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NATURAL HISTORY OF DEGENERATIVE AORTIC STENOSIS: A SYSTEMATIC REVIEW OF DISEASE COURSE AND PREDICTORS OF PROGRESSION

HISTÓRIA NATURAL DA ESTENOSE AÓRTICA DEGENERATIVA: UMA REVISÃO SISTEMÁTICA DO CURSO DA DOENÇA E DOS PREDICTORES DE PROGRESSÃO

HISTORIA NATURAL DE LA ESTENOSIS AÓRTICA DEGENERATIVA: UNA REVISIÓN SISTEMÁTICA DEL CURSO DE LA ENFERMEDAD Y LOS PREDICTORES DE PROGRESIÓN

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ABSTRACT

Introduction: Degenerative aortic stenosis (AS) is the most common valvular disease in aging populations, characterized by progressive calcification and narrowing of the aortic valve leading to left ventricular overload and heart failure. Understanding the natural history and predictors of disease progression is critical for optimizing timing of intervention and patient follow-up.

Objective: The main objective of this systematic review was to evaluate the natural course of degenerative AS and identify clinical, echocardiographic, and biochemical predictors of progression. Secondary objectives included assessing annual changes in hemodynamic parameters, incidence of adverse cardiac outcomes, and impact of comorbidities on disease acceleration.

Methods: A systematic search was performed in PubMed, Scopus, Web of Science, Cochrane Library, LILACS, ClinicalTrials.gov, and ICTRP. Observational and interventional studies published in the last 5 years were included, with extension to 10 years if fewer than 10 eligible studies were available. Two independent reviewers screened titles and abstracts, extracted data, and assessed bias using RoB 2, ROBINS-I, or QUADAS-2 as appropriate. Certainty of evidence was graded using GRADE.

Results and Discussion: 27 studies met inclusion criteria. Most cohorts demonstrated a nonlinear yet measurable progression of valve calcification and gradient increase over time. Elevated baseline aortic jet velocity, lipoprotein(a), and valvular calcium scores were consistent predictors of faster progression. The pooled annual increase in mean gradient ranged between 4–8 mmHg, and event-free survival declined significantly once peak velocity exceeded 4.0 m/s.

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Conclusion: Degenerative AS is a dynamic and heterogeneous condition influenced by metabolic, inflammatory, and structural mechanisms. Early identification of high-risk phenotypes may guide timely valve replacement and improve outcomes.

Keywords: Aortic Stenosis. Disease Progression. Echocardiography. Valve Calcification.

RESUMO

Introdução: A estenose aórtica degenerativa (EA) é a doença valvar mais comum em populações idosas, caracterizada por calcificação progressiva e estreitamento da valva aórtica, levando à sobrecarga do ventrículo esquerdo e insuficiência cardíaca. Compreender a história natural e os preditores de progressão da doença é fundamental para otimizar o momento da intervenção e o acompanhamento do paciente.

Objetivo: O objetivo principal desta revisão sistemática foi avaliar o curso natural da EA degenerativa e identificar preditores clínicos, ecocardiográficos e bioquímicos de progressão. Os objetivos secundários incluíram a avaliação das alterações anuais nos parâmetros hemodinâmicos, a incidência de eventos cardíacos adversos e o impacto das comorbidades na aceleração da doença.

Métodos: Foi realizada uma busca sistemática nas bases de dados PubMed, Scopus, Web of Science, Cochrane Library, LILACS, ClinicalTrials.gov e ICTRP. Foram incluídos estudos observacionais e intervencionais publicados nos últimos 5 anos, com extensão para 10 anos caso houvesse menos de 10 estudos elegíveis. Dois revisores independentes analisaram os títulos e resumos, extraíram os dados e avaliaram o viés usando o RoB 2, ROBINS-I ou QUADAS-2, conforme apropriado. A certeza da evidência foi classificada usando o GRADE.

Resultados e Discussão: Vinte e sete estudos atenderam aos critérios de inclusão. A maioria das coortes demonstrou uma progressão não linear, porém mensurável, da calcificação valvar e do aumento do gradiente ao longo do tempo. Velocidade elevada do jato aórtico basal, lipoproteína(a) e escores de cálcio valvar foram preditores consistentes de progressão mais rápida. O aumento anual agrupado no gradiente médio variou entre 4 e 8 mmHg, e a sobrevida livre de eventos diminuiu significativamente quando a velocidade de pico ultrapassou 4,0 m/s.

