

Myocardial fibrosis in bicuspid vs tricuspid severe aortic valve stenosis: a cardiac magnetic resonance study

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Received 19 January 2026; revised 31 March 2026; accepted after revision 8 April 2026; online publish-ahead-of-print 28 April 2026

Abstract

Background and Aims

Myocardial fibrosis is common in aortic valve stenosis (AS) and has been proposed as a marker in the timing of aortic valve replacement. We aimed to explore differences in the prevalence and degree of myocardial fibrosis between patients with severe bicuspid AS (BAV-AS) and tricuspid AS (TAV-AS), as potential differences may have implications for its clinical implementation.

Methods

Cardiac magnetic resonance was performed in 80 patients with severe symptomatic AS planned to undergo aortic valve replacement (48% bicuspid valve, 74% male, mean age 69 ± 11 years) with evaluation of native T1, extracellular volume fraction (ECV%), and late gadolinium enhancement (LGE).

Results

When comparing patients with TAV-AS to those with BAV-AS and adjusting for sex, age, and aortic peak velocity, there were no differences in native T1 [mean difference 10 ms; 95% confidence interval (CI) -5 to 25 ; $P = .18$], ECV% (mean difference 1.2; 95% CI -2 to 2.7 ; $P = .10$), nor the prevalence of LGE (OR 2.6; 95% CI $.7-11$; $P = .17$). However, BAV-AS patients had a 1.6-percentage point higher LGE volume percentage compared with TAV-AS patients (95% CI $.02-3.3$; $P = .047$).

Conclusions

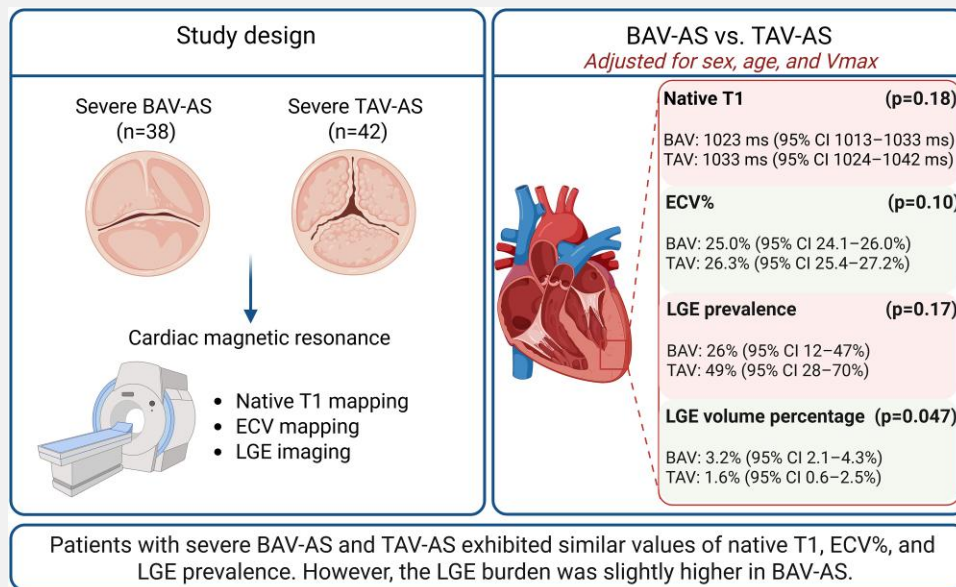
Patients with severe BAV-AS and TAV-AS exhibited similar values of native T1, ECV%, and LGE prevalence. However, the LGE burden was slightly higher in BAV-AS.

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Graphical Abstract



BAV-AS, bicuspid aortic valve stenosis; ECV%, extracellular volume fraction; LGE, late gadolinium enhancement; TAV-AS, tricuspid aortic valve stenosis; Vmax, aortic peak velocity created with BioRender.

Keywords Aortic valve stenosis • Bicuspid aortic valve • Myocardial fibrosis • Cardiac magnetic resonance • Native T1 mapping • ECV mapping

Introduction

Myocardial fibrosis is key in the development of heart failure among patients with aortic valve stenosis (AS).¹ The natural history of AS is characterized by left ventricular (LV) maladaptation to chronic pressure overload with progressive LV hypertrophy, myocyte apoptosis, and fibrosis, ultimately leading to LV diastolic and systolic dysfunction.^{2,3} The presence and extent of myocardial fibrosis estimated with cardiovascular magnetic resonance (CMR) have been associated with impaired outcomes in patients with AS, including an increased risk of cardiovascular events and mortality.^{4,5} Therefore, myocardial fibrosis has been suggested as an indicator of disease severity and may play a role in guiding the timing of aortic valve replacement (AVR).

While only ~1% of the population is born with a bicuspid aortic valve (BAV) rather than a tricuspid aortic valve (TAV),⁶ they represent up to 50% of patients undergoing isolated surgical AVR for severe AS.^{7–9} There are notable differences between patients with bicuspid aortic stenosis (BAV-AS) and tricuspid aortic stenosis (TAV-AS), including symptom onset, risk profiles, and pathogenetic mechanisms.^{10–12} Patients with BAV may face a chronically elevated afterload from early in life⁶ due to a combination of eccentric valvular opening and impaired elasticity of the ascending aorta. Further, studies have shown that patients with BAV may develop impaired LV function even before valvular dysfunction becomes apparent.¹³ Conversely, patients with TAV-AS are older, have more comorbidities, and exhibit more indicators of cardiac damage compared with BAV-AS patients.¹⁴ Consequently, differences in the development of myocardial fibrosis between patients with BAV-AS and TAV-AS are likely but have not been studied. Understanding these potential differences is essential before implementing myocardial fibrosis as a marker in clinical decision-making.

In this cross-sectional CMR study, we wished to compare the prevalence and degree of myocardial fibrosis in patients with severe BAV-AS

and TAV-AS referred for AVR without ischaemic heart disease and with a left ventricular ejection fraction (LVEF) ≥ 50%, assessed with native T1 mapping, extracellular volume (ECV) mapping, and late gadolinium enhancement (LGE). Secondary aims were to examine (i) correlations between myocardial fibrosis markers and other parameters of disease severity, and (ii) whether valve morphology (i.e. BAV-AS or TAV-AS) modifies these relationships.

