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Review

Methodological Updates in Stress Echocardiography and Multimodality Diagnostic Integration for Discordant Low-Gradient Aortic Stenosis: From True-Severe Adjudication to Risk Stratification

Yuan Li[1], Yujian Liu[2,*]

[1]Department of Ultrasound, Zigong Fourth People's Hospital, 643000 Zigong, Sichuan, China
[2]Department of Radiology, Zigong First People's Hospital, 643000 Zigong, Sichuan, China
*Correspondence: 782175536@qq.com (Yujian Liu)

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Abstract

Discordant low-gradient aortic stenosis (AS), which encompasses classical low-flow, low-gradient (LF-LG) AS, paradoxical LF-LG AS, and normal-flow, low-gradient AS, remains a major diagnostic challenge because an apparently severe aortic valve area may coexist with a low transvalvular gradient and variable flow states. Dobutamine stress echocardiography (DSE) remains central in classical LF-LG AS, particularly when left ventricular ejection fraction (LVEF) is markedly reduced, but its diagnostic performance depends on LVEF strata, achieved flow augmentation, and measurement quality. This narrative methodological review synthesizes guideline recommendations and contemporary evidence on DSE interpretation, projected aortic valve area, computed tomography aortic valve calcium (CT-AVC), cardiac magnetic resonance (CMR), advanced echocardiography, and multimodality risk stratification in discordant low-gradient AS. We aim to clarify situations in which DSE is diagnostically decisive or remains indeterminate and those in which CT-AVC, CMR, or advanced echocardiography should be activated for anatomic adjudication, myocardial damage assessment, and risk refinement. We emphasize LVEF-stratified DSE interpretation, the diminished exclusionary role of flow reserve, preferential use of projected aortic valve area when partial flow augmentation supports reliable flow-normalized extrapolation, and cautious interpretation of transaortic flow rate and volume-flow discordance as emerging metrics. We propose a six-step framework linking optimized transthoracic echocardiography, measurement-quality audit, phenotype assignment, DSE, CT-AVC, and myocardial damage assessment to clinical decision domains. The operational contribution is to match each modality to the uncertainty it best addresses: DSE for dynamic flow behavior, CT-AVC for probability-weighted structural valve burden, optimized echocardiography for measurement reliability, and CMR or advanced echocardiography for myocardial damage and timing risk.

Keywords: tomography, X-ray computed; risk assessment; aortic valve stenosis; echocardiography, stress; hemodynamics; magnetic resonance imaging; multimodal imaging; ventricular function, left; clinical decision-making

1. Introduction

Aortic stenosis (AS) is commonly graded using peak aortic jet velocity, mean transvalvular gradient, and aortic valve area (AVA). This approach is reliable in typical high-gradient severe AS but becomes less reliable when AVA and gradient are discordant [1,2,3,4]. Low-flow, low-gradient (LF-LG) AS represents the most clinically consequential form of this discordance because similar resting measurements may indicate either true-severe fixed valve obstruction or pseudo-severe valve restriction caused by reduced flow [5,6]. Discordant low-gradient phenotypes may also occur with preserved ejection fraction or normal transvalvular flow [7,8].

This distinction reveals immediate therapeutic consequences: under-recognition of true-severe LF-LG AS may delay aortic valve replacement (AVR), whereas over-diagnosis may expose patients with predominantly cardiomyopathic or afterload-driven disease to an intervention unlikely to address the principal mechanism of symptoms. LF-LG AS should therefore be considered a diagnostic and treatment-decision problem influenced by valve anatomy, loading conditions, rhythm, flow state, and measurement quality [2,3,5,6,9].

Current European and North American guidelines recommend optimized transthoracic echocardiography (TTE), dobutamine stress echocardiography (DSE) for classical LF-LG AS, and computed tomography aortic valve calcium (CT-AVC) when echocardiographic findings remain inconclusive [2,3,10,11,12]. A recent European Association of Cardiovascular Imaging (EACVI) clinical consensus document further summarizes the multimodality approach [13]. In practice, however, escalation remains heterogeneous: some laboratories emphasize stress-gradient thresholds, others prioritize projected AVA, and others proceed early to CT-AVC. This variation highlights the need to define when each test is decisive, conditional, or indeterminate.

Previous guidelines and reviews have established the importance of multimodality imaging in discordant low-

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gradient AS, but practical uncertainty remains regarding which test should be triggered by which unresolved question, how DSE and CT-AVC disagreement should be interpreted, and how myocardial-damage markers should inform reporting without being mistaken for direct proof of valve severity [2,3,5,6,14,15]. The added value of this review is operational rather than technological. It separates phenotype assignment, measurement-quality audit, dynamic flow testing, structural calcification assessment, and myocardial-damage staging into decision steps, including boundary phenotypes such as normal-flow, low-ejection fraction (EF), low-gradient AS and low-calcium or fibrosis-predominant valve disease. These concepts are translated into a six-step pathway, an evidence table, and a reporting checklist.

This article was prepared as a narrative methodological review rather than a systematic review or meta-analysis. PubMed/MEDLINE, Web of Science, and Embase were searched for English-language publications from January 1995 to April 2026 using terms related to low-flow or low-gradient AS, DSE, projected AVA, CT-AVC, cardiac magnetic resonance (CMR), myocardial fibrosis, global longitudinal strain (GLS), cardiac damage staging, and artificial intelligence. Priority was given to guidelines, prospective and multicenter studies, True or Pseudo-Severe Aortic Stenosis (TOPAS)/TOPAS-transcatheter aortic valve implantation (TAVI) investigations, CT-AVC validation studies, meta-analyses, and high-impact imaging reviews. Formal Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)-based screening, risk-of-bias assessment, and numerical pooling were not performed.

2. Hemodynamic Phenotypes and Measurement Uncertainty

Discordant low-gradient AS is a spectrum rather than a single diagnostic label. Its common feature is discordance. AVA suggests severe stenosis, whereas peak aortic jet velocity and mean transvalvular gradient remain below conventional thresholds for severe stenosis. In clinical practice, severe AS is generally defined by an AVA $\leq$1.0 cm^2, whereas low-gradient AS is characterized by a mean gradient <40 mmHg and peak velocity <4.0 m/s. A low-flow status is commonly defined by a stroke volume index (SVi) $\leq$35 mL/m^2 [2,3,5,11,12,13,14,16]. These thresholds are clinically useful but should not override the central physiological principle: transvalvular gradient is flow-dependent.

A further source of uncertainty is the intrinsic variability of the echocardiographic measurements used to define these phenotypes. The continuity equation for AVA is especially vulnerable to errors because the left ventricular outflow tract (LVOT) diameter is squared; consequently, small interobserver or test–retest differences in LVOT measurement may produce clinically meaningful changes in calculated AVA. Mean gradient and peak aortic jet velocity (Vmax) are also flow-dependent and sensitive to Doppler alignment, blood pressure, rhythm, beat averaging in atrial fibrillation, and acquisition of the highest-velocity window. Therefore, values close to diagnostic thresholds should be interpreted as a zone of uncertainty rather than as fixed categorical boundaries because a modest measurement variation can reclassify patients across low-gradient AS phenotypes [11,12,13,14,15,17,18,19].

The same caution applies to SVi-based flow classification. Because the distinction between low-flow and normal-flow phenotypes relies on a fixed SVi threshold of 35 mL/m^2, small variations in LVOT measurement, Doppler velocity–time integral, rhythm averaging, or body-surface-area indexing may shift patients across diagnostic categories, particularly when values are close to the threshold [10,11,12]. Three-dimensional echocardiography may provide complementary volumetric assessment of stroke volume and is less dependent on LVOT geometric assumptions than conventional Doppler-derived stroke volume. However, its role in discordant low-gradient AS remains insufficiently validated; at present, it should be regarded as a potential future adjunct for reducing flow misclassification rather than a routine replacement for optimized Doppler assessment.

Classical LF-LG AS occurs in the setting of reduced left ventricular ejection fraction (LVEF) and reduced forward flow. It is the phenotype for which DSE is most physiologically aligned because the central diagnostic question is whether contractile augmentation unmasks fixed valve obstruction. Paradoxical LF-LG AS occurs with preserved LVEF but reduced SVi, often related to concentric remodeling, small ventricular cavity size, impaired longitudinal function, diastolic dysfunction, high arterial afterload, or atrial fibrillation [6,20,21]. Normal-flow low-gradient AS (NF-LG AS) with preserved LVEF remains heterogeneous rather than merely a measurement-error category; it may reflect body size, indexed AVA issues, arterial load, blood pressure effects, pressure recovery, sex-related valve-vascular coupling, or genuinely severe disease with atypical flow-gradient coupling [22,23]. A distinct and increasingly recognized pattern is normal-flow, low-ejection fraction (low-EF), and low-gradient AS, in which LVEF is reduced but forward SVi is preserved [24]. In this setting, eccentric remodeling, left ventricular (LV) dilatation, concomitant valvular regurgitation, altered loading conditions, or cardiomyopathy may maintain forward flow despite impaired systolic function. Consequently, DSE becomes less straightforward, because stress-induced gradient augmentation may reflect pharmacologic hyperflow rather than true stenosis severity, and CT-AVC together with myocardial damage staging should be prioritized earlier when resting echocardiographic indices remain discordant.

These phenotypes differ in their hemodynamic profiles, measurement vulnerability, DSE interpretability, and the extent to which structural or myocardial evidence

Table 1. Hemodynamic phenotypes of low-gradient aortic stenosis and recommended diagnostic pathways.

