* Stroke volume index, *Vmax* Peak aortic jet velocity, *VTI* Velocity-time integral

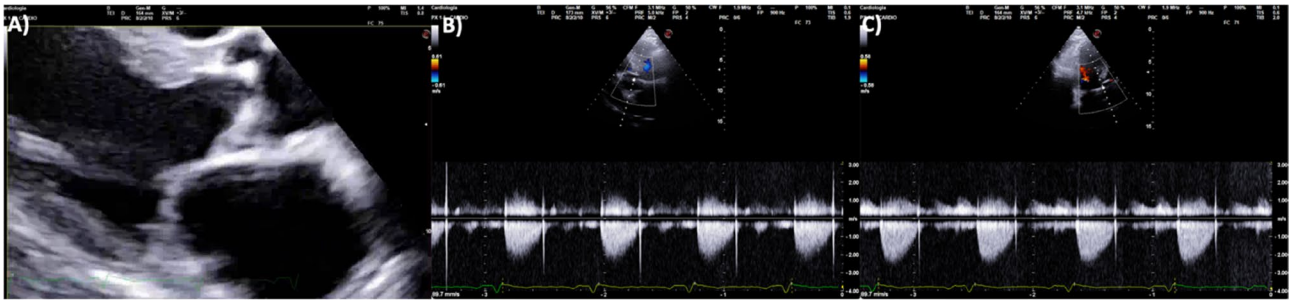


Fig. 1 Conventional trans-thoracic echocardiography: left ventricular outflow tract zoom for correct measurement (panel **A**), 4-chamber aortic flow measurement (panel **B**) and 3-chamber aortic flow measurement (panel **C**). Courtesy of Niguarda Hospital echocardiographic laboratory

Misdiagnosis and the true prevalence of moderate aortic stenosis

Echocardiographic pitfalls in grading aortic stenosis severity

Moderate AS should be considered a continuous rather than a categorical spectrum of disease. A Vmax of 3.0 m/s is clinically and prognostically distinct from values approaching the severe range (3.8–3.9 m/s). Observational studies consistently demonstrate a graded relationship between higher baseline Vmax, MG, and adverse outcomes, including faster progression to severe AS, increased risk of HF hospitalization, and mortality [6, 9].

This continuum is further reinforced by a strong association with aortic valve calcification burden measured by computed tomography (CT): patients with moderate AS and high baseline aortic valve calcium (AVC) scores tend to exhibit steeper annual increases in Vmax and more rapid hemodynamic deterioration compared with those with lower calcific load [10, 11].

Therefore, within the "moderate" category, individuals at the upper end of Vmax and gradient ranges represent a higher-risk phenotype that may warrant closer surveillance and earlier consideration of multimodality imaging [6, 11, 12].

Moderate AS is predominantly diagnosed through transthoracic echocardiography (TTE), which integrates Vmax, MG, and the AVA derived from the continuity equation, with the doppler velocity index (DVI) serving as a supporting metric in cases of discordance [2]. However, each of these parameters is subject to acquisition and measurement errors. Continuous-wave Doppler may underestimate Vmax if recordings are not systematically obtained from all acoustic windows (apical, right parasternal, and suprasternal) as demonstrated by Kebed et al. [13]. Similarly, mismeasurement of the left ventricular outflow tract (LVOT) diameter, often due to assuming circular geometry in an anatomically elliptical outflow tract, propagates cubically in the continuity equation and can substantially bias AVA. Additional errors may arise from misalignment of pulsed-wave Doppler or incorrect sample placement when obtaining LVOT velocity–time integral (VTI), further compromising AVA [13]. When

flow acceleration in the LVOT exceeds 1 m/s, the simplified Bernoulli equation ($\Delta P = 4\ V^2$) no longer accurately represents the transvalvular pressure gradient, as the proximal velocity component can no longer be neglected. In such situations, application of the complete Bernoulli formulation ($\Delta P = 4\ [V_2^2 - V_1^2]$) is required to avoid systematic overestimation of gradients and consequent misclassification of stenosis severity [14]. When this occurs, a meticulous reassessment of the LVOT signal is mandatory to rule out subvalvular obstruction, dynamic flow acceleration, or high-output states. The continuity equation remains valid provided that LVOT diameter and VTI are measured at the same anatomical site, thereby preventing overestimation of AVA. In parallel, color Doppler mapping and spectral analysis from multiple acoustic windows are essential for identifying the level of flow acceleration. Systematic interrogation of all acoustic windows—including right parasternal views and the Pedoff probe—is essential to avoid underestimation of Vmax, particularly in eccentric jets. These techniques, however, require specific training and are associated with a learning curve, underscoring the need for standardized acquisition protocols and quality control [15]. Meanwhile, multimodality imaging, particularly transesophageal echocardiography or CT, helps distinguish between valvular and subvalvular narrowing, as well as refine severity grading [16]. However, where multimodality imaging is unavailable, repeat expert echocardiography within a team-based approach remains the most pragmatic strategy.

Discordance between AVA and MG is frequent in the mild–moderate spectrum and represents a common clinical dilemma rather than an exception. In such cases, a structured stepwise reassessment is recommended before reclassifying disease severity.

Scenario A — AVA in the moderate range with a mild gradient (AVA 1.0–1.5 cm^2; MG < 20 mmHg):

- Re-measure LVOT diameter and ensure that it is obtained at the correct anatomical level in mid-systole;
- Reassess pulsed-wave Doppler alignment and LVOT VTI acquisition;
- Systematically interrogate all acoustic windows (apical, right parasternal, suprasternal, and Pedoff) to avoid underestimation of Vmax;
- Calculate stroke volume index (SVi) and transaortic FR; if SVi < 35 mL/m^2 or FR < 218 mL/s, consider a low-flow state;
- If uncertainty persists, consider CT-derived AVA (CT-AVA) for flow-independent anatomical adjudication.

Scenario B — AVA in the mild range with a moderate gradient (AVA > 1.5 cm^2; MG 20–39 mmHg):

- Recheck LVOT measurement and Doppler alignment to exclude technical error;
- Consider the potential impact of pressure recovery, particularly in patients with small aortic roots;
- Evaluate flow status (SVi and FR) and ventricular geometry;
- If discordance remains, consider CT-AVA and/or cardiac magnetic resonance (CMR) for complementary anatomical and functional assessment.

This pragmatic algorithm emphasizes that discordance should prompt careful reassessment and multimodality imaging rather than immediate reclassification of stenosis severity. Fig. 2 summarizes this stepwise approach to discordant and low-gradient presentations, integrating echocardiographic reassessment with CT and CMR adjudication.

Role and limitations of computed tomography in aortic valve assessment

To resolve such uncertainties, multimodality imaging plays a central role. CT provides both anatomical planimetry of CT-AVA and AVC scoring, which are independent of flow conditions. Sex-specific AVC thresholds (~ 400–1200 Agatston Units-AU- in women and 600–2000 AU in men) [11] enhance diagnostic accuracy, whereas CT-AVA circumvents the geometric assumptions inherent to Doppler-derived AVA (Fig. 3).

More recently, refined sex-specific CT-AVC thresholds tailored to the mild–moderate spectrum has been proposed, acknowledging that risk within moderate AS is graded rather than binary. These lower, graduated ranges aim to differentiate patients with low, intermediate, and high calcific burden within the moderate category, rather than relying solely on thresholds developed for severe AS. This is clinically relevant because baseline AVC burden shows a continuous relationship with both hemodynamic progression and adverse outcomes, even before conventional severe cut-offs are reached. Accordingly, suggested sex-specific ranges for the mild–moderate spectrum are increasingly framed as graduated tiers rather than single cut-offs, approximately:

- Women: ~300–800 AU (lower calcific burden), 800–1200 AU (intermediate burden), and > 1200 AU (higher burden within moderate AS);
- Men: ~500–1200 AU (lower burden), 1200–2000 AU (intermediate burden), and > 2000 AU (higher burden within moderate AS).