Methods

Study design and population

This was a cross-sectional study with prospective inclusion of patients with severe BAV-AS and TAV-AS. Patients with severe AS were included at the University Hospital of Copenhagen, Rigshospitalet, between July 2021 and August 2024 as part of the study *Effects of Aortic Valve Replacement on Myocardial T1 values in Severe Aortic Valve Stenosis (FIBROTIC)* (NCT05404100). The population has previously been described.¹⁵ All patients were identified and subsequently included through the Heart Team conferences for those referred for AVR, either as surgical AVR or transcatheter AVR. Patients with BAV-AS and TAV-AS were included in an approximate 1:1 ratio. Inclusion criteria were age ≥18 years, severe AS defined by aortic peak velocity (Vmax) >4 m/s and/or aortic mean gradient >40 mmHg, and acceptance for AVR. Exclusion criteria were an LVEF <50% on echocardiography, ischaemic heart disease (i.e. previous or planned primary coronary intervention or coronary artery bypass grafting), moderate or severe left-sided valvular heart disease other than AS, permanent atrial fibrillation, pregnancy, severe claustrophobia, metallic implants non-compatible with CMR, and pacemaker or implantable cardioverter defibrillator.

The study complied with the Declaration of Helsinki and was approved by the Regional Ethics Committee for the Capital Region in Denmark (H-20029458). Written informed consent was secured from all participants.

Clinical data

The medical history was assessed through a combination of questionnaires and medical charts. Aortic valve morphology was assessed based on available echocardiographic scans, computed tomography (CT) scans, and CMR scans. BAV morphology was categorized according to the Sievers classification.¹⁶ Baseline characteristics included symptomatic status, EuroSCORE II,¹⁷ hypertension, diabetes, cancer, atrial fibrillation, stroke, sleep apnoea, peripheral artery disease, chronic obstructive lung disease, and medication usage. Further, medical records were carefully reviewed for confirmed or suspected cardiomyopathies. Echocardiographic and CT data were derived from the standard preoperative examinations. The aortic valve calcium score was divided by 1200 in females and 2000 in males to obtain an aortic valve calcium ratio. Blood samples were ideally collected on the same day as the CMR examination or as close to that day as possible and always prior to AVR. Blood pressure measurements were taken in the supine position after the CMR examination.

Cardiac magnetic resonance

CMR examinations were performed on a Siemens MAGNETOM Aera 1.5 Tesla Scanner, equipped with Syngo MR E11 software and without upgrade during the study. The CMR protocol included standard cine images and native T1 mapping with three short-axis subsets of the LV using the modified Look-Locker inversion recovery (MOLLI) 3(3)5 acquisition scheme (Figure 1A and B). Intravenous Gadobutrol (Gadovist®, Bayer, Germany) was administered with a dose of .15 mmol/kg and adjusted to .1 mmol/kg for those with an eGFR <60 ml/min/1.73 m². Post-contrast T1 images were obtained 10 min after contrast administration to create ECV maps with the following imaging parameters: FOV 360 × 306.7 mm², in-plane resolution 1.4 × 1.4 × 8 mm³, TR/TE = 260.6/1.12 ms, and flip angle 35°. LGE images were obtained 12 min after contrast administration and consisted of a short-axis stack of the LV and three long-axis views. If LGE was suspected, a perpendicular plane was obtained to confirm the finding. The inversion time was determined using a T1-scout and was continually adjusted. LGE image parameters were as follows: FOV 340 × 278 mm², in-plane resolution 1.6 × 1.6 × 8 mm², TR/TE = 700/3.09 ms, and flip angle 25°.

CMR analyses were conducted using Circle CVI 42® (version 5.13.5, Calgary, Canada). LV volumes and mass were estimated using the short-axis stack with automatic endo- and epicardium contouring. The phases with the largest and smallest LV volumes were defined as end-diastole and end-systole, respectively. LV hypertrophy was determined using sex- and age-specific reference values for LV mass index.¹⁸ Global native T1 and ECV fraction (ECV%) values were quantified using the motion-corrected MyoMaps with the endo- and epicardium delineated and with a 20% offset to minimize partial volume effects (Figure 1B). Haematocrit values were derived on the same day as the CMR examination and were used to create ECV maps from pre- and post-contrast T1 images. The presence of LGE was confirmed by two independent observers and was classified as either ischaemic (i.e. subendocardial or transmural) or non-ischaemic (i.e. mid- and/or epicardial). Patients with hinge-point LGE were not considered LGE-positive in this study. If there was a disagreement between the two observers, a third observer's evaluation was deemed final. The LGE volume percentage was quantified using the Full Width Half Maximum technique, which applies half the maximal signal intensity of enhanced areas.¹⁹ Peak systolic global longitudinal strain (GLS) was estimated using two-, three-, and four-chamber views.

LGE evaluation and ECV% quantification were infeasible in 11 (14%) and 13 (16%), respectively, due to incomplete examinations related to claustrophobia or back pain, issues with intravenous access, patient refusal of contrast administration, poor LGE image quality, missing haematocrit values required for ECV% calculation, or image post-processing issues.

Statistical analyses

Statistical analyses and figures were generated using R Statistical Software (v4.4.1; R Core Team 2024). The normality of data was examined with histograms and QQ plots. Data following a normal distribution are presented as mean ± standard deviation, non-normally distributed data as median (interquartile range), and categorical variables as count (percentage). Two-sided *P*-values ≤ .05 were considered statistically significant. BAV-AS and TAV-AS patients were compared with Student's *t*-test, the Wilcoxon