Phenotype	Core profile	Dominant uncertainty	Recommended pathway
Classical LF-LG AS with markedly reduced LVEF	AVA ≤1.0 cm^2, MG <40 mmHg, LVEF <35%, usually SVi ≤35 mL/m^2	True-severe versus pseudo-severe AS under markedly reduced contractility	Optimized TTE → DSE as primary dynamic test; CT-AVC if DSE is indeterminate, flow augmentation is inadequate, or flow reserve is absent
Classical LF-LG AS with moderately reduced LVEF	AVA ≤1.0 cm^2, MG <40 mmHg, LVEF ≥35% and <50%, usually SVi ≤35 mL/m^2	Lower DSE decisiveness because flow augmentation and stress-gradient response are more variable	Optimized TTE → DSE remains reasonable; activate CT-AVC earlier if flow augmentation, projected AVA, or stress indices are unreliable
Paradoxical LF-LG AS	AVA ≤1.0 cm^2, MG <40 mmHg, LVEF ≥50%, SVi ≤35 mL/m^2	Low-flow mechanism related to small or hypertrophied LV, high afterload, diastolic dysfunction, AF, or measurement error	Optimized TTE, BP control, and phenotype confirmation → early CT-AVC when severity remains uncertain; selective DSE only for borderline or unresolved dynamic questions
Normal-flow, low-EF, low-gradient AS	AVA ≤1.0 cm^2, MG <40 mmHg, LVEF <50%, SVi >35 mL/m^2	Reduced LVEF with preserved forward flow; low gradient may reflect remodeling, loading conditions, regurgitation, or cardiomyopathy	Optimized TTE and measurement audit → earlier CT-AVC and myocardial damage assessment; selective DSE with cautious interpretation of hyperflow response
Normal-flow, low-gradient AS (NF-LG AS) with preserved LVEF	AVA ≤1.0 cm^2, MG <40 mmHg, LVEF ≥50%, SVi >35 mL/m^2	Heterogeneous phenotype involving measurement variability, body size/ indexed AVA, arterial load, BP, pressure recovery, or atypical severe AS	Repeat optimized TTE; reassess LVOT and multi-window Doppler alignment; consider indexed AVA, body size, BP, and selective CT-AVC; DSE is not routinely first-line

Abbreviations: AF, atrial fibrillation; AS, aortic stenosis; AVA, aortic valve area; BP, blood pressure; CT-AVC, computed tomography aortic valve calcium; DSE, dobutamine stress echocardiography; LF-LG, low-flow low-gradient; LV, left ventricular; LVEF, left ventricular ejection fraction; LVOT, left ventricular outflow tract; MG, mean gradient; NF-LG AS, normal-flow, low-gradient aortic stenosis; SVi, stroke volume index; TTE, transthoracic echocardiography.

should be activated early. Their diagnostic pathways are presented in Table 1.

3. Dobutamine Stress Echocardiography: Methodological Updates and Boundaries

DSE has historically been the central dynamic test for classical LF-LG AS. Low-dose dobutamine increases contractility and transvalvular flow: true-severe AS generally exhibits persistently restricted AVA with gradient rise, whereas pseudo-severe AS exhibits greater leaflet opening and larger calculated AVA [25,26,27,28,29,30]. Conventional interpretation uses stress mean gradient ≥40 mmHg, stress AVA ≤1.0 cm^2, and flow reserve, commonly defined as a ≥20% increase in stroke volume [2,3,25]. Contemporary data, however, indicate that DSE is most informative when the LVEF is markedly reduced, whereas an LVEF within the range of 35–50% often requires earlier structural corroboration when flow augmentation or stress-parameter concordance is limited.

The physiological appeal of DSE is strong, but the conventional interpretation is often too binary. A stress mean gradient that fails to reach 40 mmHg may reflect inadequate flow augmentation rather than non-severe AS. Conversely, a high stress gradient may reflect high-flow conditions across a moderately stenotic valve. Stress AVA remains flow-dependent, and flow reserve may be absent in patients who nevertheless have structurally severe AS. Therefore, DSE should be interpreted as a flow-dependent physiological assessment whose validity depends on adequate stress conditions, Doppler acquisition quality, and internal consistency, rather than as a universally decisive adjudication test.

The true-severe versus pseudo-severe distinction remains clinically relevant, but its therapeutic implications should be interpreted in a contemporary treatment context. Pre-transcatheter aortic valve replacement (TAVR) studies linked flow reserve and DSE-derived classification to operative risk and survival [25,26]. By contrast, contemporary TAVR-era data indicate that LF-LG AS remains associated with poor outcomes, but the absence of flow reserve alone should not be used as an exclusion criterion for valve intervention when other evidence supports severe AS [29,30,31,32,33].

Patients classified as pseudo-severe AS require optimization of cardiomyopathy and afterload management with surveillance rather than reflex valve intervention. Contemporary randomized evidence in heart failure with reduced ejection fraction (HFrEF) and moderate AS also does not support routine transcatheter valve intervention before severe obstruction is established [34].

3.1 LVEF-Stratified Diagnostic Performance and Flow Reserve

The most important contemporary update is that DSE performance varies across low-gradient AS phenotypes. In a study by Mogensen et al. [1], 221 patients with mean gradient <40 mmHg, AVA <1.0 cm^2, SVi ≤35 mL/m^2, DSE, and cardiac CT were stratified by LVEFs <35%, 35–50%, and >50% [1]. Against sex-specific CT-AVC thresholds, mean-gradient AUCs were 0.90, 0.67, and 0.65 across these strata, and Vmax AUCs were 0.90, 0.66, and 0.60. Guideline-based DSE thresholds in the LVEF <50% population yielded 49% sensitivity and 84% specificity.

These data delineate where DSE is most informative rather than proving that it is ineffective. A markedly reduced LVEF favors DSE as the primary dynamic test, whereas mid-range or preserved LVEFs, low-flow mechanisms driven by remodeling, diastolic dysfunction, atrial fibrillation, or ventricular–arterial coupling should lower the threshold for CT-AVC when DSE is technically limited or internally discordant.

Because Mogensen et al. [1] used CT-AVC as the reference standard, the LVEF-stratified AUC values were interpreted as performance against a clinically accepted structural comparator rather than as definitive physiological truth. This is an important methodological limitation: CT-AVC is subsequently used in clinical pathways as a downstream adjudication tool when DSE is indeterminate, creating a potential circularity if CT-AVC is considered the sole arbiter of severity. Therefore, the LVEF-stratified recommendation in this review should be considered a pragmatic signal rather than an independently validated rule. Cross-validation was derived from older DSE cohorts and TOPAS studies showing that flow reserve, stress hemodynamics, and projected AVA relate to operative risk, severity classification, and outcomes [25,27,30,35] and from contemporary outcome data showing that valve intervention and Heart Team judgment remain important when DSE variables are non-decisive [29,30,31,33]. Future studies should use multiparametric reference standards that incorporate invasive hemodynamics when available, valve morphology, CT-AVC, DSE response, treatment response, and longitudinal outcomes.

Flow reserve therefore remains useful, but its exclusionary role has narrowed. It should be reported as a myocardial recruitment marker, determinant of DSE interpretability, and procedural risk signal, not as a stand-alone gatekeeper. In the TAVR era, absent flow reserve should not deny intervention when CT-AVC, symptoms, myocardial damage, and Heart Team judgment support severe AS [25,29,30,31,32,33,35].

3.2 Flow-Normalized and Flow-Rate-Based Interpretation

Projected AVA (AVAproj) estimates AVA at a standardized transvalvular flow rate, commonly 250 mL/s, to reduce unequal flow exposure during DSE [27,28]. It is most useful when paired flow–AVA measurements are technically reliable and flow increases enough to permit extrapolation. It should not be overinterpreted when flow augmentation is minimal, rhythm is unstable, Doppler envelopes are poor, or LVOT/velocity–time integral measurements are inconsistent; in these settings, CT-AVC should be preferred.

The SVi does not account for ejection time; therefore, the transaortic flow rate may better reflect the hemodynamic driver of the gradient. Observational studies have shown that SVi-based and flow-rate-based classifications may diverge and that volume-flow discordance may carry prognostic information after TAVR [36,37]. However, until prospective thresholds and standardized ejection-time protocols are validated, the transaortic flow rate and volume-flow discordance should remain risk-refining rather than decision-driving diagnostic criteria.

These developments indicate that DSE interpretation in LF-LG AS should shift from a purely threshold-driven approach toward a phenotype-aware, flow-informed, and multimodality-linked assessment. The key methodological concepts are illustrated in Fig. 1 (Ref. [1]) and Table 2 (Ref. [1,25,27,30,35]).

4. Structural Valve Adjudication and Myocardial Damage Assessment

CT-AVC is an important structural complement to DSE because it is relatively independent of instantaneous transvalvular flow. Contemporary guidelines support CT-AVC as a probability-based tool when echocardiographic findings are discordant or inconclusive [2,3,38,39,40,41,42,43]. Recent CT-focused reviews have further emphasized its role as a structural adjunct rather than a stand-alone gold standard [14,15]. CT-AVC provides structural evidence for or against severe calcific AS, and recent low-flow AS data have shown that AVC retains prognostic value; however, its diagnostic performance still depends on sex, valve phenotype, population selection, and reference-standard ambiguity [44].

CT-AVC does not replace echocardiography, but it answers a different question. DSE tests flow-dependent valve behavior, whereas CT-AVC estimates whether calcific burden is consistent with severe degenerative AS. Therefore, after optimized TTE and blood pressure control, CT-AVC may be activated earlier in preserved-LVEF low-gradient phenotypes and whenever DSE is poorly aligned with the mechanism of discordance [5,38,39,40,41].

