




openheart Prognostic significance implications of aortic valve sclerosis in the development of aortic stenosis: a systematic review and meta-analysis

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ABSTRACT

Background Fibrocalcific aortic valve sclerosis (AVSc), the earliest manifestation of aortic stenosis (AS), is increasingly recognised as a marker of systemic vascular damage and adverse cardiovascular outcomes. While a subset of AVSc patients progresses to AS, reported rates vary widely. We conducted a systematic review and meta-analysis to better define the natural history of AVSc progression.

Methods Following Preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines, we searched PubMed, Scopus and Web of Science through July 2025 for observational studies reporting AS development in AVSc patients. Primary outcomes were progression to any degree of AS and to severe AS. Pooled event rates were calculated using a random-effects model. Heterogeneity and publication bias were assessed using standard statistical methods. Meta-regression explored associations with clinical and demographic variables.

Results Eight studies (n=12 388 patients) reported on the progression of AVSc patients to any AS stage, and nine studies (n=19 486 patients) on the progression to severe AS. Over a median follow-up of 4.0 years, 14.1% of AVSc patients progressed to any AS stage (effect size: 0.14; 95% CI 0.02 to 0.53), and 2.0% to severe AS (effect size: 0.02; 95% CI 0.003 to 0.094). Heterogeneity was high, but no publication bias was detected. Meta-regression found no significant predictors of progression.

Conclusions Approximately one in six AVSc patients progresses to AS within 4 years, and 2% develop a severe disease. These findings underscore the importance of structured echocardiographic surveillance and support AVSc as a clinically relevant marker of systemic cardiovascular risk.

INTRODUCTION

Fibrocalcific aortic valve sclerosis (AVSc), considered the earliest manifestation of aortic stenosis (AS), is increasingly recognised as a marker of systemic vascular damage and is associated with adverse cardiovascular outcomes.^{1 2} Characterised by leaflet

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Fibrocalcific aortic valve sclerosis (AVSc) is the earliest stage of aortic stenosis and a marker of systemic vascular damage. It is linked to adverse cardiovascular outcomes, with variable progression rates to aortic stenosis (AS).

WHAT THIS STUDY ADDS

⇒ This meta-analysis of over 24 000 AVSc patients shows that 14% progress to any degree of AS and 2% to severe AS within 4 years.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Findings support regular echocardiographic monitoring of AVSc, especially in older adults. AVSc should be considered a surrogate marker of systemic cardiovascular risk and integrated into preventive cardiology strategies.

thickening and calcification without significant haemodynamic obstruction, AVSc reflects underlying processes such as chronic inflammation, endothelial dysfunction and lipid deposition, which are shared with atherosclerosis and other cardiovascular diseases.³ Increasing evidence links AVSc not only to localised valvular degeneration but also to adverse cardiovascular outcomes, including myocardial infarction, stroke and cardiovascular death.⁴

Although approximately 10% of patients with AVSc may progress to AS, reported progression rates vary widely across studies, ranging from 16% over 8 years to 37% over 4 years, with severe AS developing in 2.5%–6% of cases.^{5 6} Given the importance of timely surveillance through echocardiography, particularly in elderly populations, clarifying the timeline of AS development is essential. Recently, the availability of large-scale studies that identified aortic valve disease progression

by echocardiography^{1 2 6-10} has enabled us to conduct a systematic review and meta-analysis to better define the evolution of AVSc to AS.

METHODS

We conducted a systematic literature search in PubMed, Scopus and Web of Science from inception to July 2025, following Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (figure 1), to identify observational studies involving patients with AVSc that reported summary-level outcomes on the development of any degree of AS. This protocol was registered in the International Prospective Register of Systematic Reviews (PROSPERO: CRD420251119035) to ensure transparency and reproducibility. Two independent reviewers screened and selected studies based on predefined inclusion criteria. Methodological quality was assessed using the Newcastle–Ottawa Scale (online supplemental table S1). The primary outcomes were the development of any degree of AS (mild, moderate or severe) and the development of severe AS alone during follow-up. Statistical analyses were performed using Comprehensive Meta-Analysis software, V.4 (Biostat, Englewood, New Jersey). Continuous variables were expressed as median and IQR. Event rates were expressed as mean effect sizes with corresponding 95% CIs. Heterogeneity among studies was assessed using Cochran's Q test and the I² statistic, which quantifies the proportion of total variation due to heterogeneity rather than chance. Publication bias was evaluated

through visual inspection of funnel plots and Egger's test, with a p value <0.05 considered statistically significant. A random-effects model was used for all analyses to account for between-study variability. Meta-regression analyses were conducted to explore associations between AS progression and clinical or demographic characteristics, including mean age, body mass index, total cholesterol, low-density lipoprotein, high-density lipoprotein, triglycerides, cardiovascular risk factors (hypertension, diabetes, dyslipidaemia, smoking) and the presence of coronary artery disease (online supplemental table S2 and S3).