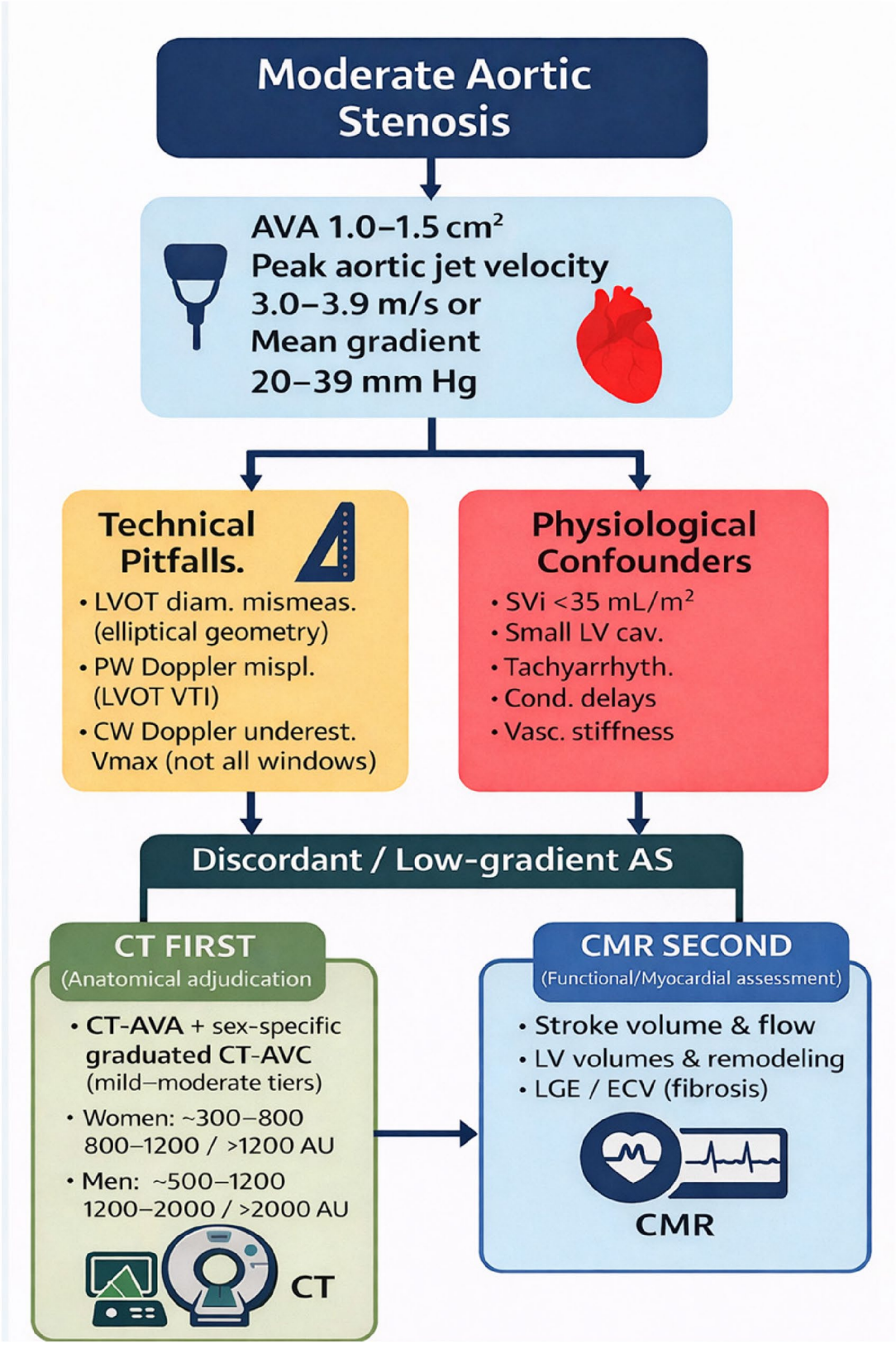


Fig. 2 Stepwise classification of moderate aortic stenosis through multimodality imaging. AS = Aortic stenosis; AVA = Aortic valve area; AVC = Aortic valve calcium; CMR = Cardiac magnetic resonance; CT = Computed tomography; CW = Continuous-wave Doppler; ECV = Extracellular volume; FR = Transaortic flow rate; LGE = Late gadolinium enhancement; LV = Left ventricle; LVOT = Left ventricular outflow tract; MG = Mean transvalvular gradient; PET = Positron emission tomography; PW = Pulsed-wave Doppler; SVi = Stroke volume index; Vmax = Peak aortic jet velocity; VTI = Velocity-time integral

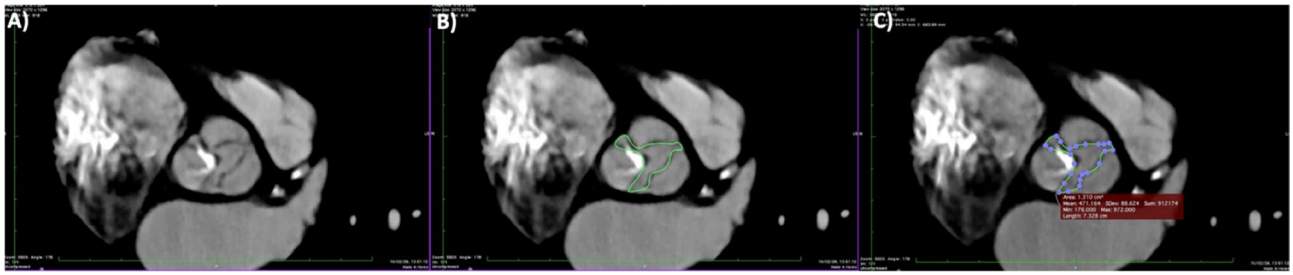


Fig. 3 Coronary tomography imaging of aortic valve (panel **A**) with aortic valve area identification (panel **B**) and measurement (panel **C**). Courtesy of Niguarda Hospital echocardiographic laboratory

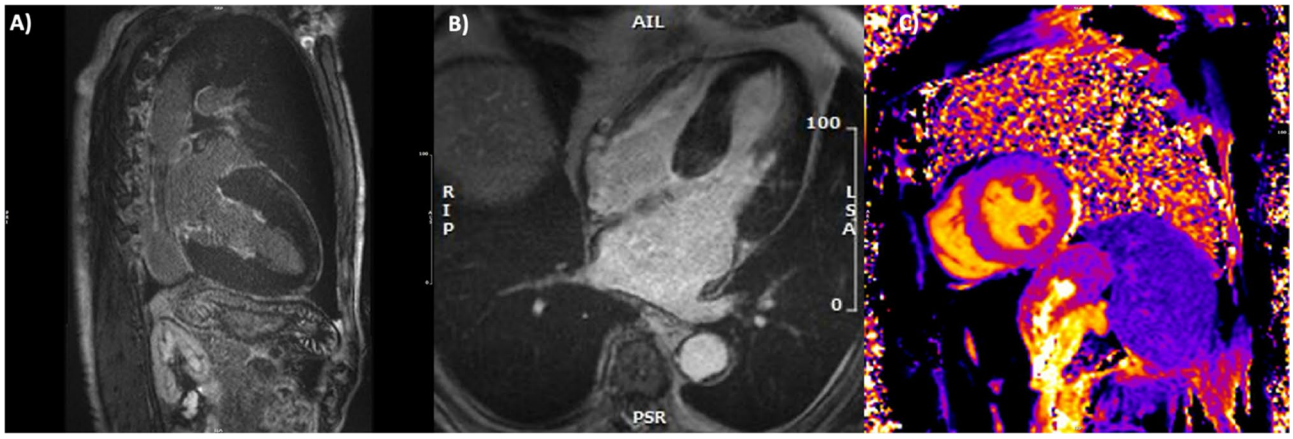


Fig. 4 Cardiac Magnetic Resonance imaging of aortic stenosis secondary left ventricular hypertrophy (panel **A** and **B**) and increased fibrosis at T1-mapping (panel **C**). Courtesy of Niguarda Hospital magnetic resonance laboratory

These values complement, rather than replace, established severe thresholds and are intended to refine risk stratification within moderate AS [17]. Nevertheless, CT-based quantification has essential caveats. In specific pathological settings, such as cardiac amyloidosis, bicuspid aortic valve, or predominant fibrotic rather than calcific degeneration, the extent of valvular calcification may not parallel the actual hemodynamic severity of stenosis. In amyloidosis, for example, leaflet thickening and restricted motion result primarily from protein infiltration rather than calcium burden. In contrast, bicuspid morphology is often associated with asymmetric and dense calcification, which can overestimate severity if interpreted using standard Agatston thresholds. Therefore, CT-derived calcium scoring should always be interpreted in the context of morphology, leaflet motion, and hemodynamic data from echocardiography or CMR, to avoid misclassification of these atypical forms of AS [11, 18, 19]. CT and CMR are complementary: CT is best for anatomical severity (AVC and CT-AVA), whereas CMR is best for flow quantification and myocardial characterization (Fig. 4).