The proposed pathway separates phenotypes by the likelihood that DSE will generate interpretable flow information. DSE is preferable when the LVEF is markedly reduced. In the 35–50% LVEF range, limited flow response, unstable AVA-flow slope, or discordant stress indices should prompt earlier CT-AVC. In paradoxical LF-LG AS and persistent NF-LG AS, CT-AVC is generally favored after TTE quality audit, phenotype confirmation, and blood

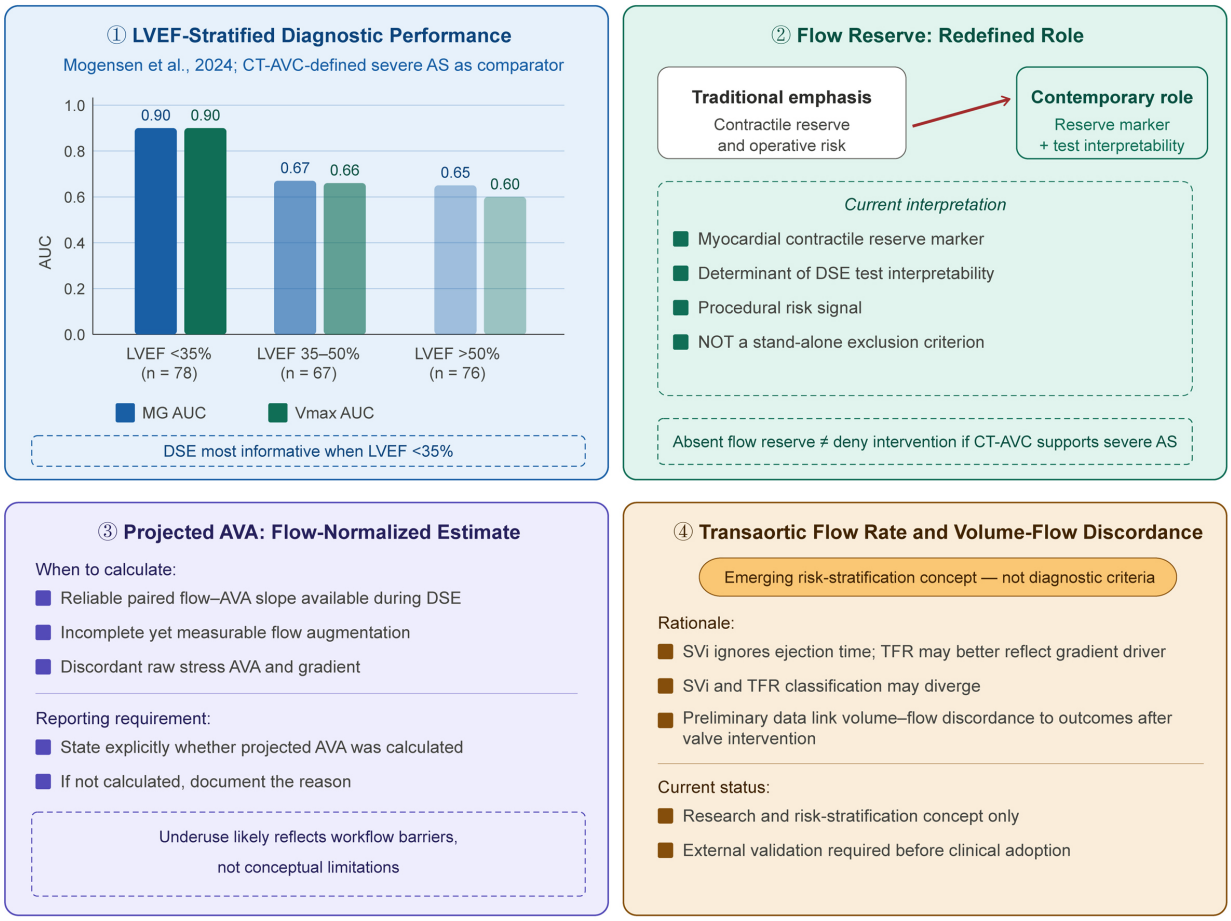


Fig. 1. Methodological updates in dobutamine stress echocardiography for low-flow, low-gradient aortic stenosis. The figure illustrates four contemporary updates in DSE interpretation: LVEF-stratified diagnostic performance, reinterpretation of flow reserve as a marker of myocardial reserve and test interpretability rather than a stand-alone exclusion criterion, use of projected AVA when flow normalization is incomplete and paired flow–AVA data are reliable, and cautious incorporation of transaortic flow rate and volume–flow discordance as emerging risk-stratification concepts rather than validated diagnostic criteria. The AUC values are derived from Mogensen et al. [1] using CT-AVC-defined severe AS as the comparator. Abbreviations: AS, aortic stenosis; AUC, area under the receiver-operating characteristic curve; AVA, aortic valve area; CT-AVC, computed tomography aortic valve calcium; DSE, dobutamine stress echocardiography; LF-LG, low-flow low-gradient; LVEF, left ventricular ejection fraction; MG, mean gradient; SVi, stroke volume index; TFR, transaortic flow rate; Vmax, peak aortic jet velocity.

pressure optimization, with DSE reserved for selected borderline or unresolved dynamic questions.

Sex-specific CT-AVC thresholds should be interpreted biologically rather than as a numerical convention. Women often have lower calcific burden for a comparable hemodynamic severity, probably reflecting differences in fibrosis, calcification patterns, and valve remodeling [41,45]. This supports lower thresholds in women and reinforces the need for caution in low-calcium or fibrosis-dominant phenotypes.

This limitation is clinically important because CT-AVC thresholds may underestimate stenosis severity when valve remodeling is predominantly fibrotic or otherwise less calcific. In these settings, calcification burden may not fully capture non-calcific leaflet restriction, and low or borderline CT-AVC should not automatically downgrade severity probability when clinical features, Doppler findings, valve morphology, symptoms, or myocardial-damage markers remain concerning. Younger patients, women, bicuspid valves, rheumatic disease, cardiac amyloidosis, and fibrosis-predominant valve remodeling may exhibit lower calcium burden relative to obstruction. Therefore, CT-AVC should be integrated with valve morphology, Doppler quality, loading conditions, functional hemodynamics, myocardial staging, and, when necessary, invasive hemodynamics rather than interpreted as a binary rule-out test or used as the sole marker of severity.

Table 2. Methodological evidence supporting updated DSE interpretation in LF-LG AS.

Study	Design/Population	Reference/Endpoint	Key DSE finding	Main limitation
Monin et al., 2003 [25]	Multicenter classical LF-LG AS cohort, pre-TAVR era	Operative risk and long-term outcome	Flow reserve and stress hemodynamic response were associated with operative risk and long-term outcomes	Older surgical era; outcome endpoints influenced by treatment selection
Blais et al., 2006 / TOPAS [27]	Multicenter LF-LG AS cohort	Projected AVA validation	Projected AVA improved severity assessment by normalizing AVA to a standardized flow rate	Requires reliable flow–AVA slope and adequate paired measurements
Quere et al., 2006 / TOPAS [35]	Multicenter LF-LG AS cohort	Clinical outcomes	DSE-derived parameters contributed to outcome prediction but remained dependent on achieved flow	Pre-modern TAVR practice; heterogeneous management
Annabi et al., 2018 [30]	Contemporary LF-LG AS management cohort	Management and outcome	DSE remained useful, whereas absence of flow reserve had reduced exclusionary value	Observational design; treatment decisions not randomized
Mogensen et al., 2024 [1]	221 low-gradient AS patients stratified by LVEF <35%, 35–50%, and >50%	CT-AVC-defined severe AS: men ≥2000 AU, women ≥1200 AU	DSE mean-gradient AUCs were 0.90, 0.67, and 0.65 across LVEF strata; guideline thresholds showed 49% sensitivity and 84% specificity in LVEF <50%	CT-AVC is a probabilistic comparator; AUC estimates may be affected by reference-standard uncertainty and DSE measurement variability

Abbreviations: AS, aortic stenosis; AU, Agatston units; AVA, aortic valve area; AUC, area under the receiver-operating characteristic curve; CT-AVC, computed tomography aortic valve calcium; DSE, dobutamine stress echocardiography; LF-LG, low-flow low-gradient; LVEF, left ventricular ejection fraction; TAVR, transcatheter aortic valve replacement.

Adrichem et al. [4] questioned the uncritical use of fixed CT-AVC thresholds in suspected LF-LG AS. Their findings suggest that CT-AVC, DSE, and resting echocardiography measure different aspects of severity and may disagree in populations enriched for reference-standard ambiguity. Table 3 presents CT-AVC threshold concepts as probability-weighted structural evidence in discordant low-gradient AS.

Beyond structural valve adjudication, CMR and advanced echocardiography primarily refine myocardial damage and prognosis. Fibrosis markers, extracellular volume fraction, strain, atrial remodeling, pulmonary pressure, right ventricular dysfunction, and regurgitant lesions do not prove stenosis severity; however, they help define myocardial injury, reversibility, timing risk, and expected benefit of intervention after severity probability has been framed by optimized TTE, DSE when appropriate, and CT-AVC [46,47,48,49,50,51,52,53,54,55,56,57,58,59,60]. Therefore, a modern assessment should separate severity probability from damage burden, integrating GLS, left atrial volume index, E/e′, pulmonary artery systolic pressure, TAPSE, right ventricular strain, regurgitant lesions, CMR late gadolinium enhancement, T1 mapping, and extracellular volume fraction.

To highlight this translational component more clearly, Table 4 (Ref. [2,38,39,40,41,42,43,44,45,46,47,48,49,50,51,52,53,54,55,56,57,58]) summarizes evidence supporting myocardial damage staging beyond conventional AS grading, including cardiac damage staging systems, GLS, CMR fibrosis markers such as late gadolinium enhancement (LGE) and extracellular volume fraction (ECV), left atrial remodeling, pulmonary hypertension, right ventricular dysfunction, and integrated risk assessment. These domains provide prognostic information and may inform timing-risk discussions, but they should be interpreted as risk-refining evidence rather than as stand-alone proof of valve severity, particularly in LF-LG AS where direct phenotype-specific validation remains limited.

