ESC European Society of Cardiology

European Heart Journal - Valvular and Structural Heart Disease (2026) **2**, xwag044
https://doi.org/10.1093/ehjvshd/xwag044

ORIGINAL ARTICLE
Aortic valvular heart disease

Evolution of echocardiographic changes in aortic stenosis and the association with rapid valvular progression

Constantijn S. Venema [1], Kees H. van Bergeijk [1], Kyriakos Panaou [1], Jan A. Krikken[1], Teresa Trenkwalder [2,3], Michael Joner [2,3], Ify R. Mordi [4], Chim C. Lang [4], Nicolas Girerd [5], Marie-Annick Clavel [6], Erik Lipsic [1], Adriaan A. Voors [1], and Joanna J. Wykrzykowska [1,*]

[1]Department of Cardiology and Cardiothoracic Surgery, Heart Centre, University of Groningen, University Medical Centre Groningen, Hanzeplein 1, Groningen 9700RB, The Netherlands; [2]School of Medicine and Health, Department of Cardiovascular Diseases, Technical University of Munich, German Heart Centre Munich, TUM University Hospital, Munich, Germany; [3]German Centre for Cardiovascular Research, Partner Site Munich Heart Alliance, Munich, Germany; [4]Division of Molecular and Clinical Medicine, University of Dundee, Ninewells Hospital and Medical School, Dundee, UK; [5]Centre D'Investigation Clinique Pierre Drouin-INSERM-Unité Mixte de Recherche U1116 DCAC—CHRU de Nancy, Institut Lorrain du Cœur et des Vaisseaux Louis Mathieu, Nancy, France; and [6]Institut Universitaire de Cardiologie et de Pneumologie de Québec/Quebec Heart & Lung Institute, Laval University, Quebec City, Quebec, Canada

Received 5 February 2026; revised 27 March 2026; accepted after revision 17 May 2026; online publish-ahead-of-print 30 May 2026

Abstract

Background Data on the chronological progression of myocardial changes during the course of aortic stenosis remain limited. In addition, it is unknown whether faster progression of aortic stenosis is associated with accelerated myocardial remodelling.

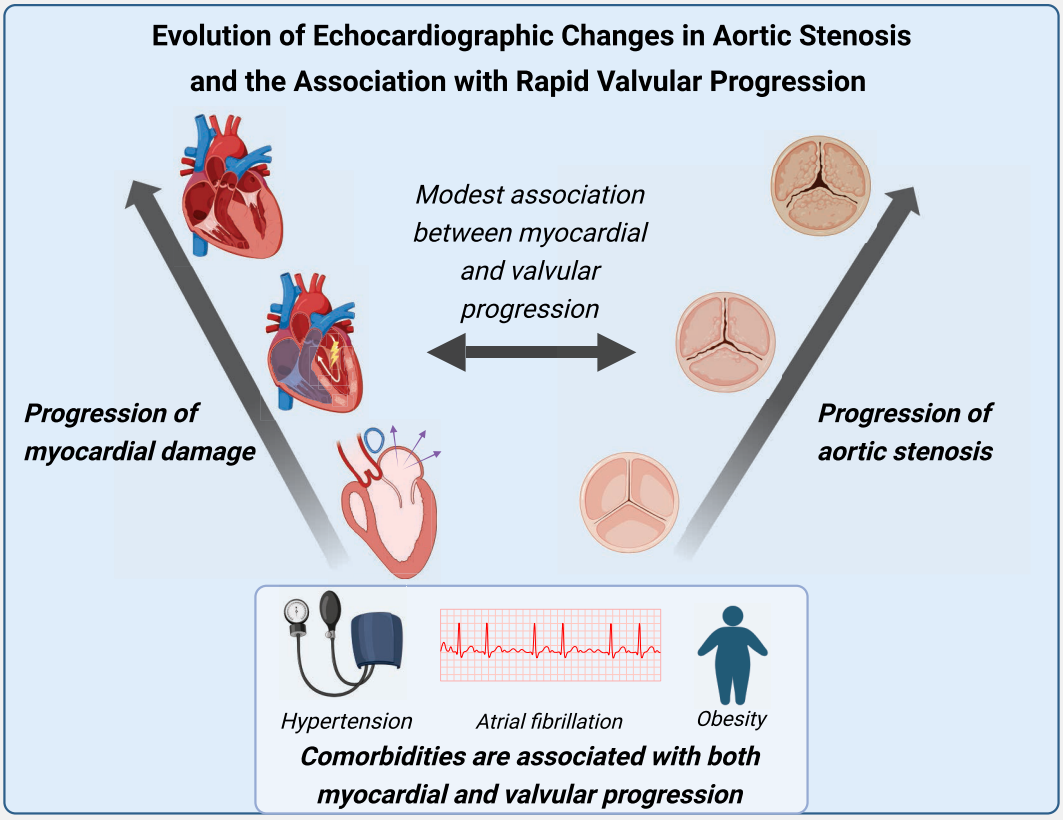
Aims To describe the evolution of structural and functional echocardiographic changes over time in patients with moderate aortic stenosis and evaluate the association with rapid valvular progression.

Methods and results In this retrospective longitudinal study, we included patients with a diagnosis of moderate aortic stenosis and serial echocardiograms. Changes in echocardiographic variables over time were analysed using linear mixed-effects models. This study included 467 patients with moderate aortic stenosis (median age 69 years, 36% female) with 2806 echocardiograms (median of six per patient). Over a median follow-up of 4.3 years, 47% of patients developed severe aortic stenosis. Most echocardiographic variables changed linearly over time, with impaired relaxation, concentric remodelling and left atrial dilatation occurring early. Concentric hypertrophy developed only after aortic stenosis became severe. Rapid valvular progression was weakly associated with the rate of myocardial changes. Rapid progression of left ventricular mass index was accelerated by comorbidities and was associated with an increased risk of heart failure hospitalizations.

Conclusions During progression of aortic stenosis, left atrial dilatation and impaired relaxation occur early, whereas concentric hypertrophy is a late finding. Rapid valvular progression is only weakly associated with enhanced myocardial remodelling, which is accelerated by comorbidities.