Conclusão: A estenose aórtica degenerativa é uma condição dinâmica e heterogênea influenciada por mecanismos metabólicos, inflamatórios e estruturais. A identificação precoce de fenótipos de alto risco pode orientar a substituição valvar oportuna e melhorar os resultados.

Palavras-chave: Estenose Aórtica. Progressão da Doença. Ecocardiografia. Calcificação Valvar.

RESUMEN

Introducción: La estenosis aórtica degenerativa (EA) es la valvulopatía más frecuente en la población de edad avanzada. Se caracteriza por la calcificación progresiva y el estrechamiento de la válvula aórtica, lo que conlleva sobrecarga ventricular izquierda e insuficiencia cardíaca. Comprender la historia natural y los factores predictivos de la progresión de la enfermedad es fundamental para optimizar el momento de la intervención y el seguimiento del paciente.

Objetivo: El objetivo principal de esta revisión sistemática fue evaluar la evolución natural de la EA degenerativa e identificar factores predictivos clínicos, ecocardiográficos y bioquímicos de su progresión. Los objetivos secundarios incluyeron la evaluación de los

cambios anuales en los parámetros hemodinámicos, la incidencia de eventos cardíacos adversos y el impacto de las comorbilidades en la aceleración de la enfermedad.

Métodos: Se realizó una búsqueda sistemática en PubMed, Scopus, Web of Science, la Biblioteca Cochrane, LILACS, ClinicalTrials.gov e ICTRP. Se incluyeron estudios observacionales e intervencionales publicados en los últimos 5 años, con una extensión a 10 años si se disponía de menos de 10 estudios elegibles. Dos revisores independientes examinaron los títulos y resúmenes, extrajeron los datos y evaluaron el sesgo utilizando RoB 2, ROBINS-I o QUADAS-2, según correspondiera. La certeza de la evidencia se clasificó mediante GRADE.

Resultados y Discusión: 27 estudios cumplieron los criterios de inclusión. La mayoría de las cohortes mostraron una progresión no lineal, pero medible, de la calcificación valvular y del aumento del gradiente a lo largo del tiempo. La velocidad del chorro aórtico basal elevada, la lipoproteína(a) y las puntuaciones de calcio valvular fueron predictores consistentes de una progresión más rápida. El aumento anual agrupado del gradiente medio osciló entre 4 y 8 mmHg, y la supervivencia libre de eventos disminuyó significativamente una vez que la velocidad máxima superó los 4,0 m/s.

Conclusión: La estenosis aórtica degenerativa es una afección dinámica y heterogénea influenciada por mecanismos metabólicos, inflamatorios y estructurales. La identificación temprana de fenotipos de alto riesgo puede orientar el reemplazo valvular oportuno y mejorar los resultados.

Palabras clave: Estenosis Aórtica. Progresión de la Enfermedad. Ecocardiografía. Calcificación Valvular.

1 INTRODUCTION

Degenerative aortic stenosis (AS) represents the leading cause of valvular heart disease in developed countries, primarily affecting elderly populations with a prevalence that rises exponentially after the sixth decade of life[1]. The condition is characterized by progressive fibrocalcific remodeling of the aortic valve leaflets, leading to obstruction of left ventricular outflow and chronic pressure overload[1]. This pathological process results in concentric hypertrophy, diastolic dysfunction, and eventual transition to symptomatic heart failure if left untreated[1].

The global burden of degenerative AS has increased due to population aging and improved survival from other cardiovascular diseases[2]. Despite advances in diagnostic imaging and therapeutic options, many patients remain asymptomatic for long periods, complicating decisions regarding optimal timing of intervention[2]. Current guidelines emphasize symptom onset and left ventricular systolic dysfunction as major determinants for surgical or transcatheter aortic valve replacement (TAVR), yet substantial heterogeneity in progression rates challenges this paradigm[2].

The pathophysiology of AS shares key molecular mechanisms with atherosclerosis, including endothelial injury, lipid infiltration, and chronic inflammation[3]. Oxidized low-density lipoprotein (LDL) and lipoprotein(a) play crucial roles in initiating calcific deposition within the valve cusps[3]. Subsequent osteoblastic differentiation of valvular interstitial cells leads to active calcification, fibrosis, and reduced cusp mobility over time[3].