The EVOLVED randomized clinical trial is particularly relevant to this distinction. In asymptomatic severe AS with CMR-detected myocardial fibrosis, early valve intervention did not significantly reduce the primary composite endpoint of all-cause death or unplanned AS-related hospitalization compared with guideline-directed conservative management [53]. These findings do not negate the prognostic value of myocardial fibrosis, but they caution against using CMR fibrosis as an automatic intervention trigger. Therefore, in discordant low-gradient AS, myocardial damage markers should refine timing, reversibility, and risk discussions, while final management should still integrate severity probability, symptoms, comorbidity, and Heart Team assessment.

Table 3. CT-AVC threshold concepts and clinical interpretation in discordant low-gradient AS.

CT-AVC threshold concept	Women	Men	Clinical interpretation	Important caveats
Guideline-supported severe-AS threshold	Approximately >1200 AU	Approximately >2000 AU	Increases the probability of severe calcific AS in the appropriate clinical and echocardiographic context	Thresholds are probabilistic; calcium is not fibrosis; interpretation is less definitive in low-flow selected cohorts
Higher-specificity threshold	Approximately >1600 AU	Approximately >3000 AU	Increases specificity for severe calcific AS when clinical and Doppler findings are concordant	May reduce sensitivity, especially in women and in low-calcification or fibrosis-predominant phenotypes
Low CT-AVC despite discordant echocardiography	Below sex-specific threshold	Below sex-specific threshold	Argues against high-probability calcific severe AS	Does not fully exclude low-calcification or fibrosis-predominant severe AS; consider valve morphology, image quality, CMR, invasive hemodynamics, and clinical context
Bicuspid valve or atypical morphology	No universally accepted adjustment	No universally accepted adjustment	Requires individualized interpretation	Valve phenotype, age, fibrosis/calcification composition, annular anatomy, and hemodynamic context matter

Abbreviations: AS, aortic stenosis; AU, Agatston units; CMR, cardiac magnetic resonance; CT-AVC, computed tomography aortic valve calcium.

5. Integrated Multimodality Decision and Reporting Framework

In LF-LG AS, risk stratification should identify the type of risk that changes management: diagnostic uncertainty, procedural risk, limited myocardial recovery, adverse outcomes, or harm from delay. Guidelines already integrate symptoms, ventricular function, imaging markers, comorbidity, anatomy, and Heart Team assessment rather than valve gradients alone [2].

We summarize five clinically relevant domains—misclassification risk, procedural risk, myocardial reversibility risk, clinical outcome risk, and timing risk—which translate multimodality imaging findings into decisions about diagnostic confidence, treatment feasibility, expected recovery, prognosis, and timing of intervention.

The proposed six-step framework operationalizes these domains by starting with discordant valve grading and measurement-quality audit, then applying phenotype-specific adjudication, selective DSE, CT-AVC support, myocardial and extravalvular risk assessment, and integrated Heart Team decision-making (Fig. 2).

Step 1: Baseline TTE identification of discordant valve grading.

Document AVA, Vmax, mean gradient, SVi, LVEF, and other core hemodynamic variables to confirm the presence of discordant low-gradient AS.

Step 2: Resting echocardiographic quality audit.

Review LVOT measurement, Doppler alignment and windows, loading conditions, rhythm, and relevant regurgitant lesions. Repeat or optimize TTE when technical or physiological factors may distort severity classification.

Step 3: Phenotype-specific adjudication.

Classify patients into classical LF-LG AS, paradoxical LF-LG AS, or NF-LG AS after quality audit. In classical LF-LG AS, DSE is used as the principal dynamic test to distinguish true-severe from pseudo-severe AS; CT-AVC is recommended when DSE is indeterminate or technically inconclusive. In paradoxical LF-LG AS, confirmation of low-flow physiology, blood pressure optimization, GLS, and early CT-AVC assessment are emphasized. In NF-LG AS, reassessment of indexed AVA, body size, and measurement discordance is prioritized, with selective CT-AVC when discordance persists.

Step 4: CT-AVC structural adjudication.

Use CT-AVC for probabilistic structural confirmation when DSE is inconclusive, when DSE is less directly aligned with the phenotype, or when symptoms and echocardiographic findings remain discordant. Sex-specific thresholds should be interpreted in the context of overall clinical probability rather than as isolated binary cut-offs.

Step 5: Myocardial and extravalvular risk assessment.

Use CMR and advanced echocardiography when myocardial damage, impaired GLS, RV–pulmonary pressure abnormalities, MR/TR burden, LV dysfunction, or timing risk may influence management.

Step 6: Final integrated Heart Team decision.

The final interpretation should state the probability of severe AS, the mechanism of low flow or discordance, the decisiveness of DSE when performed, the CT-AVC interpretation when available, the burden of myocardial or extravalvular damage, and the recommended next action, in-

Table 4. Evidence supporting myocardial damage staging beyond conventional aortic stenosis grading.

Evidence domain	Representative marker or framework	Prognostic implication and timing relevance	Key limitation in discordant low-gradient AS
Cardiac damage staging	Multichamber staging of LV, LA/mitral, pulmonary/tricuspid, and RV consequences [46,47]	Captures downstream cardiac injury beyond AVA, Vmax, and MG; may support earlier Heart Team discussion	Mostly derived from broader AS cohorts; phenotype-specific weighting remains unvalidated
Left ventricular mechanics	GLS and strain-based damage staging [46,47,55,56,57]	Detects subclinical LV dysfunction and refines risk despite preserved or mildly reduced LVEF	Vendor, loading, and rhythm dependence; uncertain phenotype-specific thresholds
Replacement fibrosis	CMR LGE and histopathologic fibrosis evidence [49,50]	Indicates irreversible myocardial injury and poorer post-intervention recovery	LGE mainly detects focal replacement fibrosis, not diffuse interstitial expansion
Diffuse interstitial remodeling	T1 mapping and ECV [50,51,52,53,54]	Reflects diffuse fibrosis and may inform reversibility and timing-risk discussions	Scanner and protocol variability; fibrosis should not be an automatic intervention trigger
Left atrial remodeling	LA size, function, and strain [58]	Reflects chronic diastolic burden, symptom status, and adverse outcome risk	Confounded by atrial fibrillation and mitral valve disease
Pulmonary hypertension and RV dysfunction	PASP, RV function/strain, and significant MR/TR [46,48]	Signals advanced multichamber damage, procedural vulnerability, and reduced recovery potential	May reflect lung disease, left-heart disease, or additional valve lesions
Integrated risk assessment	DSE response, CT-AVC, GLS, CMR markers, biomarkers, symptoms, and frailty [2,38,39,40,41,42,43,44,45,46,47,48,49,50,51,52,53,54,55,56,57,58]	Supports individualized timing when severity probability and damage burden diverge	Unified low-gradient AS-specific decision models require prospective validation

Abbreviations: AS, aortic stenosis; AVA, aortic valve area; CMR, cardiac magnetic resonance; CT-AVC, computed tomography aortic valve calcium; DSE, dobutamine stress echocardiography; ECV, extracellular volume fraction; GLS, global longitudinal strain; LA, left atrial; LGE, late gadolinium enhancement; LV, left ventricular; LVEF, left ventricular ejection fraction; MG, mean gradient; MR, mitral regurgitation; PASP, pulmonary artery systolic pressure; RV, right ventricular; TR, tricuspid regurgitation; Vmax, peak aortic jet velocity.