* Corresponding author. Tel: 0031 503616161, Email: j.j.wykrzykowska@umcg.nl

Graphical Abstract



Left atrial dilatation and impaired relaxation occur early in aortic stenosis, whereas significant concentric hypertrophy occurs when aortic stenosis has already become severe. Progression of myocardial changes and valvular progression are weakly correlated. We hypothesize that comorbidities, such as hypertension, obesity and atrial fibrillation, are the main driver of both myocardial changes and valvular progression in aortic stenosis.

Keywords Aortic stenosis • Valvular heart disease • Structural heart disease • Remodelling

Introduction

Aortic stenosis is a progressive disease that increases left ventricular afterload, eventually resulting in left ventricular hypertrophy as a compensatory mechanism to maintain wall stress. Although initially a physiological response, progressive remodelling can lead to myocardial fibrosis and left ventricular dysfunction.[1] These pathological changes may lead to development of heart failure and may not be reversible after aortic valve replacement.[2–4] This implies that the myocardial response in aortic stenosis has crucial clinical implications, and potentially could influence the timing of intervention or identify which patients benefit most from early valve replacement.[5] To incorporate the myocardial changes in the risk assessment of aortic stenosis, a staging classification has been proposed by Généreux *et al.*[6] This staging classification is based on the extent of structural and functional cardiac abnormalities, referred to as cardiac damage. It has been thoroughly validated in patients with severe aortic stenosis and demonstrates evident association with mortality and outcomes after valve replacement.[7] The staging classification was developed on a theoretical framework proposing that cardiac damage due to mechanical obstruction of the valve propagates from the left ventricle towards the right ventricle in a sequential fashion.[6,8] Yet, little is known about the actual evolution and order of cardiac structural and functional changes before the onset of severe aortic stenosis. In addition, it is unclear whether patients with faster valvular progression of aortic stenosis have more aggressive extravalvular myocardial remodelling. Therefore, the aim of this study was to describe the natural history of myocardial changes over time during progression of aortic stenosis and to evaluate the effects of rapid valvular hemodynamic progression on the extent of extravalvular myocardial remodelling.

Methods

Study design and cohort

This single-centre retrospective longitudinal study was conducted in a university hospital in the Netherlands. We included patients who had a diagnosis of moderate aortic stenosis on echocardiography between December 2011 and December 2022, with two or more available transthoracic echocardiograms that were at least 6 months apart and conducted before aortic valve replacement. Moderate aortic stenosis was defined as: aortic valve area (AVA) measured by continuity equation >1.0 and ≤1.5 cm^2, peak jet velocity ≥3.0 and <4.0 m/s and mean transvalvular gradient ≥20 and <40 mm Hg. Patients with subvalvular aortic stenosis and congenital heart disease were excluded, but patients with a bicuspid valve were included. Patients were included regardless of left ventricular ejection fraction or stroke volume. The local research ethics committee approved this study, and the requirement for informed consent was waived (METc 2022/545).

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Data collection

From each patient, measurements from all available echocardiograms conducted after December 2011 were extracted from the electronic medical records. In case the patient underwent aortic valve replacement during follow-up, only echocardiograms conducted before aortic valve replacement were collected. We excluded echocardiograms conducted before December 2011 to reduce variability in image and reporting quality and completeness. Baseline ($T = 0$) was defined as the first echocardiogram meeting the definition of concordant moderate aortic stenosis as described above.[9] Echocardiograms with no or mild aortic stenosis were therefore coded as a negative time compared with baseline. All echocardiograms were performed on GE Healthcare Vivid™ series ultrasound machines by qualified sonographers and supervised by echocardiography cardiologists.

Abnormal values for echocardiographic variables were defined according to the echocardiographic guidelines regarding quantification of chamber dimensions, diastolic function and assessment of the right heart.[10–12] AVA was calculated with the continuity equation using the velocity-time integral and the left ventricular outflow tract diameter (LVOTd). As the LVOTd has a quadratic effect on the AVA, differences in the AVA within the same patient may result from measurement error in the LVOTd. As the LVOTd is assumed constant over time within the same patient, we obtained the median LVOTd of all echocardiograms of each patient. The median LVOTd was subsequently used to compute the AVA.

In addition, we collected baseline demographic data, medical history, medication use, and laboratory values. Time of aortic valve replacement was recorded during follow-up and included both surgical and transcatheter aortic valve replacement. The decision for aortic valve replacement was based on the presence of severe aortic stenosis and symptoms or reduced left ventricular function, at the discretion of the Heart Team. Patients with moderate aortic stenosis could undergo valve replacement in case an indication for concomitant cardiac surgery existed. In addition, clinical outcomes, such as mortality and heart failure hospitalizations, were recorded.

Statistical analysis

Continuous variables are presented as median (25th and 75th percentile) unless stated otherwise, and categorical variables are reported as number (percentage). Missing data were assessed and are reported as the number of complete observations per variable at baseline.

Longitudinal changes in echocardiographic variables were modelled using linear mixed-effects models. To account for correlation and non-independence of echocardiographic measurements within the same patient, a random intercept was included for each patient. Time was included as a restricted cubic spline term to accommodate non-linear patterns over time. Estimated trajectories of echocardiographic changes over time were visualized using the R package *ggeffects*.[13]

To define rapid progression of aortic stenosis, we first fitted a linear mixed-effect model with AVA as the outcome variable and time as a linear term, including a random intercept and slope for each patient.[14] From this model, we extracted patient-specific slopes, indicating the rate of decline in AVA per year, and computed the median rate of decline. Rapid and slow progression were subsequently defined as a progression rate below or above the median rate of decline, respectively. In addition, we evaluated the correlation between progression rate of AVA with progression rates of left ventricular mass index (LVMI), relative wall thickness (RWT), left atrial volume index (LAVI), and ratio of early mitral inflow velocity to average early diastolic tissue velocity (E/e'), using Pearson correlation. The progression rates of these echocardiographic variables were obtained in an analogous manner.

To evaluate the association of rapid progression of aortic stenosis on the rate of change in myocardial structure and function, rapid progression was included in the models as an interaction effect with time. The differences between slow and rapid progressors were assessed using contrast analyses at 5 years before baseline, at baseline, and 5 years after baseline.