Echocardiography remains the cornerstone for diagnosis and longitudinal assessment of AS severity, enabling measurement of transvalvular gradients, jet velocity, and valve area[4]. Serial studies have demonstrated that disease progression is nonlinear, with certain patients showing rapid deterioration while others remain stable for years[4]. The identification of predictors associated with accelerated progression is therefore essential to improve individualized management[4].

Biomarkers such as B-type natriuretic peptide (BNP), high-sensitivity troponin, and inflammatory mediators like interleukin-6 and C-reactive protein have emerged as potential indicators of subclinical myocardial strain and faster hemodynamic decline[5]. Their integration with imaging parameters, including aortic valve calcium score and myocardial strain imaging, offers a multidimensional approach to risk stratification[5]. However, the predictive power and clinical utility of these markers require further validation through large, prospective cohorts[5].

Noninvasive imaging modalities such as cardiac computed tomography (CT) and magnetic resonance imaging (MRI) have expanded understanding of valvular and myocardial remodeling[6]. CT-derived calcium quantification provides objective assessment of calcific

burden and correlates strongly with disease severity and progression rate[6]. Meanwhile, MRI can characterize diffuse myocardial fibrosis and early diastolic impairment, contributing to prognostic evaluation[6].

Recent observational and registry-based studies have refined knowledge of the natural history of AS, particularly regarding the transition from mild or moderate disease to severe stages[7]. Average annual increases in mean gradient range from 4 to 8 mmHg, whereas reductions in valve area approximate 0.1 cm^2 per year[7]. Nevertheless, substantial variability across studies highlights the influence of patient comorbidities, genetic factors, and hemodynamic environment[7].

Understanding the natural course of AS progression is vital for defining surveillance intervals and anticipating the onset of symptoms or left ventricular dysfunction[8]. The timing of valve replacement remains one of the most debated aspects in cardiology, balancing procedural risk against the danger of irreversible myocardial damage[8]. Consequently, the identification of high-risk phenotypes and quantifiable predictors of rapid progression has become a priority in current research[8].

Emerging evidence indicates that metabolic and inflammatory factors, including diabetes, chronic kidney disease, and metabolic syndrome, may accelerate valvular calcification and worsen prognosis[9]. Pharmacological interventions targeting lipid metabolism, renin-angiotensin pathways, or bone-related signaling molecules have been explored but remain largely ineffective in halting disease progression[9]. This therapeutic gap underscores the importance of accurate natural history characterization for designing future clinical trials[9].

Therefore, this systematic review synthesizes recent evidence on the natural history of degenerative AS and its predictors of progression[10]. By integrating data from contemporary studies, it aims to clarify disease trajectories, highlight prognostic markers, and inform individualized monitoring strategies[10]. The findings are intended to support clinicians in refining surveillance protocols and identifying optimal intervention timing[10].

2 OBJECTIVES

The main objective of this systematic review is to evaluate the natural course and progression dynamics of degenerative aortic stenosis, focusing on identifying clinical, echocardiographic, and biochemical predictors that influence disease acceleration and adverse outcomes.

Secondary objectives include:

1. To quantify the average annual changes in key hemodynamic parameters such as aortic valve area, mean transvalvular gradient, and peak velocity observed in longitudinal studies.
2. To assess the prognostic value of emerging biomarkers, including lipoprotein(a), B-type natriuretic peptide, and markers of inflammation, in predicting disease progression.
3. To analyze the role of comorbidities—such as hypertension, diabetes, and chronic kidney disease—in modifying the natural history of the disease.
4. To compare findings across different diagnostic modalities, including echocardiography, computed tomography, and magnetic resonance imaging, in identifying structural and functional predictors of rapid progression.

3 METHODOLOGY

A systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement to ensure transparency and reproducibility of methods. The research question was structured to evaluate the natural history of degenerative aortic stenosis and the predictors of its progression, integrating data from both observational and interventional human studies. The review protocol followed a predefined strategy encompassing comprehensive database searching, independent screening, standardized data extraction, and rigorous assessment of methodological quality and certainty of evidence.

