

Prognostic Implications of Discordant Low-Gradient Severe Aortic Stenosis: A Comprehensive Review of Pathophysiological Mechanisms, Diagnostic Challenges, and Clinical Outcomes

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ABSTRACT

Discordant low-gradient severe aortic stenosis (DLG-SAS) represents a clinically complex and prognostically heterogeneous entity characterized by a discrepancy between aortic valve area (AVA) criteria for severe stenosis (AVA <1.0 cm²) and a non-classical transvalvular gradient (mean gradient <40 mmHg). This condition poses significant diagnostic and therapeutic dilemmas due to its multifactorial pathophysiology, which includes impaired left ventricular (LV) systolic function (classical low-flow, low-gradient SAS), preserved LV ejection fraction with paradoxical low-flow states, and measurement artifacts. Emerging evidence suggests that DLG-SAS carries distinct prognostic implications, with varying mortality risks depending on underlying hemodynamic profiles, comorbidities, and therapeutic interventions. This review synthesizes current literature on the pathophysiological substrates, advanced imaging modalities (e.g., dobutamine stress echocardiography, computed tomography-derived aortic valve calcification scoring), and risk stratification paradigms. Furthermore, we evaluate the impact of treatment strategies, including transcatheter aortic valve replacement (TAVR) versus surgical aortic valve replacement (SAVR), on long-term outcomes. By elucidating the interplay between hemodynamic parameters, myocardial remodeling, and clinical trajectories, this article aims to refine prognostic assessment and guide evidence-based management of DLG-SAS.

KEYWORDS: Aortic stenosis, low-gradient, discordant severity, prognosis, left ventricular dysfunction, transvalvular flow, valvular calcification, stress echocardiography, TAVR, SAVR

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INTRODUCTION

Aortic stenosis (AS) remains the most prevalent valvular heart disease in developed nations, with severe AS defined by echocardiographic criteria of aortic valve area (AVA) <1.0 cm² and/or mean transvalvular gradient ≥40 mmHg.

However, a subset of patients exhibits discordant low-gradient severe AS (DLG-SAS), wherein AVA meets severe thresholds despite a mean gradient <40 mmHg. This hemodynamic discrepancy, observed in up to 30% of severe

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AS cases, challenges traditional diagnostic algorithms and carries profound prognostic implications.^{1,2}

DLG-SAS encompasses three distinct phenotypes: (1) classical low-flow, low-gradient SAS (reduced LV ejection fraction [LVEF <50%] and stroke volume index [SVi <35 mL/m²]), (2) paradoxical low-flow, low-gradient SAS (preserved LVEF [≥50%] but SVi <35 mL/m² due to concentric remodeling and diastolic dysfunction), and (3) pseudo-severe AS (moderate AS with exaggerated AVA reduction secondary to low flow). The heterogeneity of these subgroups complicates risk stratification, as outcomes vary significantly based on underlying LV adaptation, flow reserve, and comorbidities (e.g., atrial fibrillation, renal dysfunction).^{2,3}

Recent advances in multimodality imaging, including calcium scoring via cardiac computed tomography (CT) (Agatston score >1,200 AU in men, >800 AU in women) and low-dose dobutamine stress echocardiography (to assess flow reserve and contractile augmentation), have refined diagnostic accuracy. Moreover, the advent of TAVR has reshaped therapeutic landscapes, yet its role in DLG-SAS—particularly in paradoxical subtypes—remains debated due to variable survival benefits reported in trials (e.g., PARTNER 2, TOPAS-TAVI).³

This review examines the prognostic determinants of DLG-SAS, integrating contemporary evidence on pathophysiology, diagnostic precision, and therapeutic efficacy. By contextualizing these insights within clinical practice, we aim to optimize patient selection for intervention and improve prognostic forecasting in this high-risk cohort.⁴

Pathophysiological Mechanisms of Discordant Low-Gradient Severe Aortic Stenosis

Discordant low-gradient severe aortic stenosis (DLG-SAS) represents a hemodynamic paradox wherein the severity of valvular obstruction, as defined by a reduced aortic valve area (AVA <1.0 cm²), coexists with a lower-than-expected transvalvular pressure gradient (mean gradient <40 mmHg). This discrepancy arises from a complex interplay of valvular, ventricular, and systemic factors that modulate flow dynamics, myocardial adaptation, and afterload mismatch. The underlying pathophysiology can be broadly categorized into three principal mechanisms: impaired forward flow, valvulo-arterial impedance mismatch, and methodological confounders in assessment.⁴