signed-rank test, or χ^2 test with Monte Carlo simulation as appropriate. Multivariable linear and logistic regression adjusted for sex, age, and Vmax were applied to compare CMR parameters between BAV-AS and TAV-AS patients, using bicuspid valve morphology as a reference. Vmax was chosen above other measures of stenosis severity as it is more reproducible and is the strongest predictor of clinical outcomes.^{20–22} For continuous outcomes, estimated marginal means and 95% confidence intervals (CIs) were derived from the linear regression models using proportional weighting to account for group size differences. For binary outcomes (i.e. presence of LGE), predicted probabilities and odds ratios (ORs) with 95% CIs were obtained from the logistic regression model. The assumptions of linear regression were checked, including plots for variance homogeneity and linearity of residuals. Multivariable linear regression analysis was applied to investigate interactions. Correlations between parameters of myocardial fibrosis and other disease severity parameters were examined. Pearson's *r* or Spearman's rho were calculated as appropriate, and the χ^2 test with Monte Carlo simulation was used to correlate LGE prevalence and disease severity parameters. *Post hoc* analyses were conducted to explore the sex-related differences in LGE prevalence. The χ^2 test with Monte Carlo simulation compared LGE prevalence between males and females, and logistic regression analysis examined the interaction between valve morphology and sex on LGE prevalence. Firth's bias reduction method was applied due to limited observations in each group, using the logistf package in R.²³ Further, a *post hoc* test was performed to test the correlation between Vmax and absolute instead of relative ECV. The absolute ECV indexed to BSA (iECV) in ml/m² was calculated as ECV% times LV myocardial volume indexed to BSA.² LV myocardial volume was defined as LV mass times myocardial density (i.e. 1.05 g/ml).

Results

Study population

The study initially included 86 patients with BAV-AS and TAV-AS, but six could not complete the CMR examination due to claustrophobia. Consequently, the analyses were conducted on 80 patients. Table 1 presents the demographics, disease characteristics, and CMR parameters. None had confirmed or suspected amyloidosis, Fabry disease, or other storage disease, hypertrophic cardiomyopathy, or myocarditis.

Bicuspid aortic stenosis vs tricuspid aortic stenosis

The segmental distribution of LGE among LGE-positive BAV-AS and TAV-AS patients is illustrated in Figure 2, while examples of myocardial fibrosis assessment in BAV-AS and TAV-AS are provided in Figure 1C and D. The sex-stratified distributions and comparisons of native T1, ECV%, LGE prevalence, and LGE volume percentage between patients with BAV-AS and TAV-AS are illustrated in Figure 3. Native T1 was higher in patients with TAV-AS compared with BAV-AS (1034 vs 1022 ms; 95% CI 1–23; *P* = .04); however, when adjusting for sex, age, and Vmax, the difference became insignificant (Table 2). There were no differences in ECV% or LGE prevalence between patients with BAV-AS and TAV-AS (Figure 3B and C; Table 2). In adjusted analysis, LGE volume percentage was 1.6% points lower in patients with TAV-AS compared with BAV-AS (Table 2). There were no differences in LV volumes and systolic function between BAV-AS and TAV-AS in adjusted analysis (Table 2). In *post hoc* analysis, LGE was more prevalent among males compared with females (52 vs 11%; χ^2 = 10; *P* = .002). Further, there was a positive interaction between sex and valve morphology on LGE prevalence (*P* = .01).

Correlation between fibrosis markers and disease severity

The correlations between myocardial fibrosis markers and other markers of disease severity (Vmax, aortic valve calcium score, NT-proBNP,