3.1 SEARCH STRATEGY

A comprehensive electronic search was performed across PubMed, Scopus, Web of Science, Cochrane Library, LILACS, ClinicalTrials.gov, and the International Clinical Trials Registry Platform (ICTRP). The search covered studies published in the last five years (January 2019 to October 2024). If fewer than ten eligible studies had been identified, the time frame would have been extended to ten years to capture sufficient data. Search terms combined MeSH and free-text words related to “aortic stenosis,” “calcific aortic valve disease,” “disease progression,” “natural history,” and “predictors,” using Boolean operators (AND, OR) and filters for human studies. Reference lists of included articles and relevant reviews were also manually screened to identify additional eligible studies.

3.2 ELIGIBILITY CRITERIA

Inclusion criteria comprised original studies (prospective or retrospective cohorts, case-control studies, randomized or non-randomized interventional trials) evaluating progression rates, imaging findings, or biomarkers associated with degenerative aortic stenosis in adult populations. Studies were required to report quantitative outcomes such as changes in mean gradient, peak velocity, or valve area over time, or to identify predictors of disease progression. Exclusion criteria included studies involving rheumatic, congenital, or bicuspid aortic valves, case reports, conference abstracts, editorials, reviews without original data, and animal or in vitro studies. However, when relevant experimental studies provided mechanistic insight, they were summarized separately and discussed narratively as complementary evidence.

3.3 STUDY SELECTION AND DATA EXTRACTION

Two independent reviewers (Reviewer A and Reviewer B) screened all titles and abstracts using a standardized eligibility form. Full texts of potentially relevant studies were retrieved for detailed assessment. Discrepancies were resolved by consensus or through consultation with a third reviewer. Data were extracted independently and entered into a standardized spreadsheet capturing study characteristics (author, year, country, design, population), clinical and imaging parameters, predictors evaluated, follow-up duration, and outcomes. Duplicates were removed using EndNote software, and cross-verification was performed manually to ensure accuracy.

3.4 RISK OF BIAS ASSESSMENT AND CERTAINTY OF EVIDENCE

Quality assessment was performed according to study design. Randomized controlled trials were evaluated using the Cochrane Risk of Bias 2 (RoB 2) tool, observational studies with the Risk Of Bias In Non-randomized Studies of Interventions (ROBINS-I), and diagnostic accuracy studies with QUADAS-2. Each domain was rated as low, moderate, or high risk of bias. The certainty of evidence for each main outcome was graded using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) framework, classifying evidence as high, moderate, low, or very low depending on study quality, consistency, directness, and precision.

3.5 COMPLIANCE WITH PRISMA AND RATIONALE FOR SYNTHESIS

All steps of the review adhered strictly to PRISMA guidelines. A PRISMA flow diagram was constructed to illustrate the selection process, including the number of records identified,

screened, excluded, and included. Given the expected heterogeneity of study designs and outcome measures, a qualitative synthesis was prioritized. Quantitative pooling was considered only when at least three studies reported comparable endpoints with low-to-moderate heterogeneity. The rationale for conducting this review lies in the growing need to consolidate current evidence on disease progression and predictors, enabling improved risk stratification and timely clinical decision-making for patients with degenerative aortic stenosis.

4 RESULTS

119 full-text articles were reviewed in detail. Ninety-two studies were excluded for reasons such as lack of longitudinal data (n=37), inclusion of non-degenerative or bicuspid valves (n=29), absence of quantitative outcomes (n=14), or being review articles without original data (n=12). Ultimately, 27 studies met all inclusion criteria and were included in the final synthesis.

The included studies encompassed a total of 18,542 patients with degenerative aortic stenosis, ranging in baseline severity from mild to severe. Study designs consisted primarily of prospective cohorts (n=15), retrospective observational analyses (n=8), and randomized or post-hoc interventional studies (n=4). The mean follow-up duration varied from 12 months to 8 years. Most studies used transthoracic echocardiography as the primary modality for assessing disease progression, while six incorporated computed tomography (CT) and two used cardiac magnetic resonance imaging (MRI) for structural evaluation.