Finally, we evaluated factors associated with rapid progression of LVMI by comparing characteristics of slow and rapid progressors. We also assessed the association between slow and rapid progression of LVMI with clinical outcomes, including aortic valve replacement, all-cause mortality, and heart failure hospitalizations. Aortic valve replacement and heart failure hospitalization were analysed using competing risk analysis with all-cause mortality as competing risk, and survival differences between groups were compared using Gray's tests.

All statistical analyses were performed in R version 4.5 (R Core Team, 2026) and two-sided *P*-values <.05 were considered statistically significant.

Results

In total, 467 patients with moderate aortic stenosis were included in this analysis, with 2806 available echocardiograms (median number of six per patient).[14] The median age was 69 years (59–76) and 36% of patients were female. At the last available echocardiogram, 202 patients (45%) had non-severe aortic stenosis, and 219 patients (47%) underwent aortic valve replacement over a median follow-up period of 4.3 years. The median rate of decline in AVA was 0.08 (0.06–0.10) cm^2 per year, and patients with a rate of decline in AVA >0.08 cm^2 per year were classified as rapid progressors.

Patients with rapid progression were older, had a higher BMI, and more often had hypertension, atrial fibrillation, and chronic kidney disease. In addition, rapid progressors more often had severe aortic stenosis at the last echocardiogram, and had a higher proportion of aortic valve replacement than slow progressors (*Table 1*). Characteristics of patients undergoing aortic valve replacement are depicted in Supplementary Table S1, showing that patients undergoing aortic valve replacement were on average in the severe aortic stenosis range at the last available echocardiogram.

Changes in structural and functional echocardiographic variables over time

Figure 1 and Supplementary Figure S1 show the trajectories of echocardiographic variables over time in the overall cohort. At baseline, aortic stenosis severity was moderate on average. Aortic valve mean gradient became greater than 40 mm Hg at 6.2 years after the onset of moderate aortic stenosis on average, and an AVA <1.0 cm^2 was reached at 4.0 years after baseline. LVMI showed a linear increase over time and became abnormally elevated at 4.5 years after the onset of moderate aortic stenosis. In contrast, RWT became abnormally elevated >0.42 at an average of 7.6 years before the onset of moderate aortic stenosis. E/e' became abnormal at 5.8 years before baseline and LAVI increased >34 ml/m^2 at 1.2 years before the onset of moderate aortic stenosis. TAPSE did not show a substantial change over time. RV peak pressure became mildly abnormal (≥35 mm Hg) at 1.4 years before the onset of moderate aortic stenosis. The chronological order of myocardial changes during the progression of aortic stenosis is summarized in *Figure 2*.

Patients with reduced baseline LVEF demonstrated increased LVMI, LAVI, and worse TAPSE at onset of moderate aortic stenosis, which persisted when aortic stenosis progressed (Supplementary Figure S2). Progression of aortic valve parameters was not significantly different between patients with reduced and preserved LVEF.

Association of slow and rapid progression with changes in structural and functional echocardiographic parameters over time

We found a weak correlation between rate of valvular progression and rates of progression of LVMI ($r = 0.22$, $P < .001$), LAVI ($r = 0.22$, $P < .001$), E/e' ($r = 0.16$, $P < .001$), and RWT ($r = 0.19$, $P < .001$) (Supplementary Figure S3).

Figure 3 and Supplementary Figure S4 show the trajectories of echocardiographic variables over time by rate of valvular progression (slow vs rapid progression). Patients with rapid valvular progression had higher LVMI ($P < .01$), E/e' ($P < .05$), LAVI ($P < .001$), and RV peak pressure ($P < .01$) at 5 years, compared with patients with slow valvular progression.

Table 1 Patient characteristics of slow and rapid valvular progressors at the baseline echocardiogram

	N	Slow *N* = 234[a]	Rapid *N* = 233[a]	*P*-value[b]
Demographics				
Age at diagnosis	467	67 (53, 76)	69 (63, 75)	.035
Gender	467			.11
Female		92 (39%)	75 (32%)	
Male		142 (61%)	158 (68%)	
BMI (kg/m^2)	467	26.6 (23.5, 30.3)	28.1 (24.6, 31.5)	.007
BMI >30 kg/m^2	467	61 (26%)	81 (35%)	.041
Medical history				
Bicuspid aortic valve	467	50 (21%)	28 (12%)	.007
Hypertension	467	130 (56%)	152 (65%)	.032
Diabetes	467	53 (23%)	54 (23%)	.9
Atrial fibrillation	467	28 (12%)	49 (21%)	.008
Chronic kidney disease (eGFR <60)	467	12 (5.1%)	32 (14%)	.001
Chronic dialysis	467	5 (2.1%)	20 (8.6%)	.002
Diabetes mellitus	467			>.9
No		181 (77%)	179 (77%)	
Type 1 diabetes		4 (1.7%)	3 (1.3%)	
Type 2 diabetes		49 (21%)	51 (22%)	
Coronary artery disease	467	46 (20%)	55 (24%)	.3
Heart failure	467	18 (7.7%)	16 (6.9%)	.7
COPD/asthma	467	39 (17%)	34 (15%)	.5
Medication				
Beta-blocker	467	91 (39%)	105 (45%)	.2
ACE-inhibitors	467	67 (29%)	78 (33%)	.3
MRA	467	5 (2.1%)	16 (6.9%)	.014
Statin	467	101 (43%)	112 (48%)	.3
Oral anticoagulant	467	23 (9.8%)	58 (25%)	<.001
Laboratory values				
Haemoglobin (mmol/l)	387	8.40 (7.60, 9.20)	8.40 (7.50, 9.20)	.6
BUN (mg/dl)	386	18 (14, 23)	18 (15, 24)	.3
NT-proBNP (ng/l)	104	337 (136, 1231)	309 (149, 768)	.7
Echocardiography				
LVEF (%)	467	57.5 (55.0, 60.0)	57.5 (55.0, 60.0)	.2
LVEF category	467			.14
<50%		16 (6.8%)	25 (11%)	
≥50%		218 (93%)	208 (89%)	
SVI (ml/m^2)	462	45 (39, 50)	46 (40, 52)	.3
Moderate/severe MR	467	6 (2.6%)	17 (7.3%)	.018
Moderate/severe TR	461	5 (2.2%)	12 (5.2%)	.085
Moderate/severe AR	465	16 (6.8%)	19 (8.2%)	.6
AVA (cm^2)	467	1.16 (1.08, 1.27)	1.24 (1.12, 1.34)	<.001
Mean gradient (mm Hg)	467	24.5 (22.4, 28.3)	25.1 (22.7, 28.3)	.4