RESULTS

We identified eight studies^{5-7 9-13} including 12 388 patients with AVSc (median age: 72 (IQR: 68–76) years; 61% male) that reported progression to any degree of AS (mild, moderate or severe), and nine studies^{1 2 5 7-9 11 12 14} including 19 486 AVSc patients (median age: 71 (IQR: 68–74) years; 67% male) that reported progression to severe AS (figure 2A).

Over a median follow-up of 4.0 years (IQR: 3.3–6.1), 1393 patients (14.1% (IQR: 9.1–28.5)) progressed to any degree of AS, with a pooled effect size of 0.14 (95% CI 0.02 to 0.53; figure 2B). Heterogeneity was high (I² = 99%), indicating that the observed variance was largely due to true differences across studies rather than sampling error. Similarly, over a median follow-up of 3.8 years (IQR: 3.4–4.6), 241 patients (2.0% (IQR: 0.9–3.2))

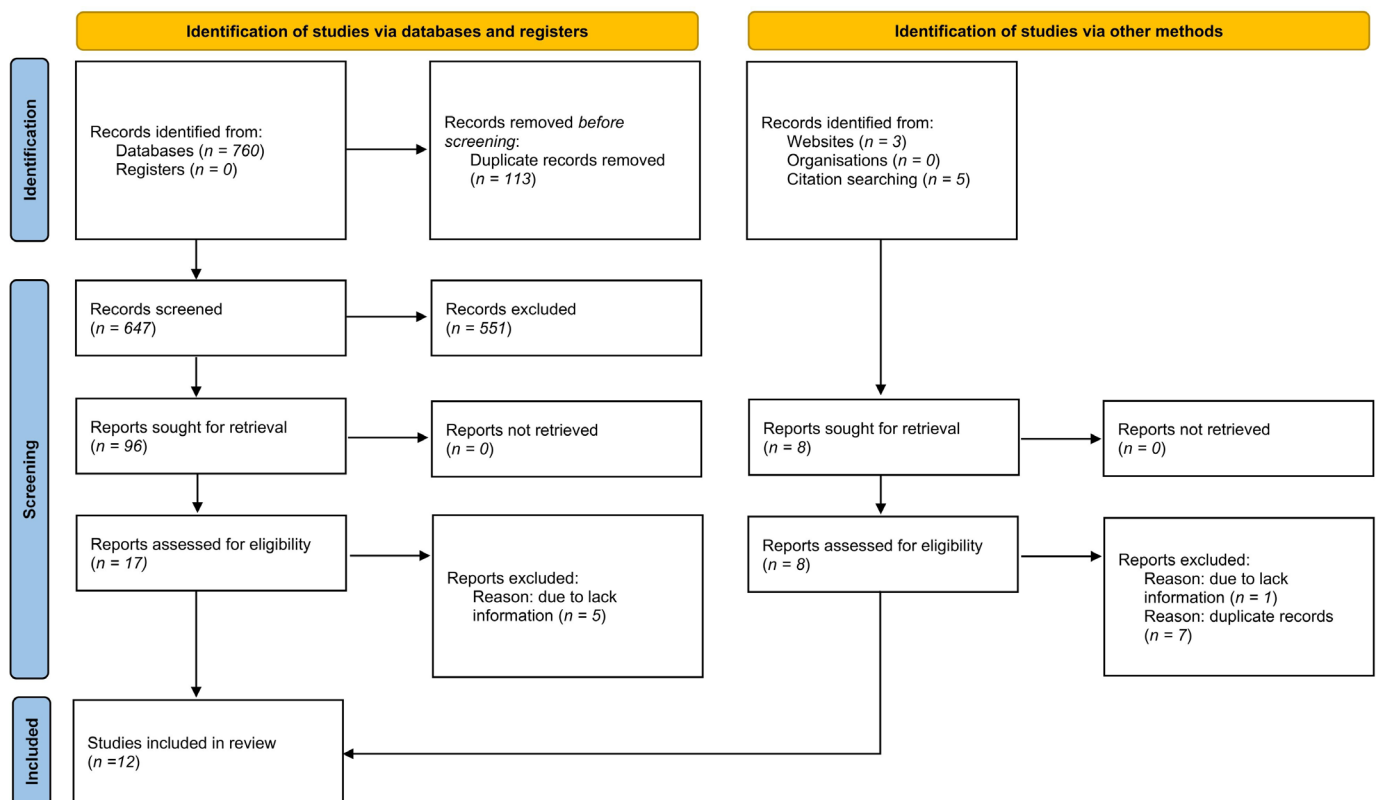


Figure 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram. The flow chart represents the number of studies evaluated according to PRISMA guidelines.