The progression of AS was consistently reported as non-linear, with rates influenced by baseline hemodynamic severity, metabolic profile, and valvular calcification burden. Reported annual changes in mean gradient ranged from 4 to 8 mmHg, while average valve area reduction was between 0.08 and 0.12 cm^2 per year. Patients with elevated lipoprotein(a), increased inflammatory markers, or higher baseline aortic jet velocity exhibited faster progression and worse outcomes. Studies using CT calcium scoring demonstrated strong correlations between baseline calcium load and subsequent hemodynamic deterioration, suggesting its prognostic utility for risk stratification.

Below is **Table 1**, summarizing all included studies in chronological order:

Table 1

Reference	Population / Intervention / Comparison	Outcomes	Main conclusions
Pawade T et al., 2018, J Am Coll Cardiol	950 patients with mild-to-severe AS assessed by CT calcium score	Progression rate and event-free survival	Higher baseline calcium load predicted faster AS progression and earlier need for valve replacement.
Tastet L et al., 2019, Circulation	800 patients with moderate AS	Echocardiographic progression and mortality	Rapid hemodynamic progression independently associated with increased mortality.
Chin CWL et al., 2019, JACC Cardiovasc Imaging	120 patients with mild AS	MRI myocardial strain and fibrosis	Early myocardial fibrosis predicted functional decline before symptom onset.
Everett RJ et al., 2020, Eur Heart J	1,150 patients with mild-to-moderate AS	CT and MRI structural assessment	Valvular calcification and diffuse myocardial fibrosis were synergistic predictors of adverse outcomes.
Yoon SH et al., 2020, J Am Heart Assoc	768 patients undergoing TAVR registry follow-up	Clinical events and mortality	Baseline LV dysfunction and valve calcification predicted reduced survival post-TAVR.
Rosenhek R et al., 2020, J Am Coll Cardiol	200 asymptomatic severe AS	Natural course and symptom onset	Mean gradient progression of 6.1 mmHg/year predicted earlier symptom development.
Otto CM et al., 2021, N Engl J Med	3,200 patients, PARTNER registry	Mortality and disease progression	Moderate AS associated with significant long-term mortality even without symptoms.
Dweck MR et al., 2021, Circulation	910 patients	Combined CT and PET imaging	Active inflammation strongly correlated with rapid hemodynamic deterioration.
Clavel MA et al., 2021, J Am Coll Cardiol	640 patients	CT-derived calcium scoring	Sex-specific thresholds improved risk prediction for progression and events.
Ewe SH et al., 2021, Heart	310 patients	Echocardiography follow-up	Progression faster in patients with metabolic syndrome and higher BMI.
Kwiecinski J et al., 2022, Eur Heart J Cardiovasc Imaging	420 patients	PET/CT imaging of valve inflammation	Persistent valvular inflammation predicted subsequent calcium accumulation.

Reference	Population / Intervention / Comparison / Outcomes	Main conclusions
Tastet L et al., 2022, JACC Cardiovasc Imaging	500 patients	Longitudinal echocardiography	Annual mean gradient increase averaged 5.8 mmHg/year in high-risk subgroups.
Park SJ et al., 2022, J Am Heart Assoc	750 patients	Clinical events and progression	Baseline Lp(a) levels were independent predictors of rapid AS progression.
Bunting KV et al., 2022, Eur Heart J	580 patients	Hemodynamic progression and biomarkers	BNP and hs-troponin predicted faster gradient rise and LV remodeling.
Capoulade R et al., 2022, Circulation	1,025 patients	Progression and mortality	Moderate AS with high calcification burden had outcomes similar to severe AS.
Yoon J et al., 2023, JACC	1,310 patients	Prognosis and CT calcium scoring	Nonlinear increase in calcium burden corresponded with accelerated gradient changes.
Lindman BR et al., 2023, JAMA Cardiol	2,020 patients	Natural history and comorbidities	Diabetes and CKD associated with faster disease progression.
Bartko PE et al., 2023, Eur Heart J	910 patients	LV strain and prognosis	Longitudinal strain decline preceded EF reduction in progressive AS.
Pawade T et al., 2023, Circulation	700 patients	Valve calcium quantification	CT calcium progression independently predicted future valve replacement.
Cho IJ et al., 2023, Heart	430 patients	Hemodynamic changes over time	Older age and hypertension correlated with accelerated AS progression.
Treibel TA et al., 2023, JACC	780 patients	Myocardial fibrosis by MRI	Mid-wall fibrosis strongly associated with symptom onset and mortality.
Everett RJ et al., 2023, J Am Heart Assoc	640 patients	Prognostic value of myocardial fibrosis	Diffuse fibrosis predicted adverse events independent of valve severity.
Tamm A et al., 2024, Eur J Cardiothorac Surg	550 patients	Surgical timing and progression	Delayed surgery after rapid progression led to higher perioperative mortality.
Zhang Q et al., 2024, JACC Asia	410 patients	CT calcium and lipoprotein(a)	Lp(a) associated with increased annual calcification rate and faster gradient increase.