In a multicenter study by Mittal et al. [20], up to 23% of patients labeled severe by echocardiography were reclassified as moderate when CT-AVA exceeded 1.0 cm^2, underscoring its corrective capacity. When noninvasive imaging remains inconclusive, invasive catheterization retains value, allowing direct gradient measurements and Gorlin-based AVA via Fick or thermodilution [21]. However, both invasive catheterization and transesophageal echocardiography are now rarely required in routine practice and should be reserved for exceptional cases in which non-invasive multimodality imaging remains inconclusive. Comparative studies show that CT-AVA correlates with both catheter-derived and Doppler values, although CT yields slightly larger areas; thus, modality-specific cut-offs are recommended (< 1.2 cm^2 for CT versus < 1.0 cm^2 for TTE) for severe AS [22, 23]. Beyond pure calcium scoring, emerging CT approaches assessing fibro-calcific burden may provide additional pathophysiological insight, particularly in women who often display more fibrotic rather than calcific valve phenotypes. However, these techniques remain largely confined to research settings and are not yet part of routine clinical practice [24].

Discordant and low-gradient aortic stenosis: diagnostic reconciliation through multimodality imaging

In low-gradient settings with either reduced or preserved left ventricular ejection fraction (LVEF), low-dose

dobutamine stress echocardiography (DSE) is crucial for distinguishing true-severe from pseudo-severe disease [9]. Beyond classical low-flow, low-gradient AS with reduced LVEF, current guidelines also describe low-flow, low-gradient AS with preserved LVEF and normal-flow, low-gradient AS (MG < 40 mmHg, AVA ≤ 1 cm^2, SVi > 35 mL/m^2, LVEF ≥ 50%), as well as discordant high-gradient AS (mean gradient ≥ 40 mmHg, AVA > 1 cm^2). In all these scenarios, multimodality imaging is crucial for resolving discrepancies and accurately reclassifying the severity of stenosis. CT-AVA and AVC scoring can confirm actual anatomic severity when flow-dependent parameters are ambiguous, while CMR may quantify stroke volume and flow independently of Doppler assumptions. Physical or exercise stress echocardiography addresses different physiological questions than DSE and should not be used interchangeably. In selected cases, physical or exercise stress echocardiography can further clarify the hemodynamic response, unmask latent gradients, and assess contractile reserve, particularly when low-dose DSE is inconclusive or contraindicated [25].

Physiological confounders and emerging flow-based indices

Beyond technical limitations, physiological confounders also contribute. Classical low-flow, defined as SVi < 35 mL/m^2, may arise from concentric remodeling, small left ventricular (LV) cavity, tachyarrhythmias, conduction delays, or increased afterload due to vascular stiffness [26]. In such cases, Doppler gradients underestimate AS severity, leading to misclassification of severe lesions as moderate or moderate as mild. More recently, transaortic FR, calculated as stroke volume divided by LV ejection time, has emerged as a robust parameter, reflecting forward flow more accurately than SVi. In a large multicenter cohort, FR < 218 mL/s was independently associated with a twofold higher risk of mortality and HF hospitalization, outperforming SVi [6]. Clavel and Tastet [26] emphasized the value of FR in characterizing low-flow physiology and recommended its systematic use, ideally with sex-specific thresholds.

Among flow-related parameters, the acceleration time/ejection time ratio (AT/ET) has emerged as a simple, reproducible marker of hemodynamic burden in AS [27].

Prolonged acceleration time relative to ejection time reflects impaired valve opening and reduced transvalvular flow, and lower AT/ET values have been associated with worse outcomes, independent of Vmax and MG. In moderate AS, AT/ET may help identify patients with concealed low-flow physiology who are at higher risk of rapid progression and adverse events, thereby complementing SVi and transaortic FR. Another important physiological confounder is pressure recovery, whereby part of the kinetic energy distal to the valve is reconverted into potential energy, leading to a lower effective pressure drop across the valve than that estimated by Doppler.

This phenomenon is more pronounced in patients with small aortic roots and relatively large valve areas, conditions frequently encountered in moderate AS.

As a result, Doppler-derived gradients may overestimate true stenosis severity, potentially leading to misclassification. Integration of aortic root dimensions from echocardiography or CT, and—when clinically indicated—invasive hemodynamic assessment, can mitigate this limitation and improve accuracy in borderline cases [28].

Clinical impact and reclassification of moderate aortic stenosis

As already discussed, discordance between AVA and MG, may lead to misclassification of AS severity. In these cases multimodality imaging is able to add substantial information and to reclassify AS severity. In particular, CT-derived AVA and sex-specific AVC scoring provide flow-independent anatomical adjudication, while CMR adds robust assessment of SV, flow status, and ventricular remodeling. Concordance between CT anatomy and CMR flow parameters increases diagnostic confidence and reduces the risk of misclassification, supporting more appropriate clinical decision-making.

Altogether, these tools (DSE, FR, CT-AVA, and AVC scoring) permit more rigorous characterization of discordant or low-flow states and directly influence prevalence estimates. Applying advanced criteria reclassifies a substantial proportion of cases as either severe or mild, with prospective studies confirming that up to one-quarter of patients initially labeled moderate by TTE are re-stratified after multimodality testing [20]. Thus, the "true" prevalence of moderate AS is likely lower than registry estimates, underscoring the need for systematic, multimodal assessment. Outcomes data further reinforce the clinical weight of moderate AS. In an extensive Australian registry (N = 3,315), the 5-year mortality rate reached 56%, comparable to that of severe disease [12]. European studies confirm an adverse prognosis: in moderate AS with LV dysfunction, 61% reached a composite endpoint of death, AVR, or HF hospitalization within 4 years, while international cohorts also show adverse events even in asymptomatic patients [29, 30]. Misdiagnosis carries significant consequences: overestimation may prompt unnecessary follow-up or premature intervention, whereas underestimation delays valve replacement, prolonging overload and myocardial damage. High mortality in "moderate" AS partly reflects unrecognized severe disease and comorbidities. Accurate identification is therefore essential for reliable epidemiology, effective surveillance, timely intervention, and optimized resource utilization, as moderate AS remains underestimated yet

poses a high risk. Such limitations in standard echocardiography have opened the way for both Artificial Intelligence (AI)-driven automation and multimodal staging approaches.

A diagnostic flowchart summarizing critical decision points that may lead to misclassification of moderate AS is shown in Fig. 1.

Diagnostic challenges in combined and mixed aortic valve disease

The accurate assessment of AS in the context of combined or mixed valve lesions remains particularly challenging. In mixed aortic valve disease, typically the coexistence of AS and aortic regurgitation (AR), the interplay between forward obstruction and diastolic volume overload results in complex pressure–volume dynamics that blur conventional Doppler indices. The increased SV and regurgitant flow may elevate transvalvular velocities and mean gradients, leading to overestimation of stenosis severity when standard echocardiographic criteria are applied [31]. Conversely, when regurgitation predominates, the true contractile state of the ventricle and the effective forward SV may be underestimated, resulting in deceptively low gradients despite a significant fixed obstruction. Similar interpretative difficulties arise in multivalvular disease, such as AS associated with mitral regurgitation (MR), where altered loading conditions and atrioventricular interactions further distort hemodynamic relationships.

In these scenarios, reliance on a single Doppler or continuity-derived parameter is insufficient, and an integrated, multiparametric approach becomes mandatory. Quantification of regurgitant fraction and effective regurgitant orifice area (EROA) should accompany standard AS metrics (Vmax, MG, AVA) to delineate the predominant lesion. Advanced imaging modalities further refine this assessment. In this context, CMR can provide more reliable assessment of regurgitation than PISA-based echocardiographic methods, which are often challenging in the presence of concomitant AS.