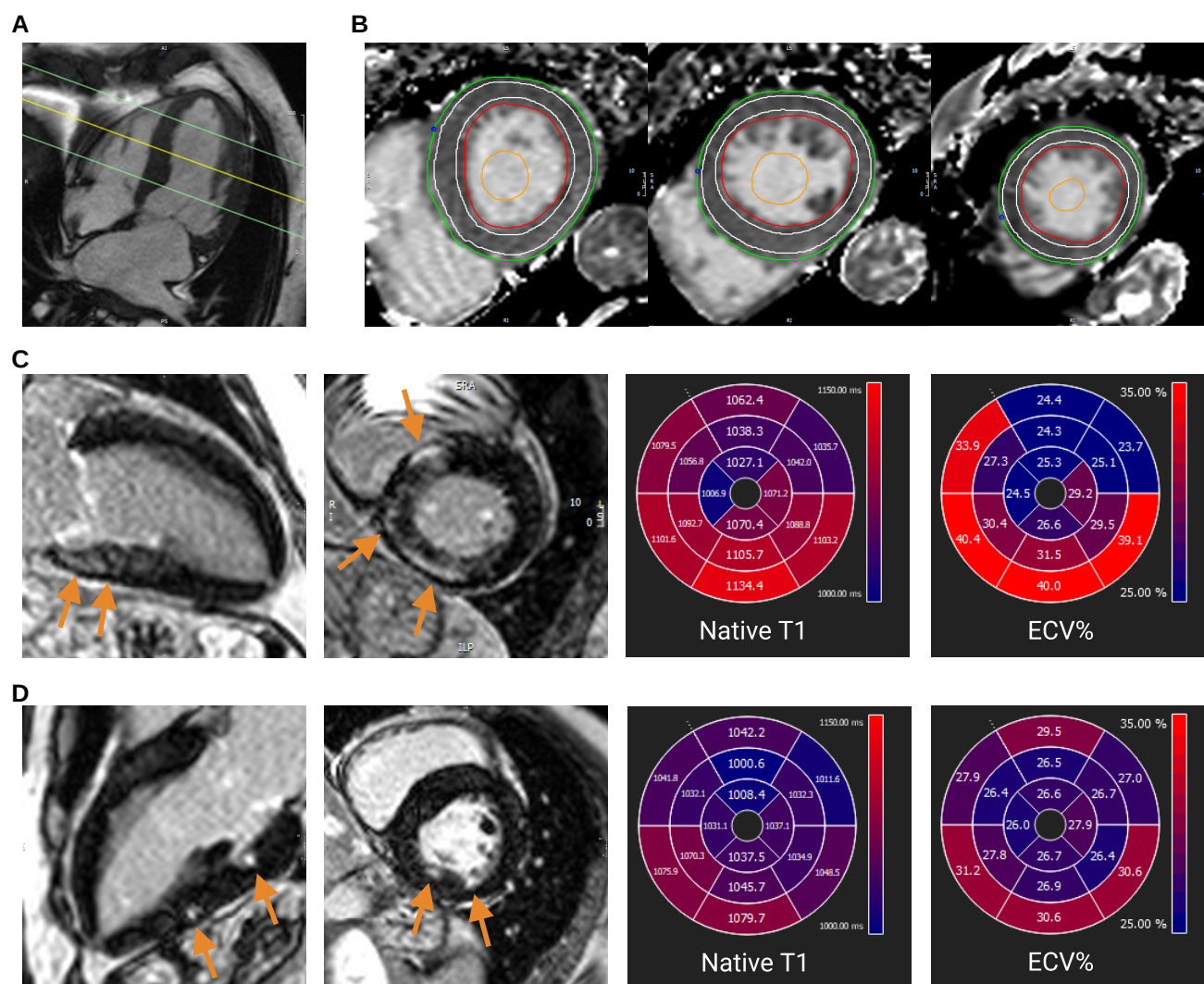


Figure 1 Cardiovascular magnetic resonance assessment of myocardial fibrosis in aortic stenosis. (A) Planning of the three short-axis slices (basal, mid, and apical) for native T1 and extracellular volume (ECV) mapping, shown in a four-chamber view. (B) Corresponding short-axis slices with delineation of endocardial and epicardial contours, including a 20% offset to define myocardial regions of interest, and blood pool contours used for ECV% calculation. (C) Example of a tricuspid aortic valve patient. Late gadolinium enhancement (LGE) images (left) demonstrate non-ischaemic mid-wall fibrosis in the basal septal and inferolateral segments. Corresponding 16-segment AHA maps (right) show elevated native T1 and ECV% values in the same regions. Red indicates higher values and blue lower values. (D) Example of a bicuspid aortic valve patient. LGE images show a more scattered pattern of non-ischaemic mid-wall fibrosis, predominantly in the basal and mid-ventricular inferoseptal segments. Native T1 and ECV% maps demonstrate increased values, primarily in the basal septal and inferolateral segments. Although panels (C) and (D) present examples of tricuspid and bicuspid aortic valve patients, the illustrated LGE patterns were not specific to valve morphology and were observed in both groups

LVEF, and GLS) in patients with severe BAV-AS and TAV-AS are presented in [Figure 4](#). In *post hoc* analysis, iECV did not correlate with Vmax ($r = .16$; $P = .20$). Correlations between myocardial fibrosis markers and LV structure are shown in [Supplementary Figure S1](#). LV mass index was associated with both native T1 ($r = .35$; $P < .01$) and LGE prevalence (84 vs 76 g/m² in LGE-positive vs LGE-negative patients; $P = .02$). The annual progression rate of Vmax within the last 6-48 months was not associated with native T1, ECV%, or LGE prevalence (all $P > .05$).

Associations modified by valve morphology

Interaction analyses assessed whether valve morphology modified the association between disease severity parameters and myocardial fibrosis. There were no interactions between valve morphology and Vmax on either native T1 ($P = .42$), ECV% ($P = .56$), or LGE prevalence ($P = .65$), and no interactions between valve morphology and aortic valve calcium score on either native T1 ($P = .21$), ECV% ($P = .76$), or

Table 1 Baseline characteristics of patients with severe bicuspid ($n = 38$) and tricuspid ($n = 42$) aortic stenosis

Characteristic	BAV-AS (n = 38)		TAV-AS (n = 42)		P-value
Patient characteristics					
Age, years	62 ± 10		76 ± 6		<.001
Male sex, n (%)	30 (79)		29 (69)		.34
BMI, kg/m ²	27 ± 5		27 ± 4		.68
BSA, m ²	2.0 ± .2		2.0 ± .2		.35
Heart rate, b.p.m.	69 ± 13		68 ± 12		n = 41 .48
Systolic blood pressure, mmHg	135 ± 13	n = 36	142 ± 16	n = 36	.04
Diastolic blood pressure, mmHg	79 ± 9	n = 36	77 ± 9	n = 36	.49
Disease characteristics					
Sievers classification, n (%)			NA		NA
Type 0	4 (11)				
Type 1	32 (84)				
Type 2	2 (5)				
Aortic valve fusion (Sievers type 1), n (%)			NA		NA
L-R	22 (69)				
N-L	2 (6)				
R-N	8 (25)				
Aortic graft planned, n (%)	8 (21)		0 (0)		.004
Aortic valve peak velocity, m/s	4.6 (4.0–4.9)		4.7 (4.3–5.0)		.20
Aortic valve mean gradient, mmHg	49 (44–58)		57 (48–67)		.03
Aortic valve area VTI, cm ²	.8 (.7–.9)	n = 37	.7 (.7–.8)	n = 41	.04
Left atrial volume index, ml/m ²	33 ± 10	n = 28	38 ± 10	n = 33	.07
E/e' ratio	12 ± 5	n = 27	12 ± 5	n = 27	.70
Aortic valve calcium score, AU	3363 (2635–5389)	n = 32	3707 (2493–4369)	n = 36	.99
Aortic valve calcium score ratio ^a	1.8 (1.3–2.7)	n = 32	2.0 (1.8–2.9)	n = 36	.45
Coronary artery calcium score, AU	94 (4–526)	n = 32	349 (145–851)	n = 36	.01
NYHA class, n (%)					.27
I	6 (16)		2 (5)		
II	25 (66)		33 (78)		
III	7 (18)		7 (17)		
IV	0 (0)		0 (0)		
CCS, n (%)					.89
0	18 (47)		22 (52)		
1	13 (34)		12 (29)		
2	7 (19)		7 (17)		
3	0 (0)		1 (2)		
4	0 (0)		0 (0)		
Syncope, n (%)	5 (13)		4 (10)		.72
EuroSCORE II	.93 (.75–1.55)		1.16 (.93–1.47)		.12
Comorbidities and risk factors					
Hypertension, n (%) ^b	21 (55)		26 (62)		.65
Diabetes mellitus, n (%) ^c	5 (13)		7 (17)		.77