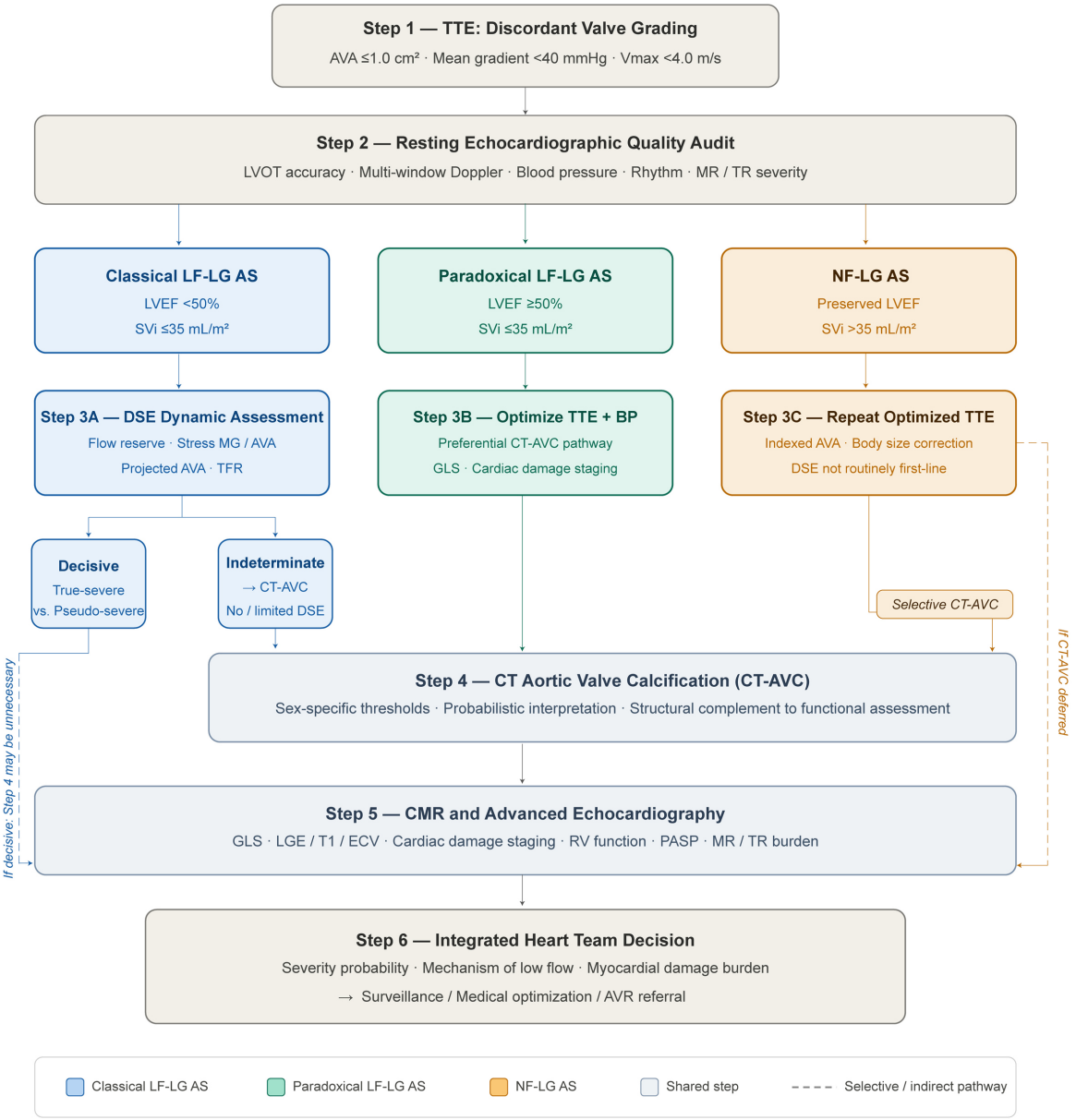


Fig. 2. Simplified phenotype-aware diagnostic and risk-stratification framework for low-gradient aortic stenosis. The framework starts with discordant valve grading and echocardiographic quality audit, then separates patients into classical LF-LG AS, paradoxical LF-LG AS, and NF-LG AS pathways. The simplified structure emphasizes phenotype-specific adjudication, selective use of CT aortic valve calcium scoring, myocardial and extravalvular risk assessment, and integrated Heart Team decision-making. Normal-flow, low-EF, low-gradient AS is not shown as a separate branch to preserve readability but is presented in Tables 1 and 5. Abbreviations: AS, aortic stenosis; AVA, aortic valve area; AVR, aortic valve replacement; BP, blood pressure; CMR, cardiac magnetic resonance; CT-AVC, computed tomography aortic valve calcium; DSE, dobutamine stress echocardiography; GLS, global longitudinal strain; LF-LG AS, low-flow, low-gradient aortic stenosis; LVOT, left ventricular outflow tract; LVEF, left ventricular ejection fraction; MR, mitral regurgitation; NF-LG AS, normal-flow, low-gradient aortic stenosis; RV, right ventricular; SVi, stroke volume index; TTE, transthoracic echocardiography; TR, tricuspid regurgitation; Vmax, peak aortic jet velocity.

cluding surveillance, medical optimization, or AVR referral.

To further operationalize this framework, Table 5 presents key decision nodes, operational definitions, and recommended next actions for reproducible escalation across discordant low-gradient AS phenotypes, including normal-flow, low-EF, low-gradient AS.

Table 5. Operational decision nodes for phenotype-specific escalation in discordant low-gradient AS.

Decision node	Operational definition	Next action
Resting discordance confirmed	AVA ≤1.0 cm^2 with MG <40 mmHg and Vmax <4.0 m/s	Proceed to TTE quality audit before advanced imaging
Technical uncertainty	Uncertain LVOT measurement, suboptimal Doppler windows, uncontrolled BP, inadequate AF averaging, or significant MR/TR affecting forward flow	Repeat optimized TTE or expert echocardiographic review
Classical LF-LG AS with LVEF < 35%	LVEF <35% and SVi ≤35 mL/m^2 after quality audit	Use DSE as the primary dynamic test; proceed to CT-AVC if DSE is indeterminate or flow augmentation is inadequate
Classical LF-LG AS with LVEF 35–50%	LVEF ≥35% and <50% and SVi ≤35 mL/m^2 after quality audit	DSE remains reasonable; activate CT-AVC earlier if flow augmentation, projected AVA, or stress indices are unreliable
Decisive DSE	Technically adequate DSE with interpretable Doppler envelopes and adequate flow rise. True-severe pattern: stress MG ≥40 mmHg with stress AVA ≤1.0 cm^2, or AVAproj ≤1.0 cm^2 when calculable. Pseudo-severe pattern: AVA increases >1.0 cm^2 with persistently low gradient and no high-probability structural evidence	Classify true-severe or pseudo-severe AS when technically reliable DSE findings support a coherent interpretation based on stress-gradient and stress-AVA criteria or projected AVA when reliably calculable; if findings remain discordant or inconclusive, report DSE as indeterminate and consider CT-AVC
Indeterminate DSE	Flow rise <20% or is insufficient for reliable AVAproj; unreliable LVOT/VTI or Doppler envelopes; discordant stress parameters; absent flow reserve without corroborating structural evidence; or BP/rhythm/technical limitation	Perform CT-AVC; consider CMR or invasive hemodynamics if structural–functional mismatch persists
Paradoxical LF-LG AS	LVEF ≥50%, SVi ≤35 mL/m^2, optimized BP and TTE acquisition	Consider early CT-AVC; assess GLS and cardiac damage stage; reserve DSE for borderline CT-AVC or unresolved dynamic questions
NF-LG AS with preserved LVEF	LVEF ≥50%, SVi >35 mL/m^2, low gradient AS despite small AVA	Repeat optimized TTE, reassess indexed AVA, and consider selective CT-AVC; DSE is not routinely first-line
Normal-flow, low-EF, low-gradient AS	LVEF <50%, SVi >35 mL/m^2, AVA ≤1.0 cm^2, MG <40 mmHg after measurement audit	Prioritize optimized TTE, loading/regurgitation assessment, early CT-AVC, and CMR/GLS evaluation; use DSE selectively and interpret hyperflow responses cautiously
Structural–functional mismatch	CT-AVC, symptoms, myocardial findings, and echocardiographic severity do not align	Use CMR, invasive hemodynamics, and Heart Team adjudication

Abbreviations: AF, atrial fibrillation; AS, aortic stenosis; AVA, aortic valve area; AVAproj, projected aortic valve area; BP, blood pressure; CMR, cardiac magnetic resonance; CT-AVC, computed tomography aortic valve calcium; DSE, dobutamine stress echocardiography; GLS, global longitudinal strain; LF-LG, low-flow low-gradient; LV, left ventricular; LVEF, left ventricular ejection fraction; LVOT, left ventricular outflow tract; MG, mean gradient; MR, mitral regurgitation; NF-LG AS, normal-flow, low-gradient aortic stenosis; SVi, stroke volume index; TTE, transthoracic echocardiography; TR, tricuspid regurgitation; Vmax, peak aortic jet velocity; VTI, velocity–time integral.

6. Reporting, Reproducibility, and Future Directions

AI is most useful in LF-LG AS as a quality-control and workflow-support tool rather than as a stand-alone adjudicator. Potential roles include automated Doppler tracing, LVOT measurement assistance, VTI consistency checks, recognition of discordant grading, CT-AVC segmentation, GLS automation, and structured reporting [61,62,63,64,65]. Because many models are trained on conventional labels vulnerable to discordance, LF-LG-specific validation should emphasize reduced measurement variability, correct uncertainty flagging, and guideline-concordant reporting rather than a binary severe/non-severe output.

The practical output is a structured report that documents six items: phenotype, measurement quality, DSE interpretability, CT-AVC probability, myocardial damage, and the next management step. The clinical value is not to add another testing layer but to render uncertainty explicit, prevent inappropriate single-test adjudication, and provide a shared language for Heart Team decisions.

Predefined CT-AVC triggers should include inconclusive DSE, inadequate flow augmentation, paradoxical LF-LG AS, NF-LG AS with preserved LVEF, normal-flow,