Three-dimensional echocardiography allows for direct planimetry of the aortic valve orifice, even in cases of eccentric jets. Meanwhile, CMR provides accurate measurements of both regurgitant volume and forward flow, enabling the calculation of the net AVA independent of Doppler assumptions [16]. CT may additionally characterize leaflet morphology, calcification pattern, and annular geometry, assisting in differentiating truly severe AS from pseudo-severe or flow-dependent presentations.

Clinically, mixed lesions confer a greater hemodynamic burden and more adverse LV remodeling compared with isolated severe AS, a finding consistently confirmed by outcome registries. Therefore, guideline-directed management emphasizes that treatment decisions should rely on the predominant lesion and the overall impact on LV function and symptom burden, rather than relying solely on rigid numeric thresholds. Accurate grading through multimodality imaging is thus crucial for identifying those patients with "balanced" mixed disease who may otherwise be under- or over-treated. In patients undergoing transcatheter treatment of concomitant mitral valve disease, careful reassessment of coexisting moderate AS is essential, as treating the mitral lesion alone may increase afterload and unmask truly severe, symptomatic AS; in selected cases this supports consideration of an "AS-first" strategy.

Role of artificial intelligence

AI has rapidly evolved from proof-of-concept tools to clinically relevant applications in the assessment of AS. Recent studies show that deep-learning models can automatically quantify key Doppler parameters on routine TTE, including peak velocity, mean gradient, LVOT VTI/diameter, and AVA, achieving strong agreement with expert readers [32]. Such "hands-off" workflows directly address operator variability and time costs, a major limitation in current practice. End-to-end classifiers trained on raw cine loops can even identify severe AS from single video acquisitions, potentially extending screening to point-of-care ultrasound when Doppler is unavailable [33]. On the CT side, automated algorithms perform annular sizing, leaflet calcification, and root segmentation with accuracy comparable to expert readers, while reducing reporting time and inter-operator variance [34]. A particularly relevant advance concerns the LVOT, where errors propagate cubically in the continuity equation. Deep-learning models now standardize LVOT measurement and VTI extraction across vendors, improving reproducibility and stabilizing AVA calculations [35]. Similarly, automated segmentation of the aortic root enhances consistency in CT-AVA and AVC scoring, aiding reconciliation of discordant echo findings [36, 37]. These pragmatic gains in standardization and reproducibility are among the most immediate contributions of AI to clinical workflow. The most promising horizon, however, lies beyond automation. By integrating imaging features with demographics, comorbidities, and laboratory data, machine-learning models can predict AS progression and outcomes from mild and moderate stages, enabling personalized surveillance strategies [38, 39]. Instead of rigid follow-up intervals, AI-derived risk scores could guide when to repeat Doppler, perform CT-AVC, or escalate to multidisciplinary review, potentially improving resource allocation and early intervention. Two domains already appear close to clinical maturity: fully automated Doppler quantification, as demonstrated by Krishna et al. [32], and automated CT-based root assessment, both of which match expert workflows

while reducing variability and analysis time [34]. More broadly, regulatory-cleared AI modules in echocardiography, such as automated LVEF and global longitudinal strain (GLS) quantification, provide proof that end-to-end AI solutions can meet quality and safety standards, paving the way for valvular applications [40]. Nonetheless, challenges remain. Dataset bias, limited generalizability across vendors and populations, and dependence on human-labeled Doppler measurements may embed systematic errors. Black-box outputs still limit trust, even if saliency maps and explainability tools provide partial reassurance [33]. Most studies remain retrospective, with few reporting patient-centered outcomes, such as reduced time to diagnosis or improved outcomes. Furthermore, no consensus benchmarks exist for automated AVA or gradient quantification. Multi-society initiatives defining standardized test suites and acceptance criteria are therefore essential to accelerate adoption. Overall, AI has proven effective in reducing inter-observer variability and optimizing AS workflows by integrating automated Doppler evaluation, standardized LVOT assessment, and quantitative CT analysis. The next step is to validate whether AI-augmented pathways can move beyond technical efficiency to improve risk stratification, harmonize multimodality imaging, and ultimately enhance patient outcomes. Beyond automation, comprehensive staging frameworks are emerging to contextualize valvular disease within the broader context of systemic cardiac involvement. Table 2 summarizes existing studies on AI applications in AS, highlighting moderate disease.

Overall, AI approaches in moderate AS are promising but remain investigational and should currently complement—not replace—expert clinical and multimodality imaging assessment.

Staging of moderate aortic stenosis

While transthoracic echocardiography remains the cornerstone for the evaluation of moderate AS, additional imaging modalities may be clinically useful in selected situations, particularly when echocardiographic findings are discordant or when symptoms and cardiac remodeling appear disproportionate to valve hemodynamics. Patients most likely to benefit from multimodality imaging can be identified based on a combination of imaging findings, clinical features, and inconclusive or conflicting echocardiographic data. In particular, the following practical criteria should prompt multimodality imaging:

- SVi < 35 mL/m² or transaortic FR < 218 mL/s, suggesting concealed low-flow physiology;
- Left ventricular global longitudinal strain (LV-GLS) less negative than – 16%, indicating early systolic dysfunction despite preserved LVEF;
- High AVC burden on CT, particularly at the upper end of the moderate range;
- Unexplained symptoms, recurrent heart failure admissions, or markedly elevated natriuretic peptides not fully explained by Doppler indices.

Table 2 Summary of published studies on artificial intelligence applications in aortic stenosis, with a specific focus on moderate disease

First Author, Year	Study Design, Cohort	AI Methodology	Key Findings	Relevance to Moderate AS
Krishna et al., 2023 [20]	Multicenter, routine TTE datasets	Deep-learning pipeline for automated Doppler quantification	Accurate extraction of Vmax, MG, LVOT, AVA; strong correlation with experts ($r = 0.76–0.97$)	Improves reproducibility of key parameters in moderate AS
Holste et al., 2023 [21]	Validation across independent echo cohorts, cine loops	3D-CNN ensemble classifier	AUROC 0.95–0.98 for severe AS detection; saliency maps confirmed clinical validity	Reduces misclassification; potential early application in moderate AS
Wang et al., 2023 [22]	Retrospective, multicenter CT study	Fully automated deep-learning algorithm for pre-TAVR CT	Automated annulus sizing, leaflet calcification, root segmentation with expert-level accuracy	Facilitates multimodality integration when echo parameters are discordant in moderate AS
Zha et al., 2023 [23]	Multicenter, 2D echocardiography	DL model for LVOT diameter measurement	Standardized LVOT quantification; reduced inter-vendor variability	Minimizes error propagation in continuity-equation AVA in moderate AS
Aoyama et al., 2022 [24]	CT imaging datasets	Cascaded deep neural networks for cusp/annulus segmentation	Robust detection of commissures and hinge points	Enhances CT-AVA and AVC scoring reliability in moderate AS
Sanabria et al., 2024 [26]	PROGRESSA registry, ML predictive modeling	ML integration of imaging + clinical data	Improved prediction of AS progression from mild/moderate stages	Supports personalized follow-up strategies in moderate AS
Sanchez-Puente et al., 2023 [27]	Prospective, echocardiographic follow-up	ML models optimizing follow-up scheduling	Identified high-risk patients; optimized reassessment intervals	Guides surveillance strategy in moderate AS

Abbreviations: AI Artificial Intelligence, *AS* Aortic Stenosis, *AVA* Aortic Valve Area, *AVC* Aortic Valve Calcium, *AUROC* Area Under the Receiver Operating Characteristic Curve, *CNN* Convolutional Neural Network, *CT* Computed Tomography, *DL* Deep Learning, *LVOT* Left Ventricular Outflow Tract, *MG* Mean Gradient, *ML* Machine Learning, *TAVR* Transcatheter Aortic Valve Replacement, *TTE* Transthoracic Echocardiography, *Vmax* Peak Aortic Jet Velocity

In these settings, CT (for flow-independent anatomical assessment and calcium burden) and/or CMR (for flow quantification and myocardial characterization) can provide complementary information that refines risk stratification and guides the intensity of surveillance or referral to the Heart Team.