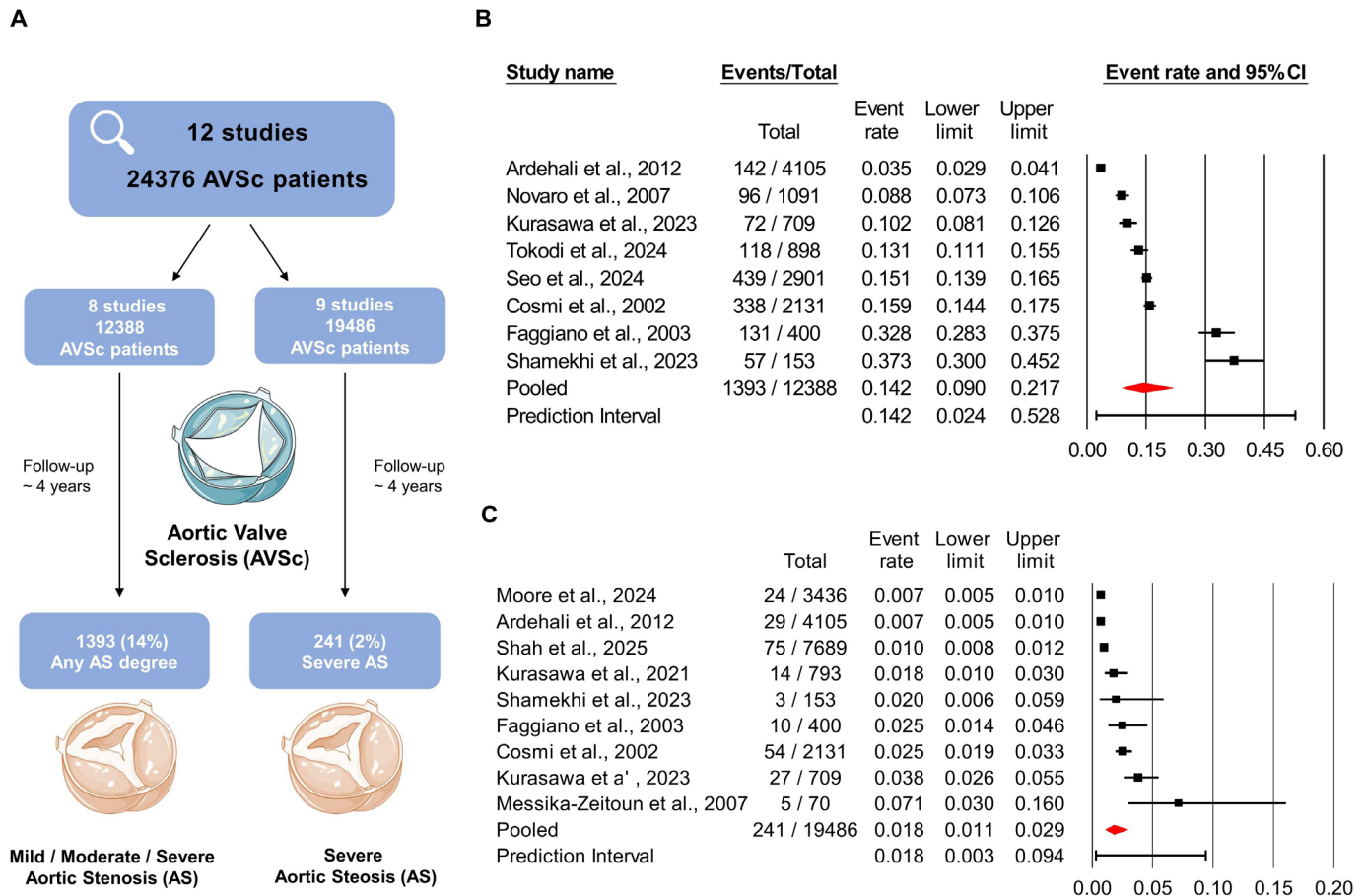


Figure 2 Progression of aortic valve sclerosis (AVSc) to aortic stenosis (AS): summary of evidence. (A) Flowchart summarising data from the studies included in the present meta-analysis on AVSc progression to any degree of AS and to severe AS. (B) Forest plot presents event rates and 95% CIs for any degree of AS (mild/moderate/severe) progression across individual studies. (C) Forest plot presents event rates and 95% CIs for severe AS progression across individual studies. The red diamonds represent the estimated overall effect.