Continued

Table 1 ***Continued***

	N	Slow *N* = 234[a]	Rapid *N* = 233[a]	*P*-value[b]
Peak jet velocity (m/s)	467	3.30 (3.10, 3.50)	3.30 (3.10, 3.50)	.6
Aortic stenosis progression and outcomes				
Rate of decline in AVA (cm^2/year)	467	−0.06 (−0.07, −0.04)	−0.10 (−0.12, −0.09)	<.001
AS severity at last echo	445			.005
High-gradient severe AS		49 (22%)	79 (36%)	
Low-flow low-gradient AS		24 (11%)	26 (12%)	
Non-severe AS		118 (53%)	84 (38%)	
Normal-flow low-gradient AS		33 (15%)	32 (14%)	
Mean gradient at last echo	447			.009
>40 mm Hg		66 (29%)	92 (41%)	
20–40 mm Hg		158 (71%)	131 (59%)	
AVR	467	99 (42%)	120 (52%)	.047
Number of echocardiograms	467	6 (4, 8)	5 (3, 7)	<.001
Follow-up duration (years)	467	4.79 (2.49, 7.79)	3.90 (2.30, 6.72)	.051

ACE, angiotensin-converting enzyme; AR, aortic regurgitation; AS, aortic stenosis; AVA, aortic valve area; AVR, aortic valve replacement; BMI, body mass index; BUN, blood urea nitrogen; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; LVEF, left ventricular ejection fraction; MR, mitral regurgitation; MRA, mineralocorticoid receptor antagonist; TR, tricuspid regurgitation.
[a]Median (Q1, Q3); *n* (%).
[b]Wilcoxon rank sum test; Pearson's χ^2 test.

Determinants of rapid progression of LVMI and association with clinical outcomes

Characteristics of patients with slow and rapid progression of LVMI are reported in Supplementary Table S2. Patients with rapid progression of LVMI were older, more often male, and more often had a BMI >30 kg/m^2, atrial fibrillation, coronary artery disease, and heart failure. Patients with rapid progression of LVMI had a higher 5-year rate of heart failure admissions than slow progressors (6.3% vs. 2.4%, $P = .035$), but the rates of aortic valve replacement or mortality were similar (*Figure 4*).

Discussion

To the best of our knowledge, this is one of the first studies to describe the actual evolution of myocardial changes accompanying the progression of moderate aortic stenosis. The main findings of this study were: (i) along the course of the progression of aortic stenosis, left atrial dilatation, concentric remodelling, and impaired relaxation occurred before or at the onset of moderate aortic stenosis, whereas significant left ventricular concentric hypertrophy only developed when aortic stenosis became severe, (ii) rapid progression of aortic stenosis was weakly associated with enhanced myocardial remodelling, and (iii) the progression of myocardial changes and valvular stenosis is driven by the same comorbidities or risk factors but these processes are not necessarily causally related to each other.

Evolution of myocardial changes during aortic stenosis progression

Our findings are not completely in line with the theoretical model as described in the cardiac damage staging system, suggesting that cardiac changes initiate in the left ventricle and sequentially propagate backwards towards the right ventricle.[6] However, it should be noted that this system was developed in and for patients with severe aortic stenosis. Our data suggest that impaired relaxation and wall thickening occurred early in the course of progression. This was accompanied by left atrial dilatation, which reflects chronically elevated left atrial pressures and became significantly elevated before aortic stenosis became severe.[15,16]

Left ventricular hypertrophy in response to chronic outflow obstruction is considered a hallmark of aortic stenosis. However, the hypertrophic response is highly variable and it has been shown in cardiac magnetic resonance studies that the degree of left ventricular hypertrophy does not correlate well with the severity of aortic stenosis.[17] We observed a clearly increasing trend of LVMI over time, but guideline-defined concentric hypertrophy only occurred when aortic stenosis became severe. In contrast, a different study by Ito et al demonstrated that increased LVMI occurred several years before the onset of severe aortic stenosis.[18] This may be explained by the fact that Ito et al only included patients who developed severe aortic stenosis—defined as an AVA below 1.0 cm^2—and then assessed echocardiographic changes during the time before the onset of severe aortic stenosis.[18] In our cohort, not all patients progressed towards severe aortic stenosis and also progressed at different rates. Although all patients started with concordant moderate aortic stenosis, this may have resulted in some patients developing low-flow, low-gradient aortic stenosis.

Rapid valvular progression of aortic stenosis is weakly associated with more aggressive myocardial changes

The median rate of decline in AVA in our cohort was 0.08 cm^2/year, which is identical to the average rate, reported in a large meta-analysis.[19] We did not observe a strong association between rapid valvular progression of aortic stenosis and the rate of progression of