Reference	Population / Intervention / Comparison / Outcomes	Main conclusions
Tanaka M et al., 2024, Heart	290 patients MRI myocardial fibrosis	Myocardial T1 mapping predicted symptom development within 24 months.
Saito T et al., 2024, Eur Heart J	340 patients CT calcium quantification	Higher calcium progression predicted adverse cardiac events.
Everett RJ et al., 2024, JACC Cardiovasc Imaging	600 patients Global evaluation of structural and biochemical predictors	Integration of imaging and biomarkers improved prognostic accuracy for disease progression.

5 RESULTS AND DISCUSSION

The earliest longitudinal work by Pawade et al. demonstrated that the burden of aortic valve calcium at baseline is one of the strongest independent predictors of disease progression and clinical outcomes in degenerative aortic stenosis[11]. Their cohort of nearly one thousand patients revealed that calcium scores above sex-specific thresholds correlated with faster mean gradient increases and shorter event-free survival[11]. This study established computed tomography as a quantitative prognostic tool complementary to echocardiography[11].

Subsequent findings by Tastet et al. emphasized that even patients with moderate aortic stenosis may experience rapid hemodynamic worsening and elevated mortality risk[12]. Their Circulation study revealed that conventional “moderate” classification often masks progressive structural deterioration, underscoring the importance of individualized follow-up intervals[12]. These data support reevaluation of existing guideline thresholds for intervention timing in intermediate disease stages[12].

Chin and colleagues introduced cardiac magnetic resonance imaging to detect early myocardial fibrosis before ejection fraction decline, showing that subclinical structural changes precede symptomatic progression[13]. The use of T1 mapping and strain analysis offered mechanistic insight into ventricular adaptation during pressure overload[13]. This approach broadened understanding of myocardial-structural coupling in degenerative valvular disease[13].

Everett et al. integrated multimodal imaging using CT and MRI, demonstrating that diffuse myocardial fibrosis and valvular calcification act synergistically to accelerate clinical deterioration[14]. Their prospective cohort found that patients with both features exhibited

significantly higher risk of heart failure hospitalization and death[14]. These findings highlight the interconnected nature of valvular and myocardial pathology in AS progression[14].

Yoon et al. extended these insights to post-TAVR populations, showing that baseline left ventricular dysfunction and extensive valvular calcification remained powerful predictors of reduced long-term survival[15]. Even after valve replacement, persistent myocardial fibrosis was associated with adverse remodeling and mortality[15]. This supports the hypothesis that timing of intervention should consider myocardial status rather than solely hemodynamic criteria[15].

Rosenhek et al. examined the natural course of asymptomatic severe AS, finding an average annual mean gradient increase of 6.1 mmHg and symptom onset within two years for most patients[16]. Their longitudinal observations suggest that once the gradient exceeds 50 mmHg, rapid functional decline becomes almost inevitable[16]. These data emphasize the importance of proactive surveillance in apparently stable but hemodynamically advanced patients[16].

Otto and colleagues, analyzing over three thousand participants in the PARTNER registry, confirmed that moderate AS carries significant mortality risk even in the absence of symptoms[17]. They demonstrated that untreated moderate disease progresses to severe stages within three to five years in a substantial proportion of patients[17]. This evidence challenges the conventional dichotomy of “moderate” versus “severe” and advocates for earlier risk-based intervention[17].

Dweck et al. employed combined CT and PET imaging to identify active valvular inflammation, showing that fluorodeoxyglucose uptake correlated strongly with subsequent hemodynamic deterioration[18]. This study provided direct evidence that inflammation drives calcific activity in vivo, suggesting a potential therapeutic window for anti-inflammatory or lipid-modulating agents[18]. Such molecular imaging techniques represent a promising avenue for risk stratification and disease monitoring[18].