progressed to severe AS, with a pooled effect size of 0.02 (95% CI 0.003 to 0.094; [figure 2C](#)), and substantial heterogeneity ($I^2 = 92\%$).

Funnel plots of the logit event rate versus SE were symmetrical, indicating no publication bias (Egger's test: progression to any degree of AS $p=0.911$ and severe AS $p=0.394$; [figure 3](#)). Meta-regression analyses did not identify any significant associations between AS progression and evaluated clinical or demographic variables.

DISCUSSION

This meta-analysis, including data from 24 376 patients with AVSc, offers valuable insights into the natural history of disease progression. We found that approximately one in six patients with AVSc progressed to any degree of AS within 4 years, and 2% reached the severe stage requiring aortic valve replacement. These results underscore the clinical relevance of AVSc as an early marker of valvular disease.

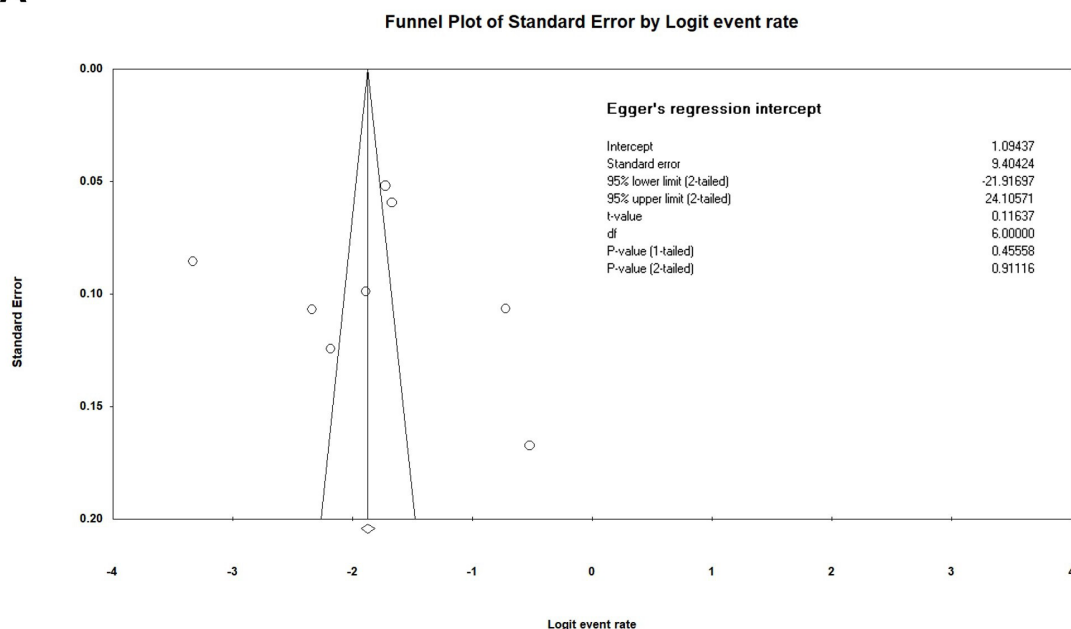
The observed progression rates are consistent with previous individual studies,^{5,7,11} though reported estimates vary. Notably, our analysis confirms that while most AVSc patients do not progress to severe AS, a non-negligible

portion advance to a clinically meaningful stage. This highlights the need for vigilant longitudinal monitoring, particularly in older adults.