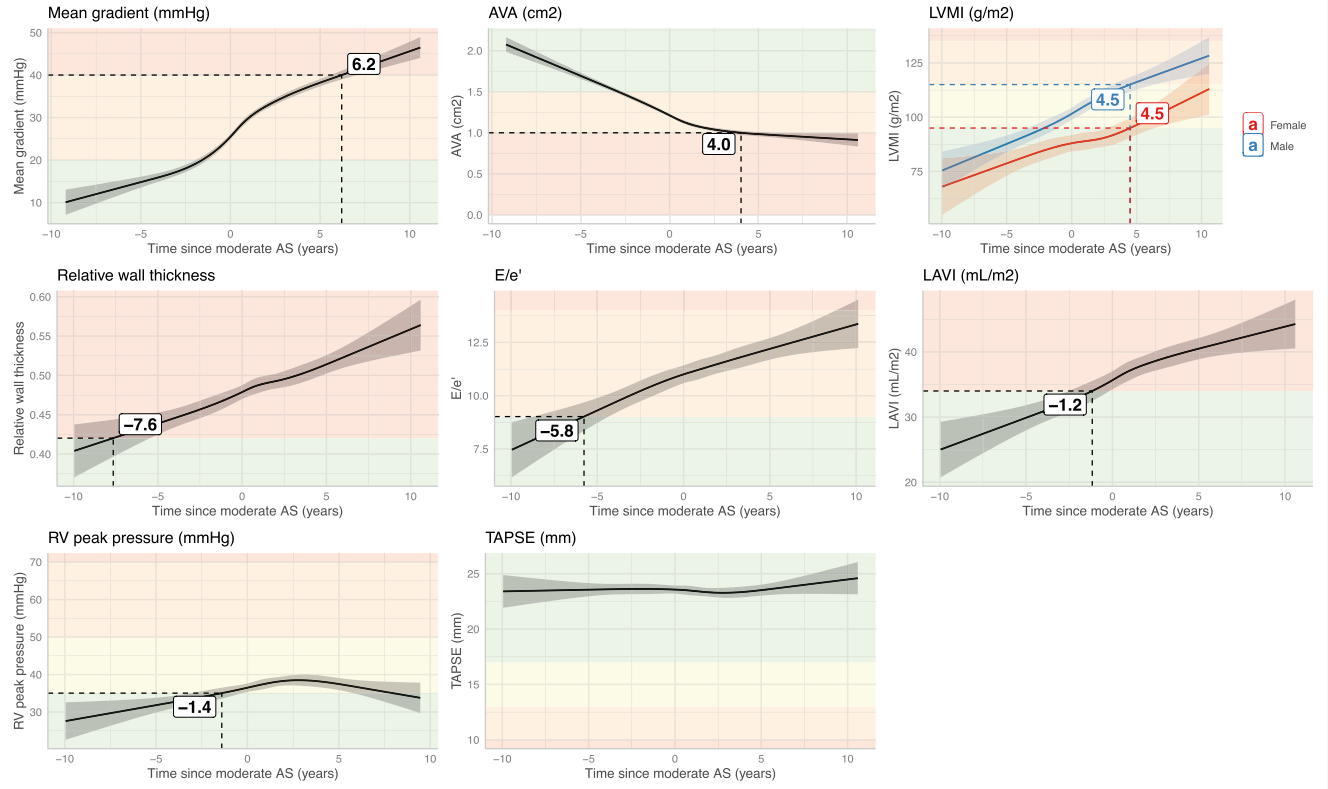


Figure 1 Changes in echocardiographic variables over time. Background colours indicate normal values (green), mildly abnormal (yellow), moderately abnormal (orange), and severely abnormal (red). Abbreviations: AVA, aortic valve area; e´, early diastolic tissue velocity; *E/e´*, ratio of early mitral inflow velocity to average early diastolic tissue velocity; IVSd, end-diastolic interventricular septum thickness; LAVI, left atrial volume index; LVEDD, left ventricular end-diastolic diameter; LVMI, left ventricular mass index; PWd, end-diastolic posterior wall thickness; RV, right ventricle; SVI, stroke volume index

myocardial changes. We hypothesize that while valvular and myocardial progression may share common risk factors, they are not necessarily causally related to each other, which may have implications for future treatment. Indeed, our findings imply that replacing the aortic valve alone may not be sufficient, as not all myocardial changes can be solely attributed to aortic stenosis and may not fully recover after valve replacement. Furthermore, rapid progression of LVMI was associated with higher risk of heart failure hospitalizations, which emphasizes the importance of incorporating the myocardium in the management of aortic stenosis. A holistic approach is likely required, including medical therapy targeted at the myocardium, both during progression of aortic stenosis and after valve replacement. On the other hand, earlier valve replacement may avoid the detrimental effects of severe aortic stenosis on the myocardium. Current ongoing trials investigating the benefit of valve replacement in moderate aortic stenosis will provide more evidence regarding this hypothesis (Management of Moderate Aortic Stenosis by Clinical Surveillance or TAVR [NCT04889872] and Evolut™ EXPAND TAVR II Pivotal Trial [NCT05149755]).

Comorbidities are an important driver of both myocardial and valvular progression

Somewhat unexpectedly, left atrial volume index, relative wall thickness and mitral annular velocities showed abnormal values at or even before the onset of moderate aortic stenosis. A recent analysis from the Atherosclerosis Risk in Communities (ARIC) cohort investigated the alterations in cardiac structure and functions during progression of aortic stenosis and found similar results compared with our study, namely that left ventricular mass and diastolic dysfunction worsen over time, and that changes occur before the onset of significant aortic stenosis.[20] Our study confirms and complements this analysis by including more measurements per patient. Also, patients with atrial fibrillation, heart failure, and previous myocardial infarction were excluded from the ARIC sub-analysis, which may have biased the findings, as these patients often develop low-gradient aortic stenosis.

It seems unlikely that these cardiac structural and functional abnormalities develop in the absence of a significant hemodynamic stenosis without another cause. They may therefore be related to comorbidities, such as coronary artery disease, hypertension or atrial fibrillation that influence hypertrophy, diastolic function as well as valvular progression. Indeed, in patients with mild aortic stenosis, comorbidities are largely related to the extent of cardiac damage, rather than the magnitude of the peak jet velocity.[21] This was also confirmed by our finding that patients with rapid progression of LVMI had more comorbidities, which were highly similar to the risk factors for rapid valvular progression.[14]

Limitations

Several important limitations of this study should be addressed. This was a single-centre, retrospective cohort study with a relatively small sample size. Also, this study was conducted in a tertiary referral centre