Before introducing imaging-based staging, it is essential to distinguish between tools currently established in clinical practice and emerging research techniques. Standard echocardiography, CT-AVC, and conventional CMR are routinely applicable for diagnosis and risk stratification in moderate AS. In contrast, CMR or CT-derived extracellular volume (ECV), positron emission tomography (PET, both with ^18F-sodium fluoride - ^18F-NaF PET -, or advanced tracers such as fibroblast activation protein inhibitor – FAPI), artificial intelligence models, and four-dimensional (4D) flow CMR should be considered promising but still investigational and requiring further prospective validation before widespread clinical implementation and should not be considered established standards for decision-making in moderate AS.

AS is increasingly recognized not only as a valvular disorder but as a systemic disease with repercussions across multiple cardiac and extracardiac structures. The concept of multi-organ staging has emerged to describe AS as a continuum of progressive damage involving the LV, left atrium (LA), right ventricle (RV), and pulmonary circulation [41]. Early stages are marked by LV hypertrophy and subclinical systolic dysfunction, while more advanced phases include LA enlargement with impaired reservoir function, secondary pulmonary hypertension, and RV dysfunction. This framework enables a more comprehensive characterization of disease burden and refines risk stratification beyond conventional Doppler hemodynamics, particularly in moderate AS, a population with a notoriously heterogeneous prognosis. In an extensive multicenter study, Tastet and colleagues extended this staging approach to asymptomatic patients, including those with moderate disease, showing that progressive stages of cardiac damage, ranging from LV remodeling and fibrosis to pulmonary vascular and right-sided involvement, were strongly and independently associated with adverse outcomes irrespective of traditional severity definitions [42]. Crucially, in moderate AS, higher stages of damage identified subsets with outcome trajectories approaching those of severe disease, underlining the prognostic relevance of systemic staging in this group. It should be emphasized that the staging framework is based on cross-sectional, associative data and does not establish causality. Extra-valvular cardiac damage may reflect coexisting conditions such as aging, HF with preserved ejection fraction, coronary artery disease, atrial fibrillation, or cardiac amyloidosis, independent of AS severity.

Although CMR-derived ECV and mid-wall fibrosis are associated with adverse outcomes, there is currently no evidence that valve replacement causally reverses these markers or improves prognosis.

Functional imaging

Within the staging framework, strain imaging has emerged as a powerful marker of subclinical dysfunction. The "all-chamber strain" approach, introduced by the Badano group, enables simultaneous assessment of LV-GLS, LA reservoir strain (LA-RS), and RV free-wall longitudinal strain (RV-FWLS) from a single apical four-chamber view, providing an integrated picture of hemodynamic burden [37]. Importantly, abnormalities in atrial and RV strain are often detectable despite preserved LV-GLS, underscoring that multi-chamber strain can anticipate overt dysfunction and refine prognostic stratification. In fact, patients with abnormal LV-GLS, LA-RS, or RV-FWLS show progressively worse outcomes, supporting the concept that multi-chamber strain identifies early systemic involvement before conventional indices. LA-RS reflects atrial compliance and predicts atrial fibrillation and reduced exercise capacity [38], while RV-FWLS provides insight into RV to pulmonary coupling and adverse prognosis [43]. Their combined interpretation therefore improves risk stratification in moderate AS, complementing anatomical and Doppler parameters. Beyond strain, CMR offers unparalleled tissue characterization, as late gadolinium enhancement (LGE) detects focal replacement fibrosis. At the same time, T1 mapping and ECV quantification reveal diffuse interstitial fibrosis, both of which are independently associated with adverse postoperative and long-term outcomes [44]. In moderate AS, the presence of mid-wall LGE or elevated ECV may therefore indicate progression to an advanced stage despite modest gradients, justifying intensified follow-up or early referral. CMR offers important strengths within the staging framework, particularly for flow quantification and volumetric assessment of the LV. However, its limitations should be acknowledged, including lower temporal resolution compared with echocardiography, potential aliasing at high velocities, and artifacts that may affect valve planimetry. When evaluating stroke volume with CMR, concordance between phase-contrast flow and volumetric methods should be sought to increase reliability. 4D-flow CMR provides detailed visualization of intracardiac hemodynamics and shear stress, but it remains primarily a research tool in AS and is not yet established for routine clinical decision-making [45].

Calcification and severity progression

In contrast to functional markers of myocardial impairment, calcific and molecular imaging techniques provide complementary information on valve biology and the

progression dynamics. Serial CT- AVC scoring captures the heterogeneity of calcification dynamics over time. In a prospective multicenter study, Doris et al. [46]. demonstrated that higher baseline AVC and accelerated annual progression were associated with both rapid hemodynamic deterioration and increased adverse events, identifying "fast progressors" who may benefit from personalized surveillance and earlier intervention. ^18F-NaF further expands this paradigm by detecting active microcalcification at the molecular level, which precedes the macroscopic calcium visible on CT. Increased ^18F-NaF uptake predicts AVC progression and correlates with accelerated hemodynamic deterioration and adverse outcomes [10]. PET imaging with ^18F-NaF and emerging tracers such as FAPI provides important insights into active microcalcification, but it should currently be considered primarily a research tool rather than part of routine clinical decision-making [47]. However, this imaging method is primarily used during research protocols or is limited to single-center experience in the clinical field.

In Table 3, we provide a summary of the imaging parameters proposed for each stage of moderate AS, including their prognostic thresholds and suggested cut-off values.

Altogether, this integrative staging strategy, encompassing strain-derived functional impairment, CMR-based fibrosis, and calcification/progression markers from CT and PET, reflects the paradigm shift from a purely valve-centric model of AS toward one that encompasses myocardial, atrial, right-sided, and pulmonary vascular involvement. Applied to moderate AS, such a framework enhances prognostic accuracy, identifies high-risk phenotypes, and enables individualized follow-up and treatment strategies, ultimately aiming to improve outcomes in a population that has been historically underestimated yet is at considerable risk. Moderate AS should no longer be viewed as a benign intermediate stage but as a complex, heterogeneous condition requiring multimodal imaging and, increasingly, AI-driven tools for accurate risk stratification. A multilevel staging diagram of moderate AS, depicting the continuum from isolated valvular involvement to systemic and multi-organ damage, is shown in Fig. 5.

Disease progression and imaging surveillance

In moderate AS, progression is often heterogeneous, with some patients remaining stable for years while others experience rapid deterioration. Meta-analyses and longitudinal cohorts have reported mean annual increases

Table 3 Imaging parameters in moderate aortic stenosis

Stage / Parameter	Imaging Modality	Prognostic Threshold	Suggested Cut-off Value	Main limitations
LV systolic function (LV-GLS)	Echocardiography	Reduced LV-GLS associated with adverse prognosis	< −16% (early systolic dysfunction)	Load-dependent; affected by blood pressure, rhythm, image quality, and vendor variability
LA function (LA-RS)	Echocardiography	Impaired LA strain is related with AF and adverse outcomes	< 23% reservoir strain	Sensitive to atrial rhythm (AF), preload conditions, and inter-vendor variability.
RV function (RV-FWLS)	Echocardiography	Reduced RV strain is associated with RV–pulmonary uncoupling and poor outcome	< −20% free-wall strain	Image-quality dependent; influenced by pulmonary pressure and loading conditions.
CT-AVC (Agatston Units)	CT	Higher AVC burden linked to accelerated progression and events	Women: >1200 AU; Men: >2000 AU	Reflects calcium but not fibrosis; influenced by scanner protocol; limited in younger patients and in predominantly fibrotic valves (especially women).
CT-AVA	CT	Flow-independent anatomical grading	< 1.2 cm^2 (moderate-severe threshold)	Planimetry affected by motion artifacts and heavy calcification; requires high-quality acquisition and gating
CMR – LGE	CMR	Presence of mid-wall fibrosis is associated with mortality	Any LGE present	Detects focal fibrosis only; cannot quantify diffuse fibrosis; influenced by timing of contrast and technique
CMR – ECV	CMR	Elevated extracellular volume indicates diffuse fibrosis and worse outcome	> 28–30%	Affected by hematocrit, technical variability, and comorbidities (e.g., amyloidosis, HFpEF); not valve-specific.
PET – 18 F-NaF uptake	PET	Active microcalcification is related withintel rapid progression and adverse events	Above background uptake (semi-quantitative increase-no validated clinical threshold)	Primarily research tool; limited availability; no validated clinical thresholds; radiation exposure.