Continued

Table 1 Continued

Characteristic	BAV-AS (n = 38)		TAV-AS (n = 42)		P-value
Smoking, n (%)					.01
Current	4 (11)		0 (0)	n = 41	
Former	15 (39)		26 (63)		
Never	29 (50)		15 (37)		
Atrial fibrillation, n (%)	4 (11)		7 (17)		.53
Stroke, n (%)	3 (8)		8 (19)		.19
Sleep apnoea, n (%)	4 (11)		3 (7)		.71
Peripheral artery disease, n (%)	0 (0)		2 (5)		.49
Cancer, n (%) ^d	2 (5)		4 (10)		.68
COPD, n (%)	2 (5)		3 (7)		1.00
Medications					
Antihypertensives, n (%)	21 (55)		23 (54)		1.00
Lipid-lowering therapy, n (%)	18 (47)		27 (64)		.16
Anti-platelet therapy, n (%)	9 (24)		14 (33)		.44
Anticoagulants, n (%)	4 (11)		7 (17)		.52
Antiarrhythmics, n (%)	0 (0)		0 (0)		NA [†]
Antidiabetics, n (%)	4 (11)		7 (17)		.51
Biochemistry					
Troponin T, ng/L	11 (9–17)	n = 32	11 (11–19)	n = 37	.09
NT-proBNP, pmol/L	34 (16–56)	n = 36	62 (29–157)	n = 41	<.001
Creatinine, $\mu\text{mol/L}$	78 $\pm$ 15	n = 37	86 $\pm$ 18		.04
eGFR, ml/min/1.73 m ²	87 $\pm$ 17	n = 37	70 $\pm$ 15		<.001
Haematocrit	.42 $\pm$.04	n = 36	.39 $\pm$.04	n = 37	<.001
HbA1c, mmol/mol	38 (36–39)	n = 36	39 (35–43)	n = 38	.54
Total cholesterol, mmol/L	4.5 (3.6–5.1)	n = 36	4.5 (3.9–5.2)	n = 38	.68
LDL cholesterol, mmol/L	2.3 (1.9–2.9)	n = 36	2.7 (2.0–3.2)	n = 39	.40
HDL cholesterol, mmol/L	1.5 (1.1–1.9)	n = 36	1.4 (1.2–1.8)	n = 39	1.00
Triglycerides, mmol/L	1.4 (.9–2.0)	n = 36	1.1 (.9–1.4)	n = 37	.14
Cardiac magnetic resonance					
LVEDVi, ml/m ²	78 $\pm$ 15		78 $\pm$ 14	n = 41	.94
LVESVi, ml/m ²	24 $\pm$ 8		26 $\pm$ 9	n = 41	.24
LVSVi, ml/m ²	53 $\pm$ 13		51 $\pm$ 10	n = 41	.44
LVMi, g/m ²	77 $\pm$ 18		81 $\pm$ 15	n = 41	.27
LV hypertrophy, n (%)	10 (26)		17 (41)	n = 41	.24
LVEF, %	68 $\pm$ 8		66 $\pm$ 9	n = 41	.34
GLS, %	–17 $\pm$ 2		–16 $\pm$ 2	n = 40	.21
Native T1, ms	1022 $\pm$ 27		1034 $\pm$ 23		.04
ECV%, %	25 $\pm$ 2	n = 33	26 $\pm$ 3	n = 34	.10
LGE present, n (%)	12 (31)	n = 35	16 (47)	n = 34	.33
LGE pattern					.61
Ischaemic	3 (25)		2 (12)		
Non-ischaemic	9 (75)		14 (88)		

Continued

Table 1 Continued

Characteristic	BAV-AS (n = 38)	TAV-AS (n = 42)	P-value
LGE volume percentage, %	1.3 (.6–3.9)	2.2 (1.2–3.0)	.61

Values are mean $\pm$ standard deviation, median (interquartile range), or count (percentage). Significant P-values are presented in bold. The total number of observations is presented for parameters with missing values.

BAV-AS, bicuspid aortic valve stenosis; BMI, body mass index; BSA, body surface area; CCS, Canadian Cardiovascular Society grading of angina pectoris; COPD, chronic obstructive pulmonary disease; ECv, extra cellular volume; eGFR, estimated glomerular filtration rate; E/e' ratio, the ratio of early diastolic transmitral flow velocity to early diastolic mitral annular velocity; GLS, global longitudinal strain; HbA1c, haemoglobin A1c; HDL, high-density lipoprotein; LDL, low-density lipoprotein; LGE, late gadolinium enhancement; LVEDV, left ventricular end-diastolic volume index; LVSVi, left ventricular end-systolic volume index; LVEF, left ventricular ejection fraction; LVMI, left ventricular mass index; LVSVi, left ventricular stroke-volume index; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association Functional Classification of heart failure; TAV-AS, tricuspid aortic valve stenosis; VTi, velocity time integral

[†]P-value cannot be calculated due to the lack of observations in both groups.

^aAortic valve calcium score ratio: aortic valve calcium score divided by 1200 for females and 2000 for males.

^bHypertension: known or use of anti-hypertensive medications (β-blockers, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, calcium inhibitors, and diuretics)

^cDiabetes mellitus: Type 1, Type 2, or HbA1c > 48 mmol/mol

^dCancer: current or former types of cancers treated with systemic therapy and/or chest radiotherapy

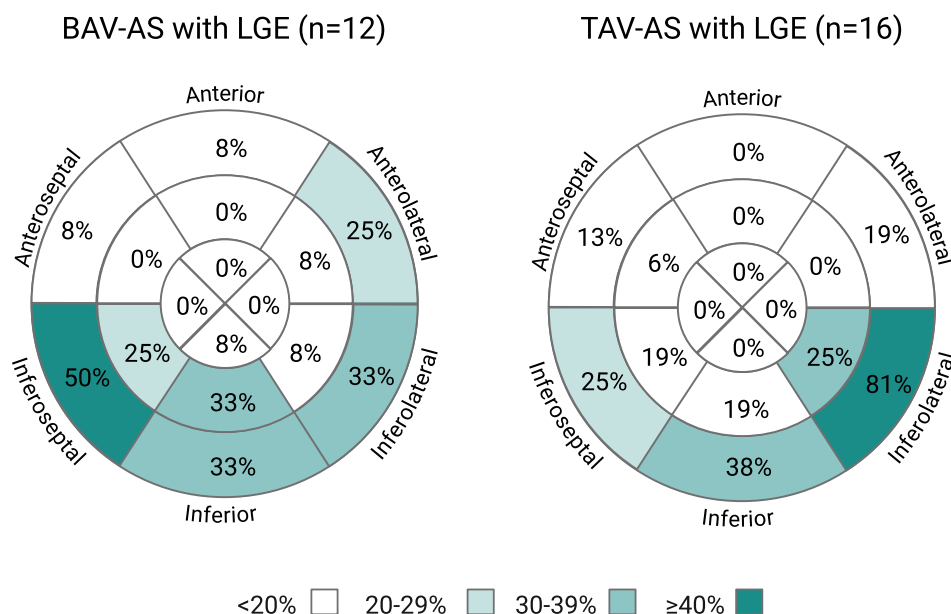


Figure 2 Sixteen-segment myocardial model, as defined by the American Heart Association, depicting the percentage of late gadolinium enhancement (LGE) observed in each segment among LGE-positive patients with bicuspid aortic valve stenosis (BAV-AS) (left) and tricuspid aortic valve stenosis (TAV-AS) (right)

LGE prevalence ($P = .45$). There were no interactions between valve morphology and native T1 on LVEF ($P = .96$) or GLS ($P = .44$), between valve morphology and ECV% on LVEF ($P = .07$) or GLS ($P = .46$), or valve morphology and LGE prevalence on LVEF ($P = .70$) or GLS ($P = .76$).