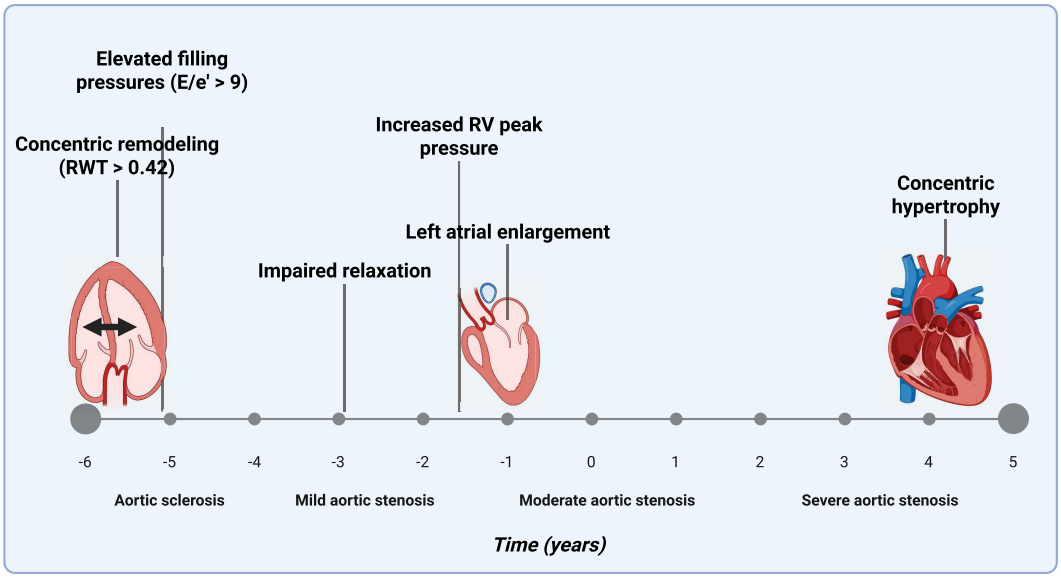


Figure 2 Summary of myocardial changes during the progression of aortic stenosis, depicting the approximate time relative to onset of moderate aortic stenosis. Abbreviations: LV, left ventricle; RV, right ventricle; *E/e´*, ratio of early mitral inflow velocity to average early diastolic tissue velocity

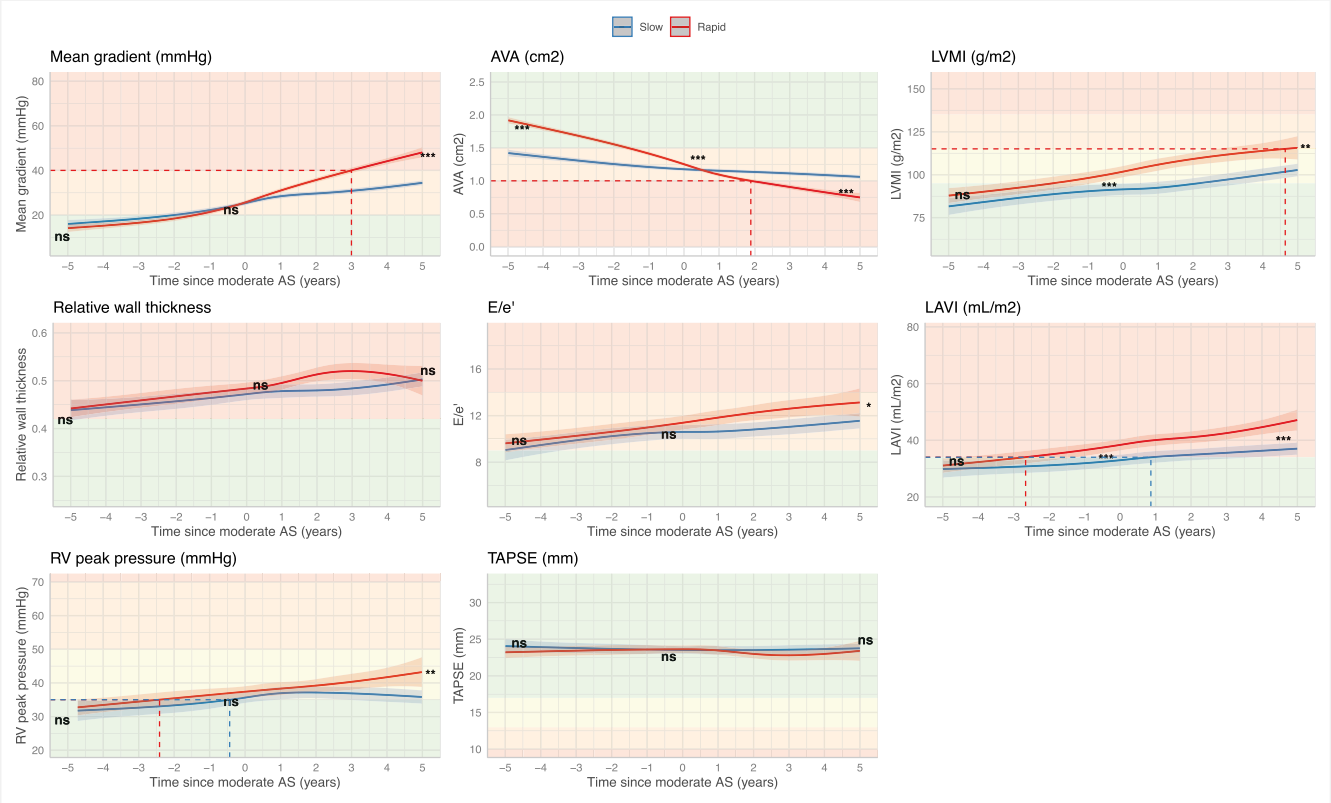


Figure 3 Unadjusted trajectories of echocardiographic variables over time in slow and rapid aortic stenosis progressors (defined as decrease in AVA >0.08 cm^2/year). Background colours indicate normal values (green), mildly abnormal (yellow), moderately abnormal (orange), and severely abnormal (red). Abbreviations: AVA, aortic valve area; *e´*, early diastolic tissue velocity; *E/e´*, ratio of early mitral inflow velocity to average early diastolic tissue velocity; IVSd, end-diastolic interventricular septum thickness; LAVI, left atrial volume index; LVEDD, left ventricular end-diastolic diameter; LVMI, left ventricular mass index; PWd, end-diastolic posterior wall thickness; RV, right ventricle; SVI, stroke volume index