Abbreviations: AS Aortic Stenosis, *AU* Agatston Units, *AVC* Aortic Valve Calcium, *AVA* Aortic Valve Area, *CMR* Cardiac Magnetic Resonance, *CT* Computed Tomography, *CT-AVA* Computed Tomography–derived Aortic Valve Area, *ECV* Extracellular Volume, *LA* Left Atrium, *LA-RS* Left Atrial Reservoir Strain, *LGE* Late Gadolinium Enhancement, *LV* Left Ventricle, *LV-GLS* Left Ventricular Global Longitudinal Strain, *PET* Positron Emission Tomography, *RV* Right Ventricle, *RV-FWLS* Right Ventricular Free-Wall Longitudinal Strain

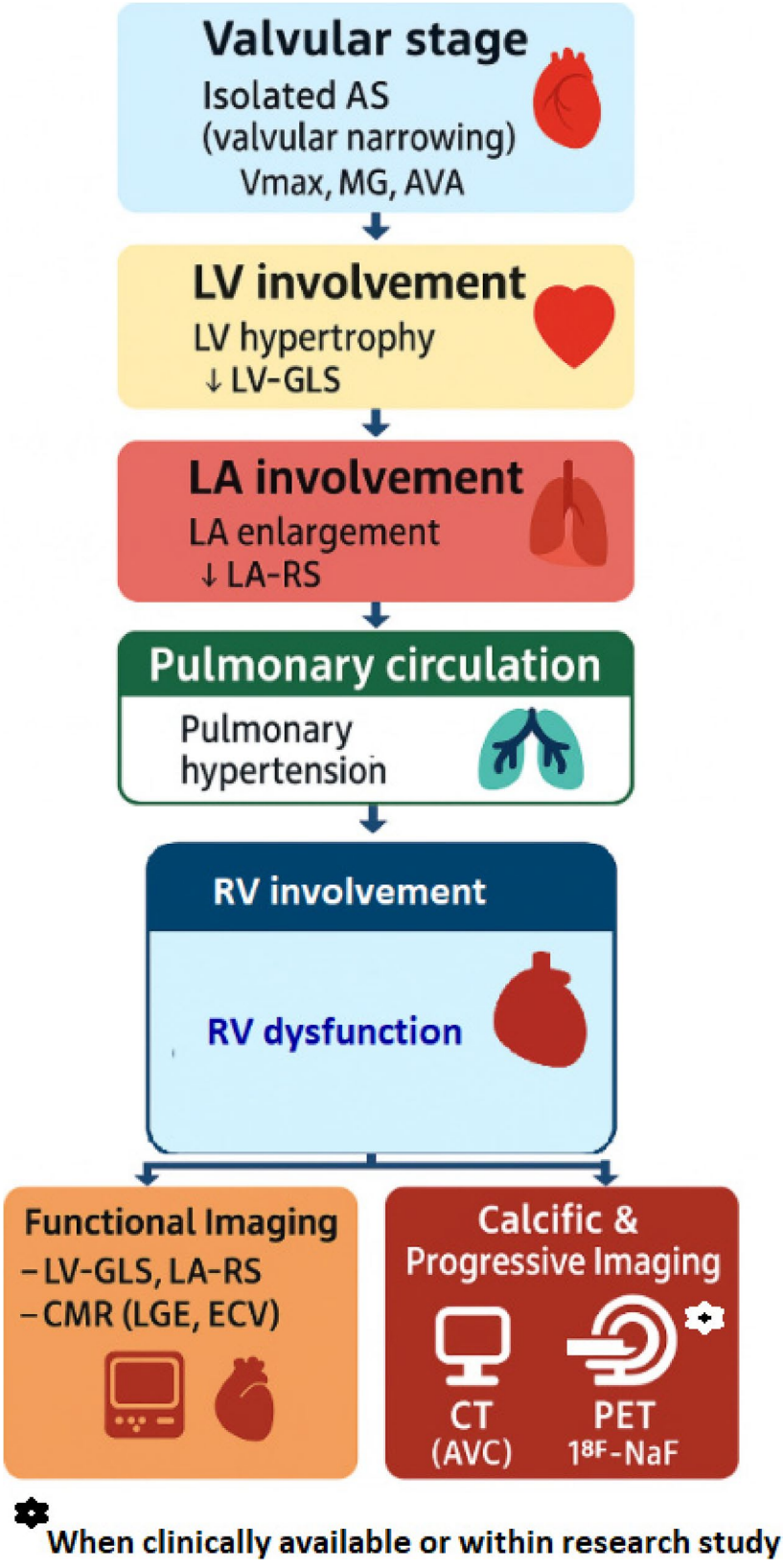


Fig. 5 (See legend on next page.)

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Fig. 5 Multilevel staging diagram of moderate aortic stenosis. ECV% by CMR and ^18F-NaF PET are currently research-oriented tools with limited routine clinical availability. Abbreviations: 18 F-NaF = Fluorine-18 Sodium Fluoride; AS = Aortic Stenosis, AVA = Aortic Valve Area; AVC = Aortic Valve Calcification; CMR = Cardiac Magnetic Resonance; CT = Computed Tomography; ECV = Extracellular Volume; LA = Left Atrium, LA-RS = Left Atrial Reservoir Strain; LGE = Late Gadolinium Enhancement, LV = Left Ventricle; LV-GLS = Left Ventricular Global Longitudinal Strain; MG = Mean Gradient; PET = Positron Emission Tomography

in Vmax of 0.2–0.3 m/s, MG rises of + 4–7 mmHg, and AVA declines of 0.05–0.10 cm^2 per year, though rates accelerate in heavily calcified valves or advanced disease stages [11, 47–51]. Among all determinants, baseline valve calcification remains the strongest predictor of hemodynamic worsening. CT-AVC provides a quantitative assessment of calcific burden and independently predicts both disease progression and clinical events [11, 46]. Complementary to CT, ^18F-NaF PET detects active microcalcification, identifying patients at risk for accelerated progression even before overt hemodynamic changes appear [52]. Beyond structural factors, metabolic comorbidities have a significant influence on disease dynamics. Elevated lipoprotein(a), poorly controlled diabetes, and high LDL-cholesterol have been consistently associated with faster AS progression through lipid-driven inflammation and pro-calcific signaling [53–57]. These findings support the concept of AS as an active, metabolically modulated disease process rather than a purely degenerative condition. Such heterogeneity highlights the importance of personalized surveillance strategies over fixed follow-up intervals. Echocardiographic parameters can also anticipate accelerated deterioration. Early impairment in GLS, LA-RS, or RV–PA coupling reflects progressive myocardial and atrial–pulmonary remodeling preceding overt systolic dysfunction [58–63]. Similarly, novel indices, such as myocardial work efficiency, integrate strain and systolic pressure to provide less load-dependent markers of contractility [64, 65].These parameters are most useful when interpreted longitudinally, as serial changes in GLS or LA-RS can identify subtle transitions to advanced disease. According to the 2025 European guidelines [2],echocardiographic follow-up should occur every 3–5 years in mild AS, every 1–2 years in moderate AS, and every 6–12 months in asymptomatic severe AS. However, intervals should be shortened when high-risk features are present, such as a rapid Vmax increase (> 0.3 m/s/year), a high CT-AVC burden, abnormal GLS or LA strain, elevated natriuretic peptides, or imaging evidence of fibrosis. Fig. 6 illustrates an algorithm for echocardiographic surveillance intervals based on baseline severity and the presence of risk modifiers.