Discussion

To our knowledge, this is the first CMR study to compare the presentation of myocardial fibrosis between patients with BAV-AS and TAV-AS without ischaemic heart disease and with normal LVEF. The main finding was that BAV-AS and TAV-AS patients had similar values for native T1, ECV%, and LGE prevalence when adjusted for sex, age,

and stenosis severity. However, the LGE volume percentage was slightly higher in patients with BAV-AS.

Our findings suggest that the overall burden of myocardial fibrosis is highly similar in BAV-AS and TAV-AS when comparing across the same sex, age, and stenosis severity. However, the 1.6-percentage point difference in LGE volume percentage raises the question of whether patients with BAV-AS are referred for AVR at a slightly more advanced disease stage. These findings are hypothesis-generating, and supporting this hypothesis is that despite not adjusting for comorbidities and other risk factors such as blood pressure and renal function, BAV-AS patients exhibited comparable levels of myocardial fibrosis to those with TAV-AS. A recent study by Wedin et al.²⁴ compared patients with BAV-AS and TAV-AS referred for AVR and found that, despite being younger, BAV-AS patients had worse LV function and higher LV mass

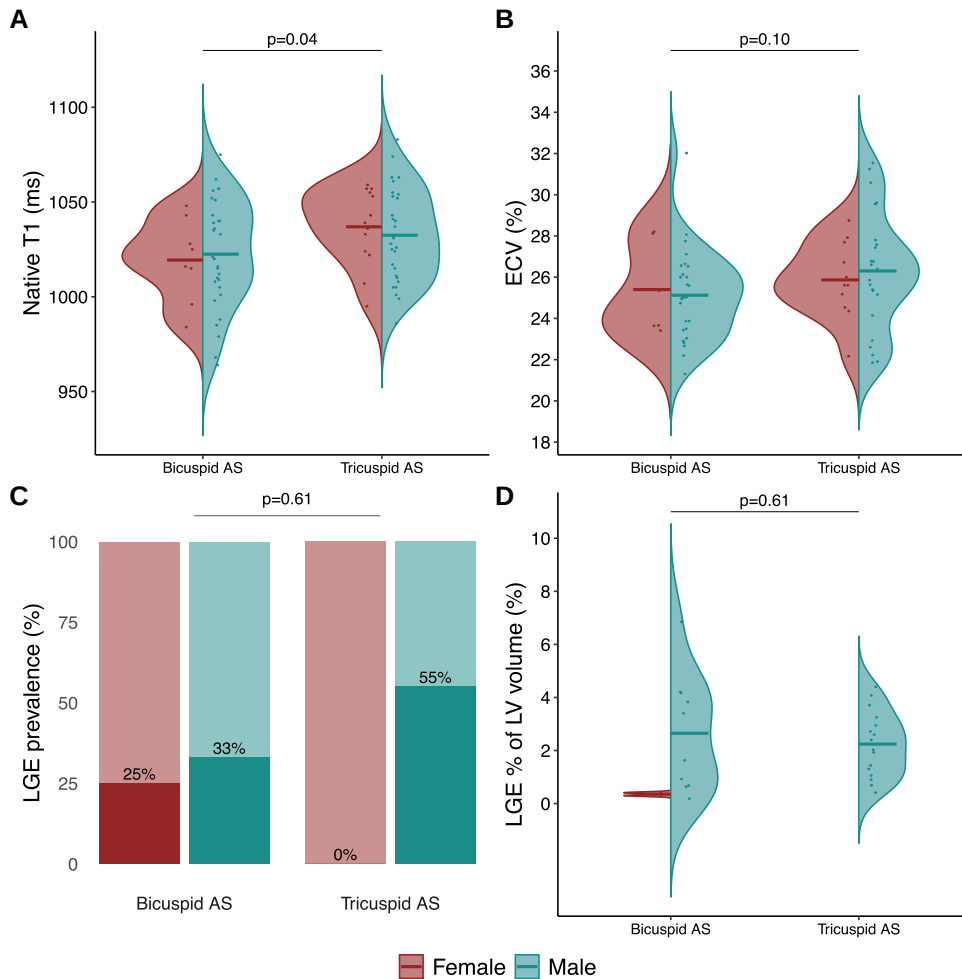


Figure 3 Unadjusted comparison of myocardial tissue characteristics in patients with bicuspid ($n = 38$) and tricuspid ($n = 42$) aortic valve stenosis. Native T1 (A), extracellular volume fraction (ECV%) (B), and late gadolinium (LGE) volume percentage (D) are illustrated using violin plots and stratified by female and male sex. Dots represent individual measurements, while mean or median values are presented as horizontal lines. LGE prevalence (D) is displayed as a sex-stratified bar chart

index. Unlike our study population, theirs had a higher comorbidity burden among TAV-AS patients and conducted unadjusted analyses, complicating direct comparisons. However, both studies may indicate that BAV-AS patients have slightly more advanced myocardial disease at the time of referral. This could partly be explained by a systematic underestimation of AS severity in BAV-AS caused by eccentric jets, combined with an overestimation of severity in TAV-AS due to pressure recovery in patients with small ascending aortas and underestimation of a more elliptical LV outflow tract.^{25–27}