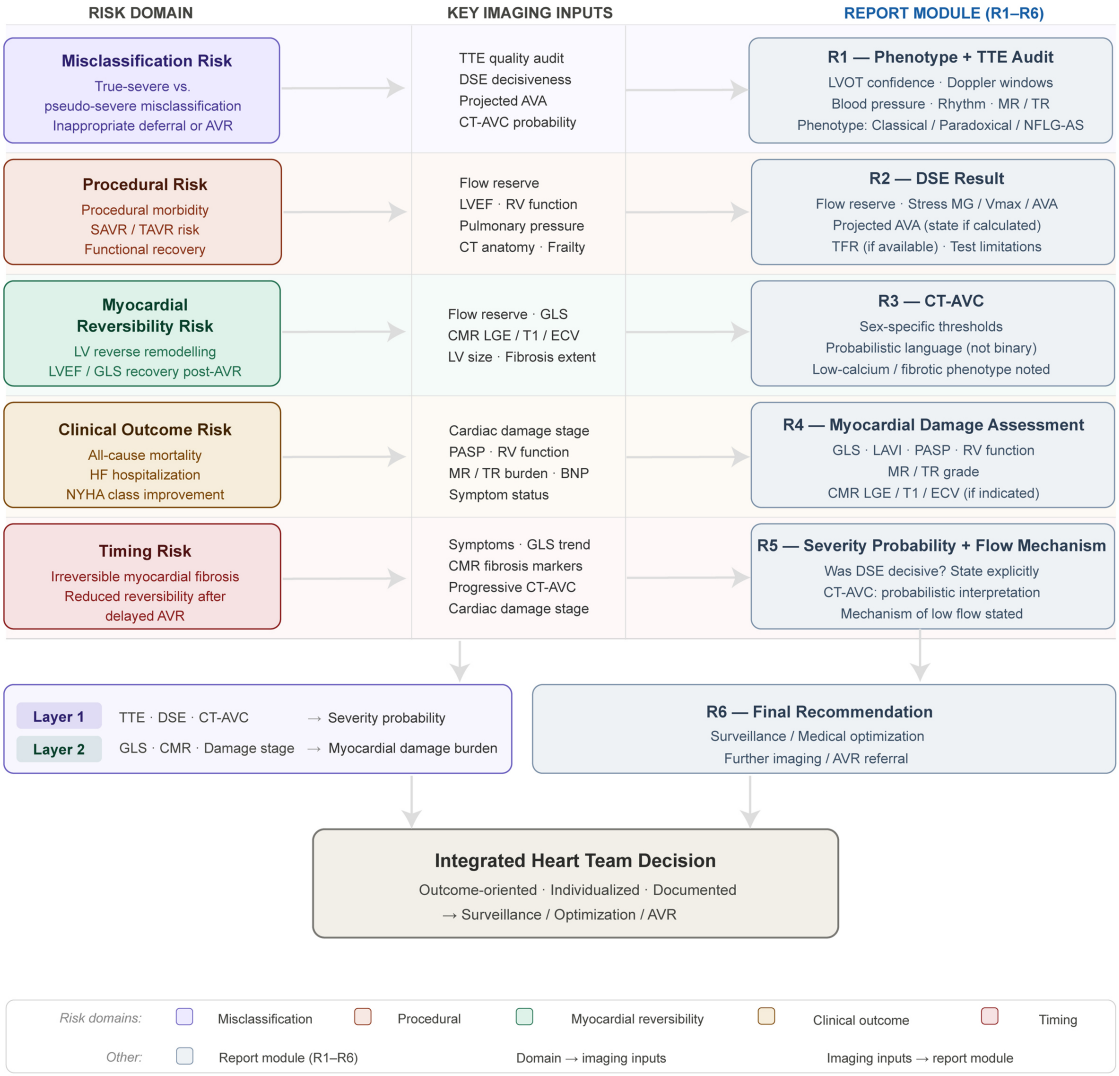


Fig. 3. Risk domains and standardized reporting modules for discordant low-gradient aortic stenosis. The figure links five clinically relevant risk domains to key imaging inputs and standardized report modules. The modules are intended to support reproducible documentation of phenotype, DSE results, CT-AVC interpretation, myocardial damage assessment, severity probability, flow mechanism, and final Heart Team recommendation. Risk domains and report modules are functionally related but not strictly one-to-one. Abbreviations: AS, aortic stenosis; AVA, aortic valve area; AVR, aortic valve replacement; BNP, B-type natriuretic peptide; CMR, cardiac magnetic resonance; CT-AVC, computed tomography aortic valve calcium; DSE, dobutamine stress echocardiography; ECV, extracellular volume fraction; GLS, global longitudinal strain; LAVI, left atrial volume index; LF-LG, low-flow low-gradient; LGE, late gadolinium enhancement; LVEF, left ventricular ejection fraction; MR, mitral regurgitation; NF-LG AS, normal-flow, low-gradient aortic stenosis; NYHA, New York Heart Association; PASP, pulmonary artery systolic pressure; RV, right ventricular; SAVR, surgical aortic valve replacement; TAVR, transcatheter aortic valve replacement; TFR, transaortic flow rate; TTE, transthoracic echocardiography; TR, tricuspid regurgitation; Vmax, peak aortic jet velocity.

low-EF, low-gradient AS, poor acoustic windows, and persistent structural-functional mismatch.

Myocardial damage assessment should be added when management depends on expected recovery, prognosis, or timing rather than valve severity alone. Fig. 3 translates these domains into standardized reporting modules; Table 5 presents the practical escalation checklist.

7. Limitations

This review has some limitations. It is a narrative methodological review rather than a PRISMA-based systematic review or meta-analysis; therefore, formal risk-of-bias assessment, evidence grading, and quantitative pooling were not performed. The proposed framework synthe-

sizes guideline, observational, registry, and selected trial evidence; however, it has not been prospectively validated as a unified clinical algorithm.

Evidence strength differs across phenotypes. DSE and projected AVA are supported most directly in classical LF-LG AS, whereas normal-flow, low-EF, low-gradient AS, NF-LG AS with preserved LVEF, flow-rate metrics, myocardial damage staging, and AI-based quality control require further validation. CT-AVC thresholds remain probabilistic, particularly in low-calcium or fibrosis-dominant phenotypes.

Accordingly, the framework should support reproducible reasoning, not replace guideline-directed Heart Team judgment.

Future work should prospectively validate integrated algorithms rather than isolated biomarkers. Prospective multicenter cohorts should include classical LF-LG AS, paradoxical LF-LG AS, normal-flow, low-EF, low-gradient AS, and NF-LG AS with preserved LVEF; use standardized TTE, DSE, CT-AVC, CMR, and strain protocols; apply multiparametric reference standards; and test whether structured reporting improves diagnostic concordance, treatment selection, reverse remodeling, heart-failure hospitalization, and survival. Flow-rate metrics, myocardial damage models, and AI tools should remain investigational until they show incremental utility and reproducibility in discordant AS subgroups.

8. Conclusion

Discordant low-gradient AS is not a single-test diagnosis. Low flow, measurement uncertainty, ventricular remodeling, and myocardial injury affect the validity of conventional grading; therefore, DSE, CT-AVC, CMR, and advanced echocardiography should be assigned to the specific uncertainty each is best suited to resolve.

A reproducible approach should begin with optimized TTE and measurement audit, use DSE for dynamic interrogation when physiologically aligned, activate CT-AVC when dynamic testing is indeterminate or phenotype-mismatched, and incorporate myocardial damage markers to refine reversibility and timing risk. The proposed framework is intended to make this reasoning explicit, reproducible, and phenotype-specific.

Author Contributions

Conceptualization, YLi and YLiu; methodology, YLi and YLiu; literature search and evidence synthesis, YLi; writing—original draft preparation, YLi; writing—review and editing, YLi and YLiu; visualization, YLi; supervision, YLiu. Both authors have read and agreed to the submitted version of the manuscript. Both authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

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The authors declare no conflicts of interest.

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

During the preparation of this work, the authors used ChatGPT 5.5 for language polishing and grammar checking. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

References

[1] Mogensen NSB, Ali M, Carter-Storch R, Annabi MS, Grenier-Delaney J, Møller JE, et al. Dobutamine Stress Echocardiography in Low-Gradient Aortic Stenosis. Journal of the American Society of Echocardiography: Official Publication of the American Society of Echocardiography. 2024; 37: 1023–1033. https://doi.org/10.1016/j.echo.2024.06.017

[2] Praz F, Borger MA, Lanz J, Marin-Cuartas M, Abreu A, Adamo M, et al. 2025 ESC/EACTS guidelines for the management of valvular heart disease: Developed by the task force for the management of valvular heart disease of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS). European Heart Journal. 2025; 46: 4635–4736. https://doi.org/10.1093/eurheartj/ehaf194

[3] Otto CM, Nishimura RA, Bonow RO, Carabello BA, Erwin JP, 3rd, Gentile F, et al. 2020 ACC/AHA Guideline for the Management of Patients With Valvular Heart Disease: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. Circulation. 2021; 143: e72–e227. https://doi.org/10.1161/CIR.0000000000000923

[4] Adrichem R, Hokken TW, Bouwmeester S, Abdelkarim O, Vogel B, Blusztein DI, et al. Diagnostic Value of Aortic Valve Calcification Levels in the Assessment of Low-Gradient Aortic Stenosis. JACC. Cardiovascular Imaging. 2024; 17: 847–860. https://doi.org/10.1016/j.jcmg.2024.03.014

[5] Weir L, Meredith T, Hayward C, Muller D, Feneley M, Namasivayam M. Low-flow low-gradient aortic stenosis: Foundations, challenges, and solutions. Current Treatment Options in Cardiovascular Medicine. 2025; 27: 27. https://doi.org/10.1007/s11936-025-01082-6

[6] Sharma N, Sachedina AK, Kumar S. Low-flow, Low-gradient Severe Aortic Stenosis: A Review. Heart International. 2023; 17: 8–12. https://doi.org/10.17925/HI.2023.17.1.8

[7] Ozkan A, Hachamovitch R, Kapadia SR, Tuzcu EM, Marwick TH. Impact of aortic valve replacement on outcome of symptomatic patients with severe aortic stenosis with low gradient and preserved left ventricular ejection fraction. Circulation. 2013; 128: 622–631. https://doi.org/10.1161/CIRCULATIONAHA.112.001094

[8] Elkaryoni A, Huded CP, Saad M, Altibi AM, Chhatriwalla AK, Abbott JD, et al. Normal-Flow Low-Gradient Aortic Stenosis: Comparing the U.S. and European Guidelines. JACC. Cardiovascular Imaging. 2024; 17: 926–936. https://doi.org/10.1016/j.jcmg.2024.03.005

[9] Vahanian A, Beyersdorf F, Praz F, Milojevic M, Baldus S, Bauersachs J, et al. 2021 ESC/EACTS guidelines for the management of valvular heart disease: Developed by the Task Force for the management of valvular heart disease of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS). European Heart Journal. 2022; 43: 561–632. https://doi.org/10.1093/eurheartj/ehab395

[10] Lancellotti P, Pellikka PA, Budts W, Chaudhry FA, Donal E, Dulgheru R, et al. The Clinical Use of Stress Echocardiography in Non-Ischaemic Heart Disease: Recommendations from the European Association of Cardiovascular Imaging and the American Society of Echocardiography. Journal of the American Society of Echocardiography: Official Publication of the American Society of Echocardiography. 2017; 30: 101–138. https://doi.org/10.1016/j.echo.2016.10.016