Adjunctive modalities, including CT-AVC, 18 F-NaF PET (when available), and CMR-based tissue characterization, provide complementary insights into the structural and biological aspects of disease activity. Meanwhile, AI-based risk models integrating multimodal data may soon enable adaptive, individualized monitoring [66]. This integrative approach, combining traditional Doppler surveillance with advanced imaging and metabolic profiling, provides a framework for identifying "fast progressors" among patients with moderate AS. Table 4 summarizes the average annual rates of hemodynamic change and their clinical correlates, supporting a tailored follow-up strategy focused on early detection of adverse remodeling. Beyond imaging surveillance, greater attention should be paid to strategies aimed at slowing AS progression, including aggressive management of modifiable risk factors (e.g., lipids, diabetes, and hypertension) and participation in ongoing clinical trials targeting valvular biology. At the same time, surveillance should be tailored to individual risk profiles—integrating imaging, biomarkers, and comorbidities—in a precision medicine approach that can optimize outcomes while reducing unnecessary testing and healthcare burden.

Prognosis

Historically, AS was considered clinically significant primarily when severe and symptomatic. However, recent evidence indicates that even moderate AS carries a substantial risk of adverse outcomes compared to age-matched controls. Large international registries demonstrate that patients with moderate AS experience markedly higher mortality and HF hospitalization rates than age-matched controls, even after adjusting for comorbidities [12, 67, 68]. Meta-analytic data involving over 35,000 patients confirm that approximately 15–20% progress to severe disease or experience major cardiovascular events within five years [69]. The coexistence of LV systolic dysfunction, myocardial fibrosis, or elevated biomarkers further amplifies risk [70–73]. Prognosis is determined not only by valvular obstruction but also by the myocardial response to chronic pressure overload. Subclinical dysfunction, detected by GLS values less negative than – 16% to – 18%, and impaired LA or RV strain identify high-risk phenotypes even when LVEF remains preserved [58–63]. Similarly, evidence of diffuse or focal fibrosis on CMR (elevated ECV or mid-wall LGE) signals advanced myocardial remodeling with adverse implications for survival [74]. Circulating biomarkers provide complementary prognostic value. An elevated BNP or NT-proBNP level (> 3 times the age- and sex-adjusted upper limit) identifies patients at increased

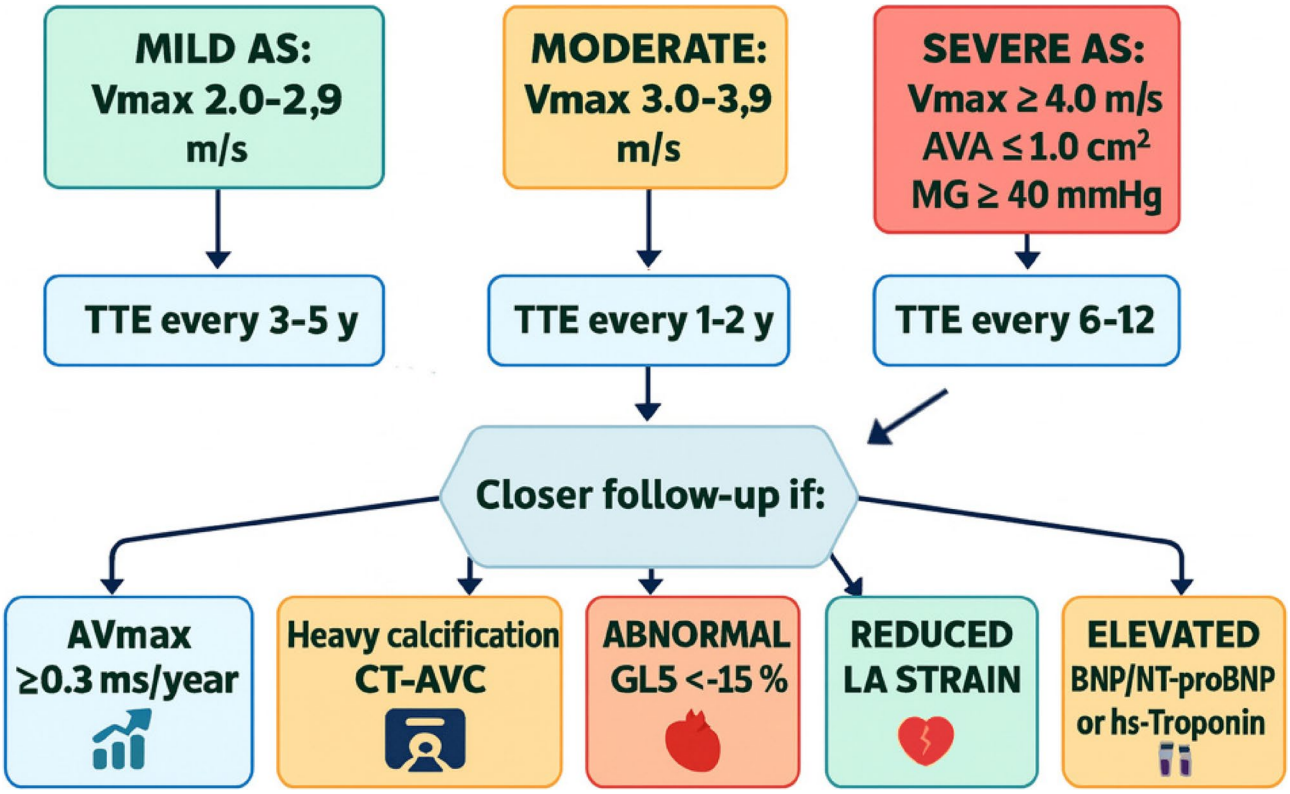


Fig. 6 Algorithm for echocardiographic surveillance intervals according to severity and risk modifiers. Abbreviations: AS = aortic stenosis; AVA = aortic valve area; Vmax = peak transvalvular velocity; MG = mean transvalvular gradient; TTE = trans-thoracic echocardiography; CT-AVC = computed tomography aortic valve calcium; GLS = global longitudinal strain; LA = left atrium; BNP = B-type natriuretic peptide; NT-proBNP = N-terminal pro-BNP; hs-Tn = high-sensitivity troponin

Table 4 Typical annual progression rates in aortic stenosis

Parameter	Average Annual Change	Clinical Notes
Vmax	+ 0.20 to + 0.30 m/s	Faster in heavily calcified valves
MGV	+ 5 to + 7 mmHg	Acceleration in advanced disease
AVA	−0.05 to − 0.10 cm^2	Decline may be nonlinear
CT-AVC score	Progressive increase	Predicts hemodynamic worsening
GLS	1–2% relative worsening	Detects early LV dysfunction

Abbreviations: AVA Aortic valve area, *Vmax* Peak transvalvular velocity, *MGV* Mean transvalvular gradient, *CT-AVC* Computed tomography aortic valve calcium, *GLS* Global longitudinal strain, *LV* Left ventricle

risk of events and an earlier need for intervention [75]. High-sensitivity troponin reflects ongoing myocyte injury and improves prediction when combined with imaging parameters [76]. Fibrosis-related biomarkers, including galectin-3, soluble ST2, and procollagen peptides, reflect extracellular matrix activation and have been shown to have independent associations with poor outcomes in AS [77–80]. By integrating imaging, functional, and biomarker data, clinicians can more accurately identify patients with moderate AS whose risk approximates that of severe disease. The prognostic profile of moderate AS differs according to LV function, with patients with reduced LVEF generally exhibiting worse outcomes than those with preserved LVEF. Most available evidence derives from hospital-based cohorts, which may be affected by referral bias; complementary insights into the natural history of moderate AS come from outpatient population studies [81]. The coexistence of moderate AS and cardiac amyloidosis is not rare and carries important diagnostic and prognostic implications. In patients with moderate AS but disproportionate symptoms or advanced cardiac remodeling, systematic evaluation for amyloidosis should be considered. In this context, multimodality imaging—including echocardiography, CMR, and nuclear imaging—can be particularly valuable to improve diagnostic accuracy and risk stratification. Table 5 summarizes key prognostic indicators used for multimodal risk stratification.