At the core of DLG-SAS lies the principle of flow-dependent gradient generation, wherein the transvalvular pressure gradient is intrinsically linked to stroke volume rather than valve area alone. In classical low-flow, low-gradient SAS, the reduced gradient stems from depressed left ventricular (LV) systolic function (LVEF <50%), often secondary to chronic pressure overload, ischemic cardiomyopathy, or afterload-induced myocyte apoptosis. The diminished contractility results in a decreased stroke volume (SVi <35 mL/m²), which fails to generate the high gradients typically seen in high-flow

severe AS. This scenario reflects an advanced stage of disease characterized by exhausted compensatory mechanisms, including myocyte hypertrophy and interstitial fibrosis, leading to irreversible myocardial dysfunction and poor prognosis.^{4,5}

In contrast, paradoxical low-flow, low-gradient SAS occurs in patients with preserved LVEF (≥50%) but similarly reduced stroke volume. Here, the primary derangement is excessive concentric remodeling, wherein severe LV hypertrophy (LVH) reduces chamber compliance and impairs diastolic filling. The resulting small, stiff left ventricle operates at reduced end-diastolic volumes, diminishing preload and thus stroke volume despite preserved contractility. Additionally, systemic vascular dysfunction—including arterial stiffening and endothelial dysfunction—elevates global afterload, further limiting forward flow. This phenotype is frequently associated with comorbidities such as hypertension, diabetes, and chronic kidney disease, which exacerbate ventricular-vascular uncoupling and contribute to adverse outcomes independent of valve severity.⁵

A third, often overlooked contributor to DLG-SAS is pseudo-severe stenosis, wherein moderate valvular calcification appears severe due to low-flow conditions that prevent full valve opening. This phenomenon, detectable via dobutamine stress echocardiography (DSE), underscores the importance of distinguishing true anatomic stenosis from functional underestimation of valve area. Furthermore, measurement variability in echocardiography—such as errors in LV outflow tract (LVOT) diameter assessment or Doppler alignment—may artifactually reduce calculated gradients or overestimate stenosis severity.⁶

The valvulo-arterial impedance (Zva), a composite measure of global afterload integrating valvular and arterial components, further elucidates the hemodynamic burden in DLG-SAS. Elevated Zva (>4.5 mmHg/mL/m²) signifies disproportionate afterload, exacerbating LV mechanical inefficiency and perpetuating a vicious cycle of worsening flow and myocardial oxygen supply-demand mismatch. This is particularly relevant in paradoxical DLG-SAS, where ventricular-arterial coupling is disrupted, accelerating progression to heart failure with preserved ejection fraction (HFpEF)-like pathophysiology.⁶

Ultimately, the heterogeneity of DLG-SAS reflects a spectrum of maladaptive responses to chronic pressure overload, with prognosis heavily influenced by the degree of myocardial fibrosis (assessed via cardiac MRI late gadolinium enhancement), pulmonary hypertension, and right ventricular dysfunction. These factors collectively determine the "point of no return" in disease progression, beyond which even valve replacement may not fully reverse LV decompensation. Understanding these intricate mechanisms is critical for risk stratification and therapeutic decision-making in this challenging patient population.⁶

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Diagnostic Challenges in Discordant Low-Gradient Severe Aortic Stenosis

The accurate diagnosis of discordant low-gradient severe aortic stenosis (DLG-SAS) represents a formidable clinical conundrum, necessitating a nuanced integration of hemodynamic principles, advanced imaging modalities, and a high index of suspicion to disentangle true severe stenosis from pseudosevere phenotypes or measurement artifacts. This diagnostic ambiguity stems from the inherent limitations of relying solely on conventional echocardiographic parameters—aortic valve area (AVA) and mean transvalvular gradient—which, when discordant, fail to provide a definitive assessment of disease severity. The resultant clinical uncertainty carries profound implications, as misclassification may either delay life-saving interventions in true severe AS or subject patients with moderate disease to unnecessary valve replacement.^{6,7}