[11] Baumgartner H, Hung J, Bermejo J, Chambers JB, Evangelista A, Griffin BP, et al. Echocardiographic assessment of valve stenosis: EAE/ASE recommendations for clinical practice. Journal of the American Society of Echocardiography: Official Publication of the American Society of Echocardiography. 2009; 22: 1–23; quiz 101–2. https://doi.org/10.1016/j.echo.2008.11.029

[12] Baumgartner H, Chair, Hung J, Co-Chair, Bermejo J, Chambers JB, Edvardsen T, Goldstein S, et al. Recommendations on the echocardiographic assessment of aortic valve stenosis: a focused update from the European Association of Cardiovascular Imaging and the American Society of Echocardiography. European Heart Journal. Cardiovascular Imaging. 2017; 18: 254–275. https://doi.org/10.1093/ehjci/jew335

[13] Dweck MR, Loganath K, Bing R, Treibel TA, McCann GP, Newby DE, et al. Multi-modality imaging in aortic stenosis: an EACVI clinical consensus document. European Heart Journal. Cardiovascular Imaging. 2023; 24: 1430–1443. https://doi.org/10.1093/ehjci/jead153

[14] Botezatu SB, Dweck MR. How to assess aortic stenosis using computed tomography: Current and emerging tools. Romanian Journal of Cardiology. 2025; 35: 237–242. https://doi.org/10.2478/rjc-2025-0028

[15] Scalia IG, Farina JM, Padang R, Jokerst CE, Pereyra M, Mahmoud AK, et al. Aortic Valve Calcium Score by Computed Tomography as an Adjunct to Echocardiographic Assessment-A Review of Clinical Utility and Applications. Journal of Imaging. 2023; 9: 250. https://doi.org/10.3390/jimaging9110250

[16] Mancusi C, Bahlmann E, Basile C, Gerdts E. New Evidence About Aortic Valve Stenosis and Cardiovascular Hemodynamics. High Blood Pressure & Cardiovascular Prevention: the Official Journal of the Italian Society of Hypertension. 2022; 29: 231–237. https://doi.org/10.1007/s40292-022-00520-x

[17] Little SH, Chan KL, Burwash IG. Impact of blood pressure on the Doppler echocardiographic assessment of severity of aortic stenosis. Heart (British Cardiac Society). 2007; 93: 848–855. https://doi.org/10.1136/hrt.2006.098392

[18] Velders BJJ, Vriesendorp MD, Asch FM, Moront MG, Dagenais F, Reardon MJ, et al. The robustness of the flow-gradient classification of severe aortic stenosis. JTCVS Open. 2023; 16: 177–188. https://doi.org/10.1016/j.xjon.2023.08.022

[19] González-García A, Pazos-López P, Calvo-Iglesias FE, Matajira-Chía TM, Bilbao-Quesada R, Blanco-González E, et al. Diagnostic Challenges in Aortic Stenosis. Journal of Cardiovascular Development and Disease. 2024; 11: 162. https://doi.org/10.3390/jcdd11060162

[20] Eleid MF, Sorajja P, Michelena HI, Malouf JF, Scott CG, Pellikka PA. Flow-gradient patterns in severe aortic stenosis with preserved ejection fraction: clinical characteristics and predictors of survival. Circulation. 2013; 128: 1781–1789. https://doi.org/10.1161/CIRCULATIONAHA.113.003695

[21] Aguilar-Molina O, Barbosa-Balaguera S, Campo-Rivera N, Cabrales-Salcedo Y, Camacho-Garcia R, Herrera-Escandón Á. Low-Flow, Low-Gradient Severe Aortic Stenosis in patients with preserved or reduced ejection fraction: a systematic literature review. Current Problems in Cardiology. 2024; 49: 102392. https://doi.org/10.1016/j.cpcardiol.2024.102392

[22] Minners J, Allgeier M, Gohlke-Baerwolf C, Kienzle RP, Neumann FJ, Jander N. Inconsistent grading of aortic valve stenosis by current guidelines: haemodynamic studies in patients with apparently normal left ventricular function. Heart (British Cardiac Society). 2010; 96: 1463–1468. https://doi.org/10.1136/hrt.2009.181982

[23] Jander N, Minners J, Holme I, Gerdts E, Boman K, Brudi P, et al. Outcome of patients with low-gradient "severe" aortic stenosis and preserved ejection fraction. Circulation. 2011; 123: 887–895. https://doi.org/10.1161/CIRCULATIONAHA.110.983510

[24] Taniguchi T, Morimoto T, Takeji Y, Shirai S, Ando K, Tabata H, et al. Low-flow and normal-flow low-gradient aortic stenosis with reduced left ventricular ejection fraction. Insights from the CURRENT AS Registry-2. Cardiovascular Intervention and Therapeutics. 2026; 41: 390–401. https://doi.org/10.1007/s12928-025-01209-3

[25] Monin JL, Quéré JP, Monchi M, Petit H, Baleynaud S, Chauvel C, et al. Low-gradient aortic stenosis: operative risk stratification and predictors for long-term outcome: a multicenter study using dobutamine stress hemodynamics. Circulation. 2003; 108: 319–324. https://doi.org/10.1161/01.CIR.0000079171.43055.46

[26] Levy F, Laurent M, Monin JL, Maillet JM, Pasquet A, Le Tourneau T, et al. Aortic valve replacement for low-flow/low-gradient aortic stenosis operative risk stratification and long-term outcome: a European multicenter study. Journal of the American College of Cardiology. 2008; 51: 1466–1472. https://doi.org/10.1016/j.jacc.2007.10.067

[27] Blais C, Burwash IG, Mundigler G, Dumesnil JG, Loho N, Rader F, et al. Projected valve area at normal flow rate improves the assessment of stenosis severity in patients with low-flow, low-gradient aortic stenosis: the multicenter TOPAS (Truly or Pseudo-Severe Aortic Stenosis) study. Circulation. 2006; 113: 711–721. https://doi.org/10.1161/CIRCULATIONAHA.105.557678

[28] deFilippi CR, Willett DL, Brickner ME, Appleton CP, Yancy CW, Eichhorn EJ, et al. Usefulness of dobutamine echocardiography in distinguishing severe from nonsevere valvular aortic stenosis in patients with depressed left ventricular function and low transvalvular gradients. The American Journal of Cardiology. 1995; 75: 191–194. https://doi.org/10.1016/s0002-9149(00)80078-8

[29] Ribeiro HB, Lerakis S, Gilard M, Cavalcante JL, Makkar R, Herrmann HC, et al. Transcatheter Aortic Valve Replacement in Patients With Low-Flow, Low-Gradient Aortic Stenosis: The TOPAS-TAVI Registry. Journal of the American College of Cardiology. 2018; 71: 1297–1308. https://doi.org/10.1016/j.jacc.2018.01.054

[30] Annabi MS, Touboul E, Dahou A, Burwash IG, Bergler-Klein J, Enriquez-Sarano M, et al. Dobutamine Stress Echocardiography for Management of Low-Flow, Low-Gradient Aortic Stenosis. Journal of the American College of Cardiology. 2018; 71: 475–485. https://doi.org/10.1016/j.jacc.2017.11.052

[31] Wagener M, Reuthebuch O, Heg D, Tüller D, Ferrari E, Grünenfelder J, et al. Clinical Outcomes in High-Gradient, Classical Low-Flow, Low-Gradient, and Paradoxical Low-Flow, Low-

Gradient Aortic Stenosis After Transcatheter Aortic Valve Implantation: A Report From the SwissTAVI Registry. Journal of the American Heart Association. 2023; 12: e029489. https://doi.org/10.1161/JAHA.123.029489

[32] Puls M, Beuthner BE, Topci R, Jacob CF, Steinhaus KE, Paul N, et al. Patients with paradoxical low-flow, low-gradient aortic stenosis gain the least benefit from TAVI among all hemodynamic subtypes. Clinical Research in Cardiology: Official Journal of the German Cardiac Society. 2025; 114: 1479–1490. https://doi.org/10.1007/s00392-024-02482-7

[33] Sato K, Sankaramangalam K, Kandregula K, Bullen JA, Kapadia SR, Krishnaswamy A, et al. Contemporary Outcomes in Low-Gradient Aortic Stenosis Patients Who Underwent Dobutamine Stress Echocardiography. Journal of the American Heart Association. 2019; 8: e011168. https://doi.org/10.1161/JAHA.118.011168

[34] Van Mieghem NM, Elmariah S, Spitzer E, Pibarot P, Nazif TM, Bax JJ, et al. Transcatheter Aortic Valve Replacement in Patients With Systolic Heart Failure and Moderate Aortic Stenosis: TAVR UNLOAD. Journal of the American College of Cardiology. 2025; 85: 878–890. https://doi.org/10.1016/j.jacc.2024.10.070

[35] Quere JP, Monin JL, Levy F, Petit H, Baleynaud S, Chauvel C, et al. Influence of preoperative left ventricular contractile reserve on postoperative ejection fraction in low-gradient aortic stenosis. Circulation. 2006; 113: 1738–1744. https://doi.org/10.1161/CIRCULATIONAHA.105.568824

[36] Chahal NS, Drakopoulou M, Gonzalez-Gonzalez AM, Manivarmane R, Khattar R, Senior R. Resting Aortic Valve Area at Normal Transaortic Flow Rate Reflects True Valve Area in Suspected Low-Gradient Severe Aortic Stenosis. JACC. Cardiovascular Imaging. 2015; 8: 1133–1139. https://doi.org/10.1016/j.jcmg.2015.04.021

[37] Hungerford SL, Song N, Loo B, Rye E, Sritharan H, Everett KD, et al. The Effect of Volume-Flow Discordance on Survival in Severe Aortic Stenosis. JACC. Asia. 2026; 6: 66–76. https://doi.org/10.1016/j.jacasi.2025.07.016