Table 5 Prognostic markers in aortic stenosis

	Conventional Markers	Advanced Echo and Integrative Markers
Valve severity	Vmax ≥ 4 m/s, MG ≥ 40 mmHg, AVA ≤ 1.0 cm^2	CT-AVC score, ^18F-NaF PET
LV function	LVEF < 50–55%	GLS >–15% to – 18%, LV concentricity index
LA function	LA volume index > 34 mL/m^2	LA reservoir strain < 25%, LA coupling index
RV–PA coupling	PASP > 50 mmHg	TAPSE/PASP < 0.35 mm/mmHg

Abbreviations: AVA Aortic valve area, *GLS* Global longitudinal strain, *LVEF* Left ventricular ejection fraction, *PASP* Pulmonary artery systolic pressure, *TAPSE* Tricuspid annular plane systolic excursion

Table 6 Ongoing randomized trials in moderate aortic stenosis

Trial	Intervention	Key population (inclusion criteria)	Comparator	Primary endpoint	Status
TAVR UNLOAD	TAVR	Moderate AS + HFrEF (LVEF ≤ 50%)	Guideline-directed medical therapy	Composite of all-cause mortality, stroke, and HF hospitalization	Ongoing
PROGRESS	TAVR	Moderate AS with evidence of cardiac damage/remodeling	Clinical surveillance / standard care	Composite of death, stroke, and HF hospitalization	Ongoing
Evolut EXPAND TAVR II	Self-expanding TAVR	Moderate AS with symptoms or cardiac damage	Best medical therapy	All-cause mortality and HF hospitalization	Ongoing

Abbreviations: TAVR Transcatheter Aortic Valve Replacement, *AS* Aortic Stenosis, *HFrEF* Heart Failure reduce Ejection Fraction, *LVEF* Left Ventricular Ejection Fraction, *HF* Heart failure

Therapeutic strategies

According to international guidelines [2, 21], the recommended management for moderate AS remains clinical and echocardiographic surveillance in asymptomatic patients without LV dysfunction (watchful waiting approach). Early valve replacement is not currently indicated, as the procedural risks of transcatheter or surgical AVR (TAVR and SAVR respectively) are not balanced by proven benefits in non-severe disease. Nowadays, the focus is on detecting progression toward severe AS and managing cardiovascular risk factors. Careful clinical evaluation is crucial, as early symptoms can be subtle and easily overlooked. However, the 2025 European Guidelines [2] introduce specific recommendations for patients with mixed moderate AS and moderate AR. In symptomatic patients, intervention is recommended if moderate AS and moderate AR are present together and the mean trans-valvular gradient is ≥ 40 mmHg or the peak one is ≥ 4.0 m/s (recommendation class I, level of evidence B). In asymptomatic patients, intervention is recommended if moderate AS and moderate AR co-exist with a peak trans-valvular gradient ≥ 4.0 m/s and LVEF < 50%, if another concomitant cardiac disease does not determine this. These additions acknowledge that mixed lesions (stenosis + regurgitation) determine a greater hemodynamic burden, and that outcomes in these patients are comparable to those with isolated severe AS [2]. Regarding pharmacological therapy, no drugs have been shown to alter the progression of AS, and previous trials on therapies initially considered promising failed to demonstrate benefit, particularly with statins [80, 82, 83]. Current management focuses on optimal control of cardiovascular risk factors and comorbidities. Standard agents (diuretics, ACE inhibitors, ARBs, beta-blockers) may be used for concomitant HF or hypertension, but they did not modify disease progression. Over mixed aortic valvular disease, debate has emerged regarding the potential role of earlier intervention in moderate AS-selected patients. The rationale for an early intervention strategy is based on evidence that LV remodeling may already shift toward maladaptation during the moderate stage of the disease. To maintain wall stress, the myocardium develops hypertrophy and altered geometry, accompanied by capillary rarefaction, increased oxygen demand, myocyte loss, and fibrotic deposition. A histological study [84] demonstrated that myocardial changes in severe AS are self-perpetuating and may persist despite valve replacement. This suggests that at advanced stages, intervention may not be able to reverse established myocardial damage. On the other hand, despite the low procedural risk associated with transcatheter treatment, patients with moderate AS are inherently younger than those with severe AS. Therefore, the lifetime management of the valve procedure is prominent. This includes careful consideration of the need and ease of future coronary access, pacemaker implantation rates, and the durability of the prosthetic valve, with the anticipation of possible second (and even third) interventions in the future. For all these reasons, guidelines mandate watchful waiting over *toutcourt* intervention despite the already mentioned overall poor outcomes associated with moderate AS.

However, there is a rationale for early treatment of moderate AS in a selected cohort of patients with a peculiar risk profile (summarized in Table 6). These trials are expected to clarify whether early transcatheter intervention can improve outcomes in selected high-risk phenotypes.

In the TAVR-UNLOAD [85] randomized clinical trial, 178 patients with moderate AS and HF with reduced LVEF were randomized to TAVR versus surveillance. During a median follow-up of 23 months, no significant reduction in all-cause mortality, disabling stroke, or HF hospitalizations was found. However, there was a substantial improvement in quality of life (evaluated through the Kansas City Cardiomyopathy Questionnaire). Although remarkable, this trial suffers from two significant limitations: the high comorbidity burden, which may have contributed to a high mortality rate in both the interventional and surveillance groups, and the high crossover rate (43% of patients shifted from surveillance to TAVR) due to the progression of AS. Furthermore, enrollment was severely impaired during the COVID pandemic, with a possible influence on trial conduct and results. Some prospective registries and retrospective studies were published and meta-analyzed. In the study with the highest number of participants (7 studies, 4,827 patients), early aortic valve replacement (both SAVR and TAVR) was associated with a 48% reduction in all-cause mortality (Hazard Ratio 0.52; 95% Confidence Interval 0.44–0.60; $p < 0.001$) [86]. Finally, two ongoing randomized clinical trials will enrich this landscape in the future. The PROGRESS trial (NCT04889872) will include 2250 patients with moderate AS and symptoms or cardiac damage to TAVR with a SAPIEN valve vs. medical therapy , while the EXPAND TAVR II Pivotal Trial (NCT05149755) will randomize 650 patients with moderate AS that are either symptomatic or with a broad range of additional risk factors (reduced functional capacity, previous HF, cardiac damage, persistent or paroxysmal atrial fibrillation, elevated AVC score or a sign of cardiac dysfunction at echocardiography) to TAVR with an EVOLUT platform vs. clinical surveillance.

Despite the limited data available to date, decision-making should not rely solely on hemodynamic cut-offs but should incorporate risk profile, comorbidities, and markers of subclinical myocardial injury. Some patients with moderate AS could benefit from an early interventional strategy. Selection should be made within the Heart Team, considering not only the AS severity measure but also symptoms, LV dysfunction (through LVEF, as well as more sensitive methods previously employed), the presence of concomitant surgical indications (e.g., coronary revascularization), and markers of subclinical myocardial damage.

Although no specific drug therapies have been found to modify AS progression, some new data with PCSK9 inhibitors [87] have increased attention on this issue. In fact, specific trials with PCSK9 inhibitors [88] or pelacarsen, an antisense oligonucleotide targeting lipoprotein(a), are currently underway [89].

Conclusions

Given the heterogeneity of moderate AS, individualized care is paramount. For patients with a preserved LVEF and no signs of cardiac damage, guideline-directed surveillance remains an appropriate approach. In contrast, those with evidence of adverse remodeling, elevated biomarkers, or recurrent HF admissions may warrant earlier referral for clinical trial enrollment or consideration of intervention. The integration of multimodality imaging and biomarker profiles can help stratify patients into risk tiers, guiding both the frequency of surveillance and therapeutic decision-making. Ultimately, personalization should extend beyond valve severity to encompass comorbidities, frailty, and patient preferences. Large, multicenter collaborations are essential not only to test the efficacy of interventions but also to delineate better the heterogeneity of disease progression and response to therapy and to further promote the use of multimodality imaging and to clarify which patients will benefit more from its use.

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Authors' contributions
A.M, P.F. and G.S. contributed to the conception or design of the work. G.S, A.M, C.T, M.M., C.M, A.B., A.M, C.G., S.G. and P.F. contributed to the acquisition, analysis, or interpretation of data for the work. A.M., G.S., C.T, M.M. and C.M. drafted the original version of the manuscript. G.S, A.M, C.T, M.M., C.M, A.B., A.M, C.G., S.G. and P.F.critically revised the manuscript. All gave final approval and agree to be accountable for all aspects of work ensuring integrity and accuracy.

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