Despite our study suggesting only subtle differences in myocardial fibrosis between BAV-AS and TAV-AS, significant underlying pathophysiological mechanisms may exist. Individuals with BAV are exposed to a higher afterload from birth,⁶ potentially leading to chronic myocardial stress and a greater propensity for myocardial fibrosis accumulation over time. Further, specific genetic variants, including mutations in *NOTCH1*,²⁸ have been identified in BAV and could impact myocardial tissue properties. However, this is hypothetical and requires further investigation. Conversely, factors such as older age and higher prevalence of comorbidities in TAV-AS could drive fibrosis development beyond valvular obstruction. Even though BAV-AS and TAV-AS

patients appeared comparable in our study in terms of comorbidities, TAV-AS patients exhibited higher systolic blood pressure, higher coronary artery calcium score, and impaired renal function. This suggests a greater systemic disease burden, and it may not only be attributed to older age. A retrospective study by Yang et al.¹⁴ found that TAV-AS patients exhibited more indicators of cardiac damage than BAV-AS patients, independent of sex, age, and comorbidities. Moreover, TAV-AS patients developed more signs of cardiac damage and had higher mortality at 12 years compared with sex- and age-matched BAV-AS patients. Although that study did not include markers of myocardial fibrosis, the results suggest that cardiac damage in TAV-AS may arise from more complex factors, including unknown factors extrinsic to the aortic valve. In our study, there was a difference in the sex distribution of LGE prevalence between BAV-AS and TAV-AS, with 0% female and 55% male TAV-AS patients being LGE-positive, compared with a more equal distribution among BAV-AS patients (25% in females vs 33% in males), indicating that having a TAV increases the likelihood of LGE presence in males compared with females. While this *post hoc* analysis is hypothesis-generating, it supports the notion that differences in pathophysiological mechanisms may exist. Further,

Table 2 Comparison of patients with bicuspid ($n = 38$) and tricuspid ($n = 42$) aortic stenosis adjusted for sex, age, and peak aortic velocity

Parameter	BAV-AS Estimated mean or probability (95% CI)	TAV-AS Estimated mean or probability (95% CI)	Estimated difference β or OR (95% CI)	P-value
Left ventricular geometry and function				
LVEDVi, ml/m ²	75 (70–80)	80 (75–85)	5 (–3 to 13)	.24
LVESVi, ml/m ²	24 (21–28)	26 (23–29)	2 (–3 to 7)	.50
LVSVi, ml/m ²	51 (47–55)	54 (50–58)	3 (–3 to 10)	.35
LVMi, g/m ²	76 (70–82)	83 (77–88)	7 (–2 to 16)	.13
LVEF, %	68 (64–71)	67 (64–71)	.3 (–5 to 5)	.92
GLS, %	–16 (17 to –16)	–17 (–17 to –16)	–.1 (–1.4 to 1.2)	.85
Myocardial tissue characterization				
Native T1, ms	1023 (1013–1033)	1033 (1024–1042)	10 (–5 to 25)	.18
ECV%, %	25.0 (24.1–26.0)	26.3 (25.4–27.2)	1.2 (–.2 to 2.7)	.10
LGE present	26 (12–47) [%]	49 (28–70) [%]	2.5 (.7–11) [OR]	.17
LGE volume percentage (%)	3.2 (2.1–4.3)	1.6 (.6–2.5)	–1.6 (–3.3 to –.02)	.047

Estimated marginal means and β estimates were obtained from linear regression models, while predicted probabilities and odds ratio for LGE presence were derived from a logistic regression model. Estimated difference represents TAV-AS relative to BAV-AS (reference group). All values are adjusted for age, sex, and peak aortic velocity. Significant P-values are presented in bold.

Abbreviations as in Table 1.

although we did not formally compare LGE distribution between BAV-AS and TAV-AS patients, Figure 1 suggests a tendency towards greater inferoseptal fibrosis in BAV-AS and more inferolateral fibrosis in TAV-AS. Given the small sample size, these observations should be considered exploratory and hypothesis-generating only.

In our population of severe AS, correlations between myocardial fibrosis parameters and stenosis severity were inconsistent. Native T1 and LGE prevalence correlated with aortic valve calcium score but not with Vmax or the annual progression rate of Vmax. This may suggest that echo-derived transvalvular velocities and gradients do not fully capture the myocardial consequences of AS severity, highlighting the need for complementary markers of disease severity. However, the limited range of Vmax in severe AS and modest statistical power may have limited the detection of such associations. Unexpectedly, ECV% correlated negatively with Vmax. To explore whether this reflected a proportionally greater myocyte hypertrophy relative to fibrosis, we examined the correlation between Vmax and the absolute ECV (i.e. iECV) but found no significant correlation. This contrasts with previous studies,^{29,30} potentially due to differences in patient characteristics and methodology. While native T1 and LGE both correlated with LV systolic function, native T1, ECV%, and LGE prevalence did not correlate uniformly among the examined disease parameters, indicating that each captures slightly different aspects of myocardial tissue properties. This corroborates previous histology-correlation studies, finding that no single CMR marker can fully characterize myocardial fibrosis.^{31,32}

Our study carries several potential implications. The overall similar extent and prevalence of myocardial fibrosis in BAV-AS and TAV-AS suggest that valve morphology is not a major determinant of myocardial fibrosis. This is supported by our interaction analyses, showing that the association between stenosis severity and myocardial fibrosis was similar in BAV-AS and TAV-AS, and that the detrimental effect of myocardial fibrosis on LV systolic function appeared independent of valve morphology. However, we cannot exclude that other unmeasured aspects of myocardial remodelling differ between groups and may still carry clinical relevance. Nonetheless, we did find a slight difference in LGE volume percentage between BAV-AS

and TAV-AS. While this difference seems minor from a clinical perspective, it raises the possibility that BAV-AS patients may be referred for AVR at a slightly later stage of the disease, especially considering that we were unable to adjust for comorbidities. However, this finding is hypothesis-generating and needs confirmation in future studies. Generally, trials should aim to differentiate between BAV-AS and TAV-AS, as pathophysiology and treatment effects may differ. Furthermore, sex- and age-specific reference values for native T1 may be necessary, given the differences observed in unadjusted analyses. Finally, the sex disparities in LGE prevalence, supported by previous studies,^{33,34} should be considered, and the potential interaction between sex and valve morphology warrants further investigation.