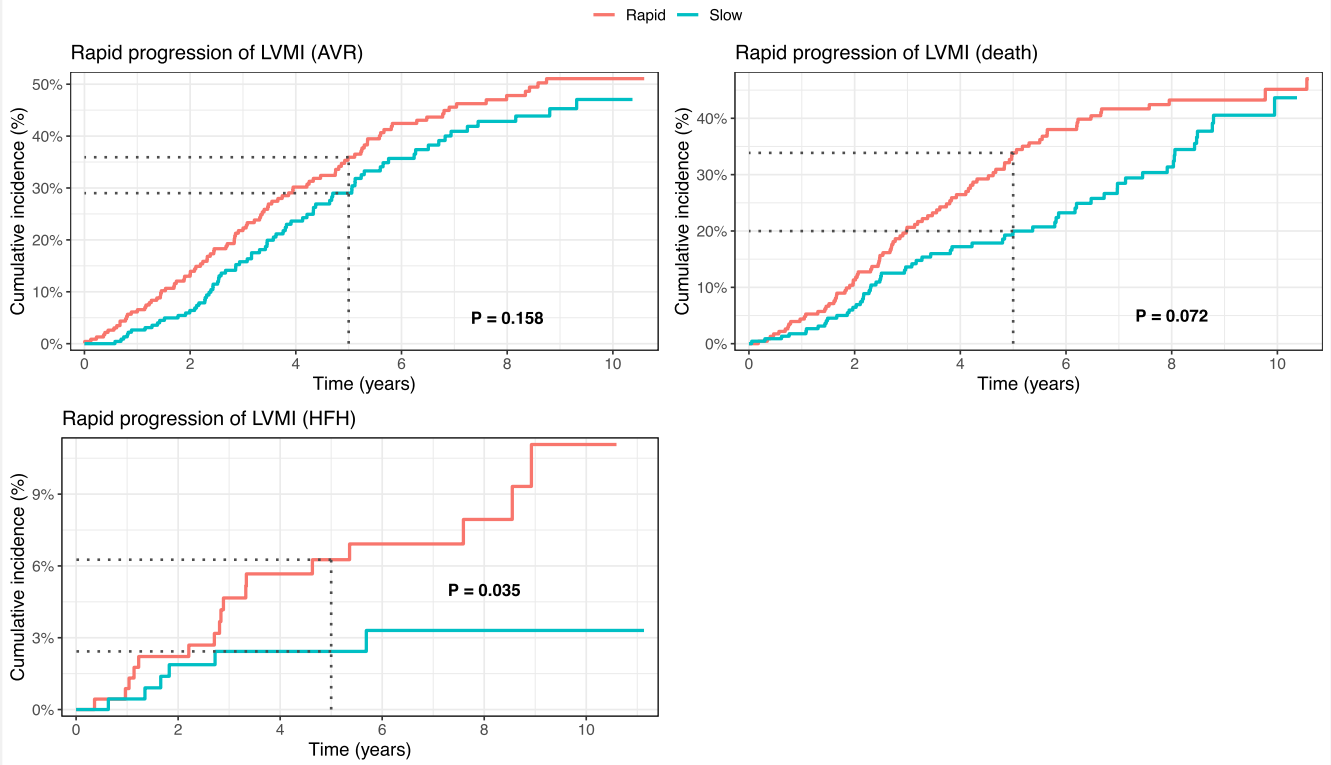


Figure 4 Cumulative incidence of aortic valve replacement (AVR), all-cause mortality and heart failure hospitalizations (HFH) in patients with slow and rapid progression of left ventricular mass index (LVMI). *P*-values indicate Gray's test

and may therefore not generalize to other settings. In addition, we used echocardiographic measurements from clinical echocardiography reports and did not evaluate echocardiograms in a central core laboratory. Also, we did not assess important markers of left ventricular systolic function, such as global longitudinal strain or left ventricular ejection fraction, or other sensitive markers of diastolic function such as left atrial strain, or valvuloarterial impediance, as these markers were not often quantified in the echocardiographic reports and hence not available. Although echocardiography is the standard method for the monitoring of aortic stenosis, other imaging modalities such as cardiac magnetic resonance imaging would have allowed more detailed assessment of myocardial structure and function, and CT and dobutamine stress echocardiography would have provided more insight into the severity of aortic stenosis. As this was a clinical cohort, these investigations were only performed if clinically indicated and not routinely, and we therefore lack information on the specific progression of changes in low-flow, low-gradient aortic stenosis. Finally, we did not consider the influence of medical therapy on progression of myocardial changes as these are difficult to assess in a non-randomized cohort.

Conclusion

This hypothesis-generating study showed that specific myocardial changes occurred at different stages of aortic stenosis progression. In the early phase, increases in left-sided diastolic pressures and wall thickness, impaired relaxation and increased left atrial volume were observed. Significant concentric hypertrophy is likely to occur only once aortic stenosis becomes severe. Rapid valvular progression of aortic stenosis was weakly correlated with progression of myocardial changes. Patients with more comorbidities demonstrated faster myocardial changes. We hypothesize that these comorbidities, such as hypertension, obesity, and atrial fibrillation, may be an important driver of both myocardial changes and valvular progression in aortic stenosis.

Author contributions

Constantijn Sebastiaan Venema (Conceptualization, Formal analysis, Investigation, Methodology, Writing—original draft [lead]), Kees H. Van Bergeijk (Methodology, Writing—review & editing [supporting]), Kyriakos Panaou (Formal analysis, Methodology, Writing—review & editing [supporting]), Jan A. Krikken (Data curation, Methodology, Writing—review & editing [supporting]), Teresa Trenkwalder (Writing—review & editing [supporting]), Michael Joner (Writing—review & editing [supporting]), Ify R. Mordi (Writing—review & editing [supporting]), Chim C. Lang (Writing—review & editing [supporting]), Nicolas Girerd (Writing—review & editing [supporting]), Marie-Annick Clavel (Writing—review & editing [supporting]), Erik Lipsic (Conceptualization, Investigation, Methodology, Supervision, Writing—review & editing [supporting]), Adriaan A. Voors (Conceptualization, Investigation, Supervision, Writing—review & editing [supporting]), and Joanna J. Wykrzykowska (Conceptualization, Investigation, Methodology, Supervision, Writing—review & editing [supporting])

Supplementary data

Supplementary data are available at *European Heart Journal – Valvular and Structural Heart Disease* online.

Declarations

Data Availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Disclosure of Interest

M.A.C. received funding from Edwards Lifesciences and Novartis for CT core laboratory analyses and research grant from Medtronic, Edwards Lifesciences, Rednvia, and Pi-Cardia with no direct personal compensation and unrelated to the present work. The employer of AAV (UMCG) has received consultancy fees and/or grant support from Anacardio, AstraZeneca, Bayer, Boehringer Ingelheim, BMS, Corteria, Cytokinetics, EliLilly, Merck, Moderna, Novartis, Novo Nordisk, Roche Diagnostics, and Salubrisbio. The employer of JJW (UMCG) has received consultancy and speaker fees from Medtronic, Abbott, Edwards, Meril Life, and Boston Scientific. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

Funding

Not applicable.