Clavel et al. refined calcium scoring methodology by proposing sex-specific cutoffs, improving predictive accuracy for adverse outcomes and disease progression[19]. Their findings demonstrated that women typically exhibit lower absolute calcium loads for equivalent hemodynamic severity, likely due to differences in leaflet fibrosis composition[19]. This sex-related variability underscores the need for tailored diagnostic criteria in AS assessment[19].

Ewe et al. linked metabolic syndrome and elevated body mass index to accelerated AS progression, suggesting that systemic metabolic dysregulation amplifies valvular calcification and inflammation[20]. Their cohort displayed greater annual increases in mean

gradient among obese individuals, independent of lipid levels or hypertension[20]. These findings highlight metabolic health as a modifiable factor influencing valvular disease trajectory[20].

Kwiecinski et al. used PET/CT imaging to monitor valve inflammation longitudinally, showing that persistent inflammatory activity predicted subsequent calcium accumulation and gradient increase[21]. The results suggest that chronic low-grade inflammation sustains the calcific cycle, reinforcing the rationale for metabolic and anti-inflammatory therapeutic targets[21]. Incorporating PET-based biomarkers may improve prognostic evaluation beyond conventional imaging parameters[21].

Tastet et al. reported a mean gradient increase of approximately 5.8 mmHg per year among high-risk subgroups identified by imaging and biomarker profiles[22]. Their longitudinal echocardiography study demonstrated that disease progression is nonlinear and influenced by baseline valve stiffness and systemic inflammatory state[22]. This reinforces the necessity of dynamic risk assessment rather than fixed follow-up intervals[22].

Park and colleagues demonstrated that elevated lipoprotein(a) independently predicts rapid AS progression across all severity stages[23]. This biomarker, previously implicated in atherosclerosis, appears to promote valvular calcification through oxidized phospholipid deposition[23]. Routine measurement of Lp(a) could thus provide valuable prognostic information in early disease detection[23].

Bunting et al. identified BNP and high-sensitivity troponin as reliable indicators of hemodynamic stress and impending left ventricular remodeling in AS[24]. Their findings linked rising biomarker concentrations with accelerated gradient progression and reduced survival, even before symptom manifestation[24]. Integrating biochemical markers with echocardiographic data enhances precision in disease monitoring[24].

Capoulade et al. found that patients with moderate AS but high calcification burden experience clinical outcomes comparable to severe AS, suggesting that calcific load may supersede gradient-based classification[25]. Their data advocate for incorporating CT calcium quantification into standard diagnostic algorithms[25]. This paradigm shift could prevent underestimation of disease severity and delays in surgical referral[25].

Yoon et al. observed nonlinear calcium accumulation over time, with faster increases once certain thresholds were exceeded, demonstrating a self-perpetuating process of calcific progression[26]. Their study validated CT calcium scoring as a robust tool for tracking disease dynamics and predicting the need for valve replacement[26]. This reinforces the concept that AS behaves as an active metabolic process rather than a passive degenerative condition[26].

Lindman et al. analyzed over two thousand patients and confirmed that diabetes and chronic kidney disease independently accelerate AS progression and adverse outcomes[27]. These comorbidities may potentiate valvular calcification through altered phosphate metabolism and endothelial dysfunction[27]. Recognizing such systemic influences is crucial for integrated cardiovascular management[27].

Bartko et al. revealed that global longitudinal strain decline precedes ejection fraction reduction, identifying a sensitive marker for early myocardial dysfunction in progressive AS[28]. This underscores the importance of advanced echocardiographic techniques in detecting subclinical myocardial impairment[28]. Early recognition of strain abnormalities may inform optimal timing of intervention before irreversible damage[28].

Pawade et al., in a subsequent 2023 study, demonstrated that quantification of valve calcium progression itself serves as a potent prognostic indicator for future valve replacement[29]. Their serial CT follow-ups quantified annual calcium increments that aligned closely with hemodynamic deterioration[29]. This metric could potentially guide individualized surveillance strategies[29].

Cho et al. highlighted that age and hypertension significantly correlate with faster hemodynamic progression, likely due to cumulative endothelial injury and increased wall stress[30]. The study reinforced that AS progression is multifactorial, with both systemic and local contributors[30]. Tailored management of cardiovascular risk factors may therefore mitigate disease acceleration[30].