Limitations

The study was limited by the sample size, which prevented adjustment for potential confounders beyond sex, age, and Vmax, and increased the risk of a type II error. Matching or adjusting for comorbidities would have been favourable, as comorbidities such as diabetes,³⁵ hypertension,³⁶ and chronic kidney disease³⁷ are all associated with myocardial fibrosis. As such, conclusions drawn from this study need confirmation in larger trials. The study is further limited by the cross-sectional design, and a larger study with long-term follow-up of BAV-AS and TAV-AS with mild or moderate AS would be highly valuable. Finally, while several studies have correlated native T1 and ECV% with histologically assessed fibrosis,^{2,38,39} recent studies have not confirmed the correlation with ECV% in AS,^{31,32} indicating that native T1 and ECV% should be regarded as fibrosis surrogates pending further research.

Conclusions

In patients with severe AS without ischaemic heart disease and normal LVEF, there were no differences in native T1, ECV%, and LGE prevalence between those with BAV and TAV when adjusting for sex, age, and stenosis severity. However, the relative LGE burden was slightly higher in patients with BAV.

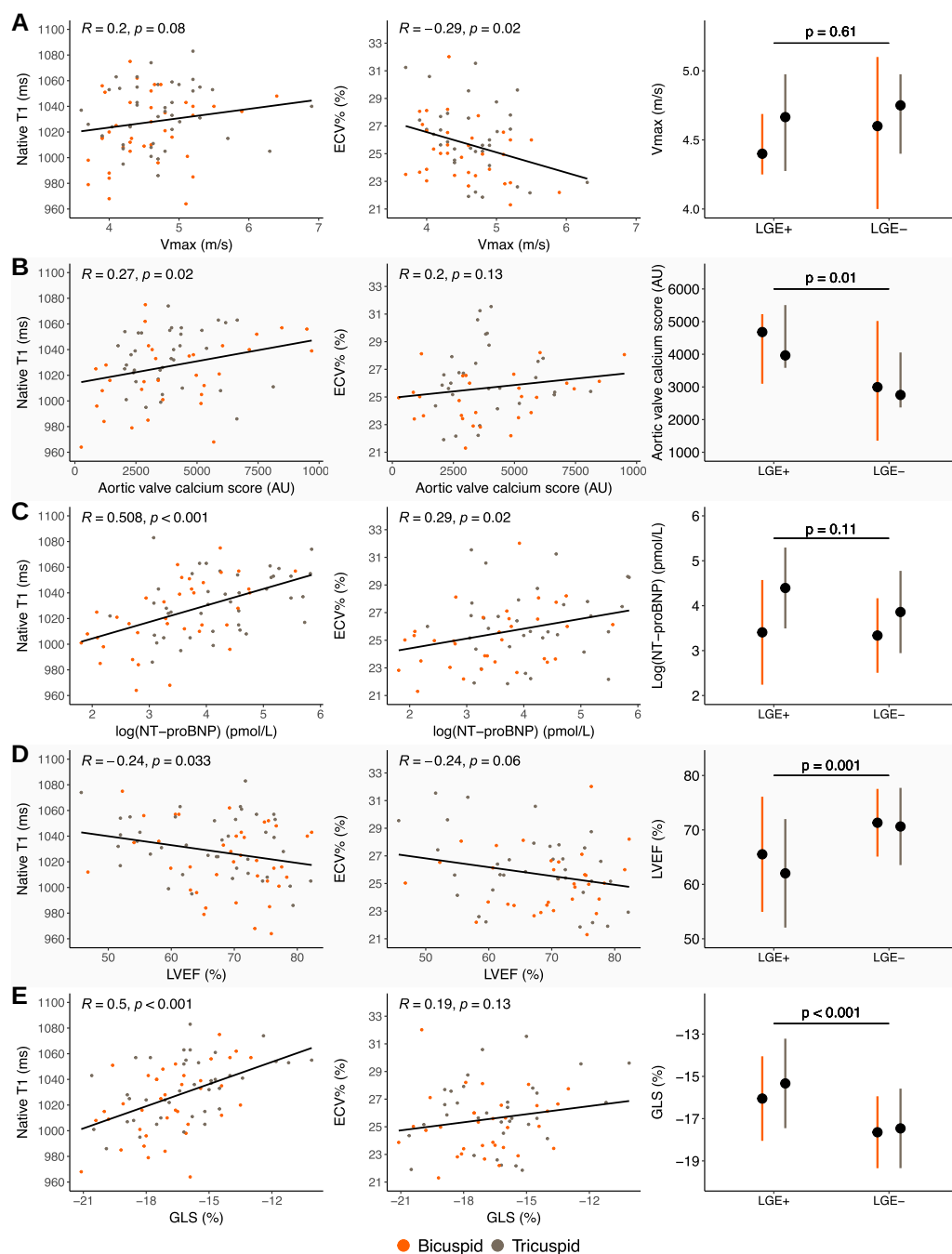


Figure 4 Correlation between peak aortic valve velocity (Vmax) (A), aortic valve calcium score (B), log (NT-proBNP) (C), left ventricular ejection fraction (LVEF) (D), global longitudinal strain (GLS) (E), and the following markers of myocardial fibrosis: native T1 (left), extracellular volume fraction (ECV%) (middle), and late gadolinium enhancement (LGE) (right). Correlations for continuous variables are presented as scatter plots with regression lines and corresponding Pearson's r or Spearman's ρ with P -values, as appropriate. Correlations between LGE-positive and LGE-negative patients are presented as whisker plots with mean $\pm$ standard deviation or median (interquartile range) with P -values.

Acknowledgements

We would like to thank the Rigshospitalet radiographers for their invaluable logistic and technical support throughout this study. We would also like to thank Matilde Winther-Jensen for her statistical support.

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Supplementary data

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

Declarations

Disclosure of Interest

All authors declare no disclosure of interest for this contribution.

Data Availability

The data underlying this article will be shared on reasonable request.

Funding

The Danish Cardiovascular Academy (DCA) supported the study, funded by the Novo Nordisk Foundation, grant number NNF20SA0067242, and the Danish Heart Foundation. Additionally, the work was funded by Rigshospitalet's Research Fund (Rigshospitalets forskningspuljer), Eva og Henry Frønkels Mindefond, Snedkermester Sophus Jacobsen og hustru Astrid Jacobsens Fond, and Fru Asta Bolding, Født Andersens Mindelegat. The funding sources had no part in designing the study, data management, writing the paper, or submission.

Ethical Approval

Ethical Approval was not required.

Pre-registered Clinical Trial Number

None supplied.

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