Central to the diagnostic dilemma is the flow-dependence of gradient estimation, wherein the transvalvular pressure gradient is intrinsically linked to stroke volume rather than valve obstruction alone. In classical low-flow, low-gradient SAS with reduced ejection fraction (LVEF <50%), the diminished stroke volume (SVi <35 mL/m²) results in an artificially attenuated gradient, obscuring the true severity of valve stenosis. This scenario demands meticulous differentiation from primary cardiomyopathy with secondary mild-to-moderate AS, where the primary pathology lies in the myocardium rather than the valve. Dobutamine stress echocardiography (DSE) has emerged as a pivotal tool in this context, aiming to augment stroke volume and unmask the true gradient and AVA reserve. However, DSE interpretation is fraught with challenges, including the risk of provoking arrhythmias in fragile patients, the confounding effects of inotropic stimulation on afterload, and the ambiguous prognostic significance of a lack of contractile reserve—a marker of advanced myocardial dysfunction and post-intervention mortality.^{7,8}

The diagnostic intricacies are further compounded in paradoxical low-flow, low-gradient SAS (preserved LVEF ≥50%), where the reduced stroke volume arises not from systolic impairment but from excessive concentric remodeling, diastolic dysfunction, and reduced ventricular compliance. Here, the thickened, noncompliant left ventricle operates at diminished end-diastolic volumes, generating insufficient flow to produce high gradients despite severe valve obstruction. This phenotype overlaps hemodynamically with heart failure with preserved ejection fraction (HFpEF), creating a diagnostic gray zone wherein symptoms may be erroneously attributed to diastolic dysfunction rather than valvular pathology. Moreover, the frequent coexistence of hypertension, atrial fibrillation, and pulmonary hypertension in these patients further obscures the contribution of AS to symptom onset, necessitating a multimodal diagnostic approach.^{8,9}

Pseudo-severe AS, a condition wherein moderate stenosis appears severe due to low-flow conditions preventing full valve opening, represents another critical diagnostic pitfall. Distinguishing pseudo-severe from true severe AS requires dynamic assessment, typically via DSE, to evaluate whether AVA increases with augmented flow. However, this approach is imperfect, as some patients with true severe AS may exhibit limited AVA reserve due to fixed valvular calcification, while others with pseudo-severe AS may show only marginal improvements, leading to indeterminate results.¹⁰

Beyond echocardiography, computed tomography (CT) aortic valve calcium scoring has gained traction as an adjunctive tool, particularly in cases where echocardiographic data are inconclusive. Severe aortic valve calcification (Agatston score >1,200 AU in men, >800 AU in women) strongly suggests true severe AS, even in the presence of low gradients. However, this technique is limited by its inability to assess hemodynamic significance, its variability across imaging protocols, and its reduced specificity in younger patients or those with bicuspid valves, where calcification patterns may differ.¹¹

The integration of biomarkers, such as B-type natriuretic peptide (BNP) or high-sensitivity troponins, has been proposed to aid in risk stratification and diagnostic clarity. Elevated levels may reflect the hemodynamic burden of AS or concomitant myocardial injury, but their nonspecificity in the context of multimorbidity (e.g., renal dysfunction, coronary disease) limits their standalone diagnostic utility.¹¹ Ultimately, the diagnostic odyssey in DLG-SAS underscores the imperative for a comprehensive, patient-centered approach, harmonizing data from echocardiography, CT, clinical context, and—in select cases—invasive hemodynamic assessment. The absence of a single gold-standard test mandates clinical vigilance and often, multidisciplinary deliberation to navigate the labyrinth of discordant parameters and optimize therapeutic decision-making.¹¹

Clinical Outcomes in Discordant Low-Gradient Severe Aortic Stenosis: A Prognostic Conundrum

The long-term clinical outcomes of patients with discordant low-gradient severe aortic stenosis (DLG-SAS) present a complex prognostic landscape characterized by heterogeneous trajectories that challenge conventional risk stratification paradigms. This hemodynamic entity, which defies the traditional correlation between valve area and transvalvular gradient, carries distinct prognostic implications that vary according to underlying ventricular function, flow reserve, and therapeutic interventions. The clinical course of these patients is marked by higher mortality rates compared to classical high-gradient severe AS, with outcomes heavily influenced by the delicate interplay between valvular obstruction, myocardial remodeling, and systemic comorbidities.¹²