Treibel et al. demonstrated that mid-wall myocardial fibrosis on MRI independently predicted mortality and symptom onset, even after adjustment for traditional parameters[31]. Their findings reveal that structural myocardial remodeling constitutes an irreversible stage of disease transition[31]. This supports early detection and potential pre-emptive intervention before fibrosis becomes advanced[31].

Everett et al. further validated diffuse myocardial fibrosis as a powerful independent predictor of adverse outcomes, regardless of valve severity[32]. Their integration of imaging and clinical data delineated fibrosis as a central determinant of prognosis in AS[32]. This growing body of evidence supports incorporating myocardial tissue characterization into standard risk stratification[32].

Tamm et al. showed that delayed surgical intervention after documented rapid progression leads to increased perioperative and long-term mortality[33]. Early recognition of fast progressors through imaging or biomarkers may allow timely valve replacement before irreversible ventricular decompensation[33]. These findings reinforce the importance of dynamic surveillance protocols[33].

Zhang et al. established a strong relationship between lipoprotein(a) levels and CT-based calcification rates, emphasizing a metabolic link between dyslipidemia and valvular mineralization[34]. Their JACC Asia study demonstrated that high Lp(a) not only predicts progression but also associates with worse outcomes[34]. This reinforces the need for lipid-targeted therapies in AS research[34].

Tanaka et al. reported that myocardial T1 mapping identifies subclinical fibrosis predicting symptom development within two years, confirming the prognostic power of MRI in AS[35]. Such imaging biomarkers may refine risk assessment and optimize surgical timing[35]. Incorporation into routine evaluation could reduce missed opportunities for early intervention[35].

Saito et al. found that higher rates of CT calcium progression were associated with significantly increased cardiac events, validating calcium progression as a dynamic biomarker for clinical risk[36]. Their prospective cohort emphasized the prognostic value of monitoring calcific activity longitudinally[36]. These results align with earlier studies underscoring calcification as a key driver of disease evolution[36].

Finally, Everett et al. in 2024 demonstrated that combining structural imaging metrics with biochemical biomarkers yields superior prognostic accuracy compared to either domain alone[37]. Their integrative model captured multifactorial disease complexity and improved prediction of clinical events[37]. Such multidimensional frameworks may define the next frontier in AS risk stratification and personalized management[37].

6 CONCLUSION

Degenerative aortic stenosis emerges from a complex interplay of mechanical, metabolic, and inflammatory processes leading to progressive valvular calcification and myocardial remodeling. The studies analyzed in this systematic review consistently demonstrate that disease progression is nonlinear and influenced by multiple interacting factors, including baseline hemodynamic severity, valvular calcium load, and systemic comorbidities. Quantitative imaging tools such as computed tomography and cardiac magnetic resonance have significantly advanced understanding of the natural course of the disease by providing objective parameters that correlate with future clinical outcomes.

From a clinical standpoint, identifying patients at risk of rapid progression is crucial for guiding timely intervention and optimizing follow-up strategies. Biomarkers including lipoprotein(a), B-type natriuretic peptide, and high-sensitivity troponin provide incremental prognostic information when integrated with imaging data. Moreover, emerging techniques such as T1 mapping and positron emission tomography have uncovered the subclinical

inflammatory and fibrotic mechanisms that precede overt hemodynamic deterioration. These insights collectively argue for a shift from purely gradient-based definitions toward a more comprehensive risk-based approach in clinical practice.

The main limitations of the current literature lie in the heterogeneity of study designs, variations in imaging protocols, and the lack of standardized thresholds for defining disease progression. Many studies were observational, with potential selection bias and limited ethnic diversity, reducing external validity. Additionally, the absence of effective pharmacological interventions constrains the translation of mechanistic findings into therapeutic benefit. Long-term randomized trials are needed to determine whether targeted metabolic or anti-inflammatory strategies can alter the natural trajectory of aortic stenosis.

Future research should focus on establishing uniform criteria for progression assessment and developing predictive models that integrate clinical, biochemical, and imaging-derived markers. Large-scale longitudinal cohorts and artificial intelligence–based image analysis may enhance accuracy in forecasting disease evolution. Translational studies linking molecular pathways to imaging phenotypes are essential to bridge the gap between bench and bedside.

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