Ethical Approval

Ethical Approval was not required.

Pre-registered Clinical Trial Number

None supplied.

References

1. Mengi S, Januzzi JL Jr, Cavalcante JL, Avvedimento M, Galhardo A, Bernier M, *et al.* Aortic stenosis, heart failure, and aortic valve replacement. *JAMA Cardiol* 2024;**9**:1159–68. https://doi.org/10.1001/jamacardio.2024.3486
2. Musa TA, Treibel TA, Vassiliou VS, Captur G, Singh A, Chin C, *et al.* Myocardial scar and mortality in severe aortic stenosis: data from the BSCMR valve consortium. *Circulation* 2018;**138**:1935–47. https://doi.org/10.1161/CIRCULATIONAHA.117.032839
3. Thornton GD, Vassiliou VS, Musa TA, Aziminia N, Craig N, Dattani A, *et al.* Myocardial scar and remodelling predict long-term mortality in severe aortic stenosis beyond 10 years. *Eur Heart J* 2024;**45**:2019–22. https://doi.org/10.1093/eurheartj/ehae067
4. Chin CWL, Everett RJ, Kwiecinski J, Vesey AT, Yeung E, Esson G, *et al.* Myocardial fibrosis and cardiac decompensation in aortic stenosis. *JACC Cardiovasc Imaging* 2017;**10**:1320–33. https://doi.org/10.1016/j.jcmg.2016.10.007
5. 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: the EVOLVED randomized clinical trial. *JAMA* 2025;**333**:213–21. https://doi.org/10.1001/jama.2024.22730
6. Généreux P, Pibarot P, Redfors B, Mack MJ, Makkar RR, Jaber WA, *et al.* Staging classification of aortic stenosis based on the extent of cardiac damage. *Eur Heart J* 2017;**38**:3351–8. https://doi.org/10.1093/eurheartj/ehx381
7. Abdelfattah OM, Jacquemyn X, Sá MP, Jneid H, Sultan I, Cohen DJ, *et al.* Cardiac damage staging predicts outcomes in aortic valve stenosis after aortic valve replacement: meta-analysis. *JACC Adv* 2024;**3**:100959. https://doi.org/10.1016/j.jacadv.2024.100959
8. Omar W, Généreux P. The staging of cardiac damage for aortic stenosis: a review. *Struct Heart* 2025;**9**:100370. https://doi.org/10.1016/j.shj.2024.100370
9. 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. *Eur Heart J* 2025;**46**:4635–736. https://doi.org/10.1093/eurheartj/ehaf194
10. Mukherjee M, Rudski LG, Addetia K, Afilalo J, D'Alto M, Freed BH, *et al.* Guidelines for the echocardiographic assessment of the right heart in adults and special considerations in pulmonary hypertension: recommendations from the American society of echocardiography. *J Am Soc Echocardiogr* 2025;**38**:141–86. https://doi.org/10.1016/j.echo.2025.01.006
11. Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, *et al.* Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *J Am Soc Echocardiogr* 2015;**28**:1–39.e14. https://doi.org/10.1016/j.echo.2014.10.003
12. Nagueh SF, Appleton CP, Gillebert TC, Marino PN, Oh JK, Smiseth OA, *et al.* Recommendations for the evaluation of left ventricular diastolic function by echocardiography. *J Am Soc Echocardiogr* 2009;**22**:107–33. https://doi.org/10.1016/j.echo.2008.11.023
13. Lüdecke D. Ggeffects: tidy data frames of marginal effects from regression models. *J Open Source Softw* 2018;**3**:772. https://doi.org/10.21105/joss.00772
14. Venema CS, van Bergeijk KH, Hadjicharalambous D, Andreou T, Tromp J, Staal L, *et al.* Prediction of the individual aortic stenosis progression rate and its association with clinical outcomes. *JACC Adv* 2024;**3**:100879. https://doi.org/10.1016/j.jacadv.2024.100879
15. Popescu BA, Beladan CC, Nagueh SF, Smiseth OA. How to assess left ventricular filling pressures by echocardiography in clinical practice. *Eur Heart J Cardiovasc Imaging* 2022;**23**:1127–9. https://doi.org/10.1093/ehjci/jeac123
16. Tighe DA, Aurigemma GP. C'est LAVi: what left atrial dilatation tells us about diastolic function in aortic stenosis. *Circ Cardiovasc Imaging* 2016;**9**:e005683. https://doi.org/10.1161/CIRCIMAGING.116.005683
17. Dweck MR, Joshi S, Murigu T, Gulati A, Alpendurada F, Jabbour A, *et al.* Left ventricular remodeling and hypertrophy in patients with aortic stenosis: insights from cardiovascular magnetic resonance. *J Cardiovasc Magn Reson* 2012;**14**:50. https://doi.org/10.1186/1532-429X-14-50
18. Ito S, Miranda WR, Nkomo VT, Lewis BR, Oh JK. Sex differences in LV remodeling and hemodynamics in aortic stenosis: sex-specific criteria for severe stenosis? *JACC Cardiovasc Imaging* 2022;**15**:1175–89. https://doi.org/10.1016/j.jcmg.2022.02.007
19. Willner N, Prosperi-Porta G, Lau L, Nam Fu AY, Boczar K, Poulin A, *et al.* Aortic stenosis progression: a systematic review and meta-analysis. *JACC Cardiovasc Imaging* 2023;**16**:314–28. https://doi.org/10.1016/j.jcmg.2022.10.009
20. Shelbaya K, Claggett B, Dorbala P, Skali H, Solomon SD, Matsushita K, *et al.* Alterations in cardiac structure and function associated with sub-severe aortic stenosis progression: the ARIC study. *J Am Heart Assoc* 2026;**15**:e045047. https://doi.org/10.1161/JAHA.125.045047
21. Dahl JS, Julakanti R, Ali M, Scott CG, Padang R, Pellikka PA. Cardiac damage in early aortic stenosis: is the valve to blame? *JACC Cardiovasc Imaging* 2024;**17**:1031–40. https://doi.org/10.1016/j.jcmg.2024.05.003