[38] Cueff C, Serfaty JM, Cimadevilla C, Laissy JP, Himbert D, Tubach F, et al. Measurement of aortic valve calcification using multislice computed tomography: correlation with haemodynamic severity of aortic stenosis and clinical implication for patients with low ejection fraction. Heart (British Cardiac Society). 2011; 97: 721–726. https://doi.org/10.1136/hrt.2010.198853

[39] Juhász D, Vecsey-Nagy M, Jermendy ÁL, Szilveszter B, Simon J, Vattay B, et al. Prognostic and therapeutic implications of a low aortic valve calcium score in patients with low-gradient aortic stenosis. European Heart Journal. Cardiovascular Imaging. 2025; 26: 287–298. https://doi.org/10.1093/ehjci/jeae276

[40] Ye Z, Clavel MA, Foley TA, Pibarot P, Enriquez-Sarano M, Michelena HI. Computed tomography calcium scoring in aortic stenosis: bicuspid versus tricuspid morphology. Heart (British Cardiac Society). 2024; 110: 594–602. https://doi.org/10.1136/heartjnl-2023-323281

[41] Mousavi RA, Argulian E, Basera P, Enwere C, Soroa M, Alizadeh L, et al. Impact of sex-specific aortic valve calcification thresholds on reclassification of normal-flow, low-gradient aortic stenosis. Journal of Cardiovascular Computed Tomography. 2026; 20: 451–452. https://doi.org/10.1016/j.jcct.2026.01.007

[42] Hammerer M, Knapitsch C, Schörghofer N, Lichtenauer M, Mirna M, Prinz E, et al. Very severe aortic valve stenosis: Diagnostic value of computed tomography aortic valve calcium scoring. Journal of Cardiovascular Computed Tomography. 2025; 19: 191–200. https://doi.org/10.1016/j.jcct.2024.11.004

[43] Mogensen NSB, Sanchez Dahl J, Ali M, Annabi MS, Haujir A, Powers A, et al. Usefulness of Aortic Valve Calcification in Patients With Low-Flow Aortic Stenosis. Circulation. Cardiovascular Imaging. 2025; 18: e017122. https://doi.org/10.1161/CIRCIMAGING.124.017122

[44] Wang TKM, Flamm SD, Schoenhagen P, Griffin BP, Rodriguez LL, Grimm RA, et al. Diagnostic and Prognostic Performance of Aortic Valve Calcium Score with Cardiac CT for Aortic Stenosis: A Meta-Analysis. Radiology. Cardiothoracic Imaging. 2021; 3: e210075. https://doi.org/10.1148/ryct.2021210075

[45] Simard L, Côté N, Dagenais F, Mathieu P, Couture C, Trahan S, et al. Sex-Related Discordance Between Aortic Valve Calcification and Hemodynamic Severity of Aortic Stenosis: Is Valvular Fibrosis the Explanation? Circulation Research. 2017; 120: 681–691. https://doi.org/10.1161/CIRCRESAHA.116.309306

[46] Gutierrez-Ortiz E, Olmos C, Carrión-Sanchez I, Jiménez-Quevedo P, Nombela-Franco L, Párraga R, et al. Redefining cardiac damage staging in aortic stenosis: the value of GLS and RVAc. European Heart Journal. Cardiovascular Imaging. 2023; 24: 1608–1617. https://doi.org/10.1093/ehjci/jead140

[47] Vollema EM, Amanullah MR, Prihadi EA, Ng AC, Van Der Bijl P, Sin YK, et al. Incremental value of left ventricular global longitudinal strain in a newly proposed staging classification based on cardiac damage in patients with severe aortic stenosis. European Heart Journal - Cardiovascular Imaging. 2020; 21: 1248–1258. https://doi.org/10.1093/ehjci/jeaa220

[48] Zilberszac R, Gleiss A, Schweitzer R, Bruno P, Andreas M, Stelzmüller M, et al. Prognostic Value of Right Ventricular Dysfunction and Tricuspid Regurgitation in Patients with Severe Low-Flow Low-Gradient Aortic Stenosis. Scientific Reports. 2019; 9: 14580. https://doi.org/10.1038/s41598-019-51166-0

[49] Chin CWL, Everett RJ, Kwiecinski J, Vesey AT, Yeung E, Esson G, et al. Myocardial Fibrosis and Cardiac Decompensation in Aortic Stenosis. JACC. Cardiovascular Imaging. 2017; 10: 1320–1333. https://doi.org/10.1016/j.jcmg.2016.10.007

[50] Thornton GD, Musa TA, Rigolli M, Loudon M, Chin C, Pica S, et al. Association of Myocardial Fibrosis and Stroke Volume by Cardiovascular Magnetic Resonance in Patients With Severe Aortic Stenosis With Outcome After Valve Replacement: The British Society of Cardiovascular Magnetic Resonance AS700 Study. JAMA Cardiology. 2022; 7: 513–520. https://doi.org/10.1001/jamacardio.2022.0340

[51] Treibel TA, Kozor R, Schofield R, Benedetti G, Fontana M, Bhuva AN, et al. Reverse Myocardial Remodeling Following Valve Replacement in Patients With Aortic Stenosis. Journal of the American College of Cardiology. 2018; 71: 860–871. https://doi.org/10.1016/j.jacc.2017.12.035

[52] Kwak S, Singh A, Everett RJ, Treibel TA, Lim J, Won S, et al. Sex-Specific Association of Myocardial Fibrosis With Mortality in Patients With Aortic Stenosis. JAMA Cardiology. 2025; 10: 446–455. https://doi.org/10.1001/jamacardio.2024.5593

[53] Loganath K, Craig NJ, Everett RJ, Bing R, Tsampasian V, Molek P, et al. Early Intervention in Patients With Asymptomatic Severe Aortic Stenosis and Myocardial Fibrosis: The EVOLVED Randomized Clinical Trial. JAMA. 2025; 333: 213–221. https://doi.org/10.1001/jama.2024.22730

[54] Kwak S, Lee SP. Prognostic role of myocardial fibrosis markers in aortic stenosis: Implications for clinical decision-making. Journal of the Heart Valve Society. 2024; 1: 30494826241296412. https://doi.org/10.1177/30494826241296412

[55] Kusunose K, Goodman A, Parikh R, Barr T, Agarwal S, Popovic ZB, et al. Incremental prognostic value of left ventricular global longitudinal strain in patients with aortic stenosis and preserved ejection fraction. Circulation. Cardiovascular Imaging. 2014; 7: 938–945. https://doi.org/10.1161/CIRCIMAGING.114.002041

[56] Stens NA, van Iersel O, Rooijakkers MJP, van Wely MH, Nijveldt R, Bakker EA, et al. Prognostic Value of Preprocedural LV Global Longitudinal Strain for Post-TAVR-Related Morbidity

and Mortality: A Meta-Analysis. JACC. Cardiovascular Imaging. 2023; 16: 332–341. https://doi.org/10.1016/j.jcmg.2023.01.005

[57] Xiao Y, Bi W, Qiao W, Wang X, Li Y, Ren W. Prognostic value of ventricular longitudinal strain in patients undergoing transcatheter aortic valve replacement: A systematic review and meta-analysis. Frontiers in Cardiovascular Medicine. 2022; 9: 965440. https://doi.org/10.3389/fcvm.2022.965440

[58] Tan ESJ, Jin X, Oon YY, Chan SP, Gong L, Lunaria JB, et al. Prognostic Value of Left Atrial Strain in Aortic Stenosis: A Competing Risk Analysis. Journal of the American Society of Echocardiography: Official Publication of the American Society of Echocardiography. 2023; 36: 29–37.e5. https://doi.org/10.1016/j.echo.2022.10.011

[59] Otto CM, Prendergast B. Aortic-valve stenosis–from patients at risk to severe valve obstruction. The New England Journal of Medicine. 2014; 371: 744–756. https://doi.org/10.1056/NEJMra1313875

[60] Ossola P, Ghidini S, Gualini E, Daus F, Politi F, Ciampi C, et al. Aortic Valve Stenosis: Progress from Diagnosis to Treatment. Journal of Clinical Medicine. 2026; 15: 659. https://doi.org/10.3390/jcm15020659

[61] Krishna H, Desai K, Slostad B, Bhayani S, Arnold JH, Ouwerkerk W, et al. Fully Automated Artificial Intelligence Assessment of Aortic Stenosis by Echocardiography. Journal of the American Society of Echocardiography: Official Publication of the American Society of Echocardiography. 2023; 36: 769–777. https://doi.org/10.1016/j.echo.2023.03.008

[62] Holste G, Oikonomou EK, Mortazavi BJ, Coppi A, Faridi KF, Miller EJ, et al. Severe aortic stenosis detection by deep learning applied to echocardiography. European Heart Journal. 2023; 44: 4592–4604. https://doi.org/10.1093/eurheartj/ehad456

[63] Yang F, Zhang Y, Gao Y, Wang B, Lin X, Chen X, et al. Deep learning-assisted aortic stenosis detection and grading based on multiview versus single-view echocardiography. Quantitative Imaging in Medicine and Surgery. 2025; 15: 11192–11204. https://doi.org/10.21037/qims-2025-415

[64] Park J, Kim J, Jeon J, Yoon YE. Utilizing deep learning for accurate assessment of aortic valve stenosis: case series for clinical applications. Journal of Cardiovascular Imaging. 2025; 33: 3. https://doi.org/10.1186/s44348-025-00047-4

[65] Zha SZ, Rogstadkjernet M, Klæboe LG, Skulstad H, Singstad BJ, Gilbert A, et al. Deep learning for automated left ventricular outflow tract diameter measurements in 2D echocardiography. Cardiovascular Ultrasound. 2023; 21: 19. https://doi.org/10.1186/s12947-023-00317-5