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In classical low-flow, low-gradient SAS with reduced ejection fraction (LVEF <50%), the prognosis is particularly ominous, with medical management alone associated with dismal survival rates comparable to metastatic malignancies. These patients exhibit a mortality rate approaching 50% at 2 years when treated conservatively, reflecting the advanced stage of both valvular and myocardial disease. The impaired ventricular function in this subgroup represents the culmination of chronic pressure overload leading to irreversible fibrotic changes, microvascular ischemia, and depleted contractile reserve. Even after aortic valve replacement (AVR), outcomes remain suboptimal compared to high-gradient AS cohorts, with perioperative mortality rates nearly doubling those observed in patients with preserved flow. The presence of restrictive physiology, pulmonary hypertension, or right ventricular dysfunction further exacerbates postoperative risk, often predicting incomplete ventricular recovery and persistent heart failure symptoms despite procedural success.¹²

The paradoxical low-flow, low-gradient SAS phenotype (preserved LVEF $\geq$ 50%) demonstrates somewhat better but still concerning outcomes, with intermediate survival rates between classical low-gradient and high-gradient AS. These patients frequently experience delayed diagnosis due to the masquerading nature of their condition, where symptoms are often erroneously attributed to aging or comorbid conditions rather than the underlying valvular pathology. When managed medically, their annual mortality ranges from 5-10%, significantly higher than age-matched controls without significant AS. Following AVR, this subgroup shows more favorable survival than their reduced-EF counterparts, yet still lags behind high-gradient AS patients, likely due to persistent diastolic dysfunction and the irreversibility of long-standing concentric remodeling. The presence of marked myocardial fibrosis, as detected by cardiac magnetic resonance imaging, appears to be a particularly ominous prognostic marker in this population, predicting limited functional improvement post-intervention.¹²

The advent of transcatheter aortic valve replacement (TAVR) has substantially altered the therapeutic landscape for DLG-SAS patients, particularly those deemed high-risk for surgical AVR. Registry data suggest that TAVR outcomes in low-flow, low-gradient SAS approximate those observed in high-gradient AS when patients are carefully selected, challenging historical notions about the futility of intervention in this population. However, the presence of poor flow reserve continues to portend worse outcomes regardless of treatment modality, with 30-day mortality rates nearly threefold higher in patients without contractile reserve on dobutamine stress echocardiography. Late recovery of ventricular function post-TAVR occurs in approximately 40-50% of patients with reduced EF, but this recovery is often incomplete and dependent on the degree of baseline fibrosis.¹²

Quality-of-life metrics following intervention reveal persistent challenges in DLG-SAS populations. While most patients experience symptomatic improvement, the magnitude of benefit is frequently attenuated compared to high-gradient AS cohorts, with slower recovery trajectories and higher rates of residual dyspnea. This observation likely reflects the multifactorial nature of symptoms in these patients, where concomitant diastolic dysfunction, pulmonary vascular disease, and extracardiac comorbidities contribute substantially to functional limitation. The complex interplay between these factors creates a clinical scenario where successful valve replacement may not fully restore normal exercise capacity or quality of life.¹³

Long-term survival analyses demonstrate that approximately 30-40% of DLG-SAS patients die from non-cardiac causes, highlighting the critical importance of comprehensive geriatric assessment in this typically elderly population with multiple comorbidities. Cancer, pulmonary disease, and neurodegenerative disorders compete with cardiovascular causes of mortality, particularly in patients surviving beyond 2-3 years post-intervention. This competing risk scenario necessitates a holistic approach to prognosis that extends beyond traditional cardiovascular risk factors.¹⁴

The prognostic implications of DLG-SAS extend to hard clinical endpoints beyond mortality. These patients experience higher rates of acute decompensated heart failure admissions, more frequent need for pacemaker implantation (particularly post-TAVR), and greater incidence of sudden cardiac death compared to high-gradient AS cohorts. The arrhythmic risk appears particularly pronounced in patients with extensive ventricular fibrosis, creating a substrate for malignant ventricular arrhythmias even after successful valve replacement.¹⁴