The association between AVSc progression and adverse cardiovascular outcomes has been previously documented.^{2,6} Seo *et al*⁶ showed that patients with AVSc who progressed to AS experienced higher rates of cardiovascular death, myocardial infarction, stroke or revascularisation than those without progression, but the underlying mechanisms remain unclear. While it is well known that progressive leaflet calcification and stiffening lead to haemodynamic obstruction and ultimately AS,¹⁴ AVSc may also reflect a broader systemic process, such as chronic inflammation or endothelial dysfunction, contributing to both valvular and vascular pathology.¹³

Our findings reinforce the importance of AVSc not only as a localised valvular condition but also as a potential surrogate marker of systemic cardiovascular risk. This has important implications for clinical practice. Given the relatively high progression rate and ageing population, structured echocardiographic surveillance strategies should be considered to enable early detection and timely intervention. Moreover, our results support the

A



B

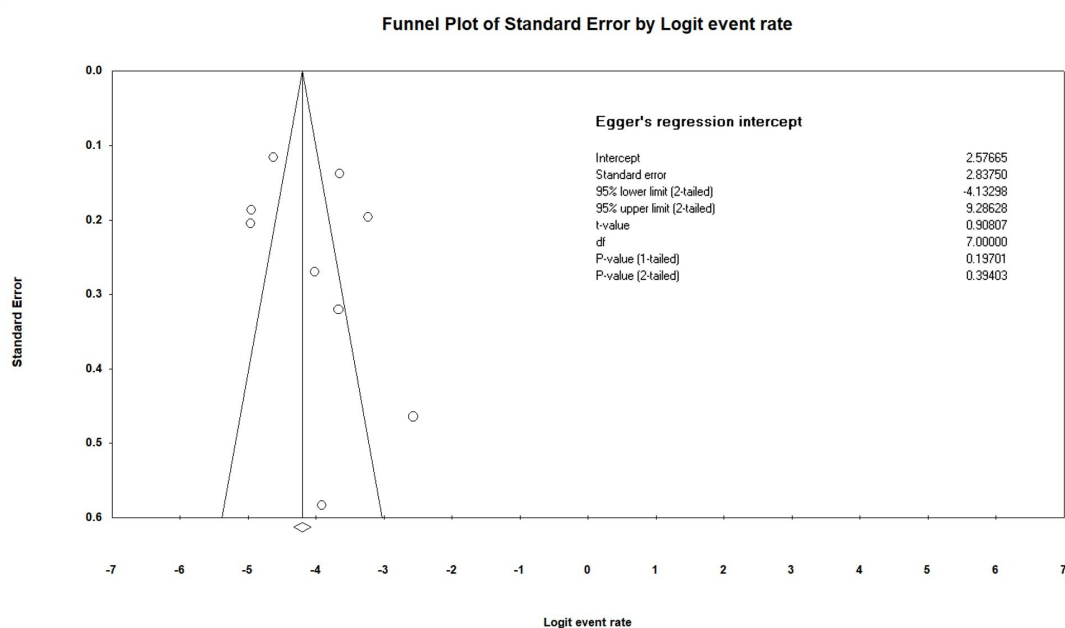


Figure 3 Funnel plots of the logit event rate versus SE for studies assessing aortic valve sclerosis (AVSc) progression to aortic stenosis (AS). (A) Studies included in any degree of AS progression. (B) Studies included in progression to severe AS only.

integration of AVSc assessment into broader preventive cardiology frameworks.

LIMITATIONS

Despite the strengths of our study, including rigorous methodology and a large pooled sample size, several limitations should be acknowledged. First, the lack of granular data on comorbidities limited our ability to explore their role in disease progression. Second, echocardiographic assessment of AVSc is inherently operator-dependent

and lacks quantitative precision. Third, stratification by valve morphology¹⁵ (bicuspid vs tricuspid), symptomatic status and echocardiographic predictors (such as peak aortic flow velocity, systemic vascular resistance index, left ventricular ejection fraction and global longitudinal strain) was not feasible due to insufficient reporting across studies. Future investigations involving subjects with AVSc and employing advanced imaging modalities such as CT or MRI,¹⁶ together with standardised echocardiographic protocols and longitudinal symptom assessment, may

provide more accurate characterisation of valvular structure, refine risk stratification and ultimately guide earlier and more personalised therapeutic interventions.

CONCLUSIONS

This meta-analysis highlights the clinical and prognostic significance of AVSc. Nearly one in six patients develops AS within 4 years, and a subset progresses to severe disease requiring valve replacement. These findings emphasise the need for regular echocardiographic follow-up and further research to refine risk prediction using advanced imaging and comprehensive clinical data.

Contributors The guarantor is VAM. All authors contributed to the study design, acquisition, analysis and interpretation of the data. VAM and PP drafted the initial manuscript, and VV, IM, FB, GM and VR critically revised the manuscript for important intellectual content. All authors gave final approval and agree to be accountable for all aspects of the work, ensuring integrity and accuracy.

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