Emerging data suggest that the timing of intervention in DLG-SAS may significantly influence outcomes, with evidence accumulating in favor of earlier intervention before the development of advanced ventricular dysfunction or pulmonary vascular disease. However, the optimal risk-benefit ratio for intervention in asymptomatic DLG-SAS patients remains undefined, creating ongoing clinical uncertainty in management decisions. The development of sophisticated risk prediction models incorporating imaging biomarkers, functional capacity assessments, and molecular markers of myocardial fibrosis may help refine prognostic stratification in this challenging patient population.¹⁵

CONCLUSIONS

Discordant low-gradient severe aortic stenosis (DLG-SAS) represents a complex clinical entity that continues to challenge contemporary cardiology practice, embodying the intricate interplay between valvular pathology, ventricular adaptation, and systemic hemodynamics. The prognostic implications of this condition extend far beyond simple echocardiographic parameters, reflecting instead a spectrum

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of disease states where the discordance between valve area and transvalvular gradient serves as a marker of advanced pathophysiological derangements. The heterogeneous nature of DLG-SAS outcomes underscores the critical importance of comprehensive phenotyping that integrates imaging biomarkers, functional assessment, and molecular markers of disease progression.

The current body of evidence consistently demonstrates that DLG-SAS carries significantly worse prognosis compared to classical high-gradient severe AS, with outcomes varying substantially across different hemodynamic subtypes. Patients with reduced ejection fraction face particularly dire prognoses when managed medically, with mortality rates rivaling aggressive malignancies, while those with preserved ejection fraction exhibit intermediate outcomes that reflect the dual burden of valvular obstruction and diastolic dysfunction. The prognostic stratification in these patients must account not only for traditional echocardiographic parameters but also for markers of myocardial fibrosis, pulmonary vascular remodeling, and right ventricular-pulmonary arterial coupling, all of which contribute substantially to the clinical trajectory.

Therapeutic interventions, particularly transcatheter aortic valve replacement, have modified but not eliminated the poor prognosis associated with DLG-SAS. While contemporary outcomes have improved significantly compared to historical controls, persistent gaps remain in post-procedural recovery, long-term survival, and quality-of-life metrics when compared to high-gradient AS populations. The incomplete ventricular functional recovery observed in many patients, particularly those with advanced myocardial fibrosis or significant comorbidity burdens, highlights the importance of timely intervention before irreversible end-organ damage occurs. However, the optimal timing of such intervention remains a subject of ongoing investigation, with current evidence suggesting benefit from earlier referral in carefully selected patients.

The prognostic evaluation of DLG-SAS patients demands a paradigm shift from purely valve-centered assessment to a more holistic approach that considers the complex interplay between the aortic valve, left ventricular performance, pulmonary circulation, and systemic comorbidities. Advanced imaging modalities including strain echocardiography, cardiac magnetic resonance, and computed tomography calcium scoring have emerged as indispensable tools in this comprehensive evaluation, providing insights that extend beyond conventional parameters. Similarly, biomarkers of myocardial stress and injury may offer incremental prognostic value, particularly in identifying patients at highest risk for adverse outcomes.

Future directions in prognostic assessment should focus on developing integrated risk models that combine clinical, imaging, and molecular markers to better predict individual patient trajectories. Particular attention should be paid to

identifying reversible components of myocardial dysfunction that may respond favorably to intervention, as well as irreversible changes that portend limited therapeutic benefit. The growing understanding of myocardial fibrosis pathways, microvascular dysfunction, and ventricular-arterial coupling abnormalities may provide novel therapeutic targets to improve outcomes beyond valve replacement alone.

In clinical practice, the management of DLG-SAS requires meticulous patient selection, individualized risk assessment, and multidisciplinary decision-making that considers not only procedural risks but also long-term functional outcomes and quality-of-life expectations. The prognostic complexity of this condition serves as a reminder that severe aortic stenosis exists not as an isolated valvular lesion but as a systemic disease with far-reaching consequences for cardiovascular performance and overall health. As therapeutic options continue to evolve, so too must our understanding of the factors that determine clinical outcomes in this challenging patient population.

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