ESC European Society of Cardiology

European Heart Journal - Valvular and Structural Heart Disease (2026) **2**, xwag052
https://doi.org/10.1093/ehjvshd/xwag052

ORIGINAL ARTICLE
Aortic valvular heart disease

Preoperative symptoms and survival after SAVR in bicuspid and tricuspid aortic stenosis

Johan O. Wedin[1,2], Nathalie Hjert[2], Sergey Rodin[1,2], Oscar E. Simonson[1,2], Frank A. Flachskampf [3,4], Stefan K. James[3,4,5], Elisabeth Ståhle [1,2], and Karl-Henrik Grinnemo[1,2,*]

[1]Department of Surgical Sciences, Entrance 70, 1st floor, Uppsala University Hospital, SE-751 85 Uppsala, Sweden; [2]Department of Cardiothoracic Surgery and Anesthesiology, Uppsala University Hospital, Uppsala, Sweden; [3]Department of Medical Sciences, Uppsala University, Uppsala, Sweden; [4]Department of Clinical Physiology and Cardiology, Uppsala University Hospital, Uppsala, Sweden; and [5]Uppsala Clinical Research Center, Department of Medical Sciences, Uppsala University, Uppsala, Sweden

Received 5 March 2026; revised 29 May 2026; accepted after revision 10 June 2026; online publish-ahead-of-print 28 July 2026

Abstract

Background This study evaluated the prognostic impact of preoperative symptom severity in patients with bicuspid (BAV) and tricuspid (TAV) valve morphology undergoing surgical aortic valve replacement (SAVR) for severe aortic stenosis.

Methods In this single-centre observational study, 1054 patients with preserved left ventricular ejection fraction undergoing isolated SAVR (± concomitant aortic surgery) between 2005 and 2021 were included. Patients were stratified by valve morphology (516 BAV; 538 TAV) and symptom burden using the New York Heart Association (NYHA) classification. NYHA I–II defined mildly symptomatic and NYHA III–IV highly symptomatic patients. The primary endpoint was all-cause mortality. Survival was assessed using Kaplan–Meier analysis and multivariable Cox regression including the interaction between valve morphology and symptom severity. Relative survival was calculated using age-, sex-, and calendar year–matched life tables.

Results BAV patients were younger with fewer comorbidities than TAV patients. Over a median follow-up of 8.6 years, 15-year survival among mildly vs highly symptomatic patients was 78% vs 54% in BAV ($P < .001$) and 41% vs 26% in TAV ($P = .005$). A significant interaction between valve morphology and symptom severity ($P = .029$) demonstrated a disproportionately worse prognosis in highly symptomatic BAV patients. At 15 years, relative survival was 82% (95% CI 69-97%) in highly symptomatic BAV patients vs 105% (95% CI 93%–119%) in mildly symptomatic BAV patients, whereas TAV patients showed reduced relative survival regardless of symptom severity.

Conclusions Preoperative symptom severity significantly influenced long-term outcomes in BAV but not TAV patients, suggesting earlier surgery may be particularly beneficial in BAV patients.

* Corresponding author. Tel: +46 708868968, Email: karl-henrik.grinnemo@uu.se

Graphical Abstract

Impact of symptom status on survival after SAVR in bicuspid vs tricuspid AS

Study & groups

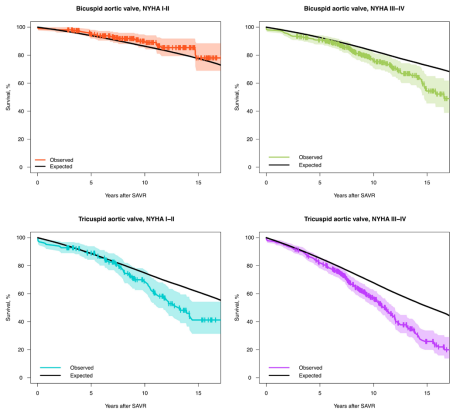
Single-center SAVR cohort with severe AS, preserved LVEF, no CAD (n = 1054).

Bicuspid aortic valve (BAV): n = 516
- younger, fewer comorbidities

Tricuspid aortic valve (TAV): n = 538
- older, more comorbidities

Stratification by symptom severity
- Mild: NYHA I–II
- Severe: NYHA III–IV

Key results



15-year relative survival vs general population:
- BAV mild: 105%
- BAV severe: 82%
- TAV mild: 72%
- TAV severe: 60%

Clinical implications

BAV with severe AS:
- Symptom severity strongly predicts survival.
- Mild (NYHA I–II): survival ≈ general population.
- Severe (NYHA III–IV): substantially reduced survival.

→ Consider early SAVR before advanced symptoms in BAV.

TAV with severe AS:
- Older, more comorbid.
- Worse survival vs general population regardless of NYHA class.
- Symptom status less prognostic.

→ Outcome driven more by age/comorbidities than timing of SAVR.

Keywords Bicuspid aortic valve • Early intervention • Survival • Outcome • Tricuspid aortic valve

Introduction

Severe aortic stenosis (AS) represents the most prevalent valvular heart disease requiring surgical intervention.[1] Although aortic valve replacement (AVR) remains the only treatment option for patients with severe AS, there is less clarity about whether symptom status at the time of intervention influences postoperative prognosis. The optimal timing of intervention remains controversial and has been a topic of debate for over two decades, with the risks of intervention and valve-related complications needing to be balanced against the risk of developing irreversible myocardial damage.[2–4]

Symptom onset has historically guided clinical decisions for AVR owing to its association with adverse outcomes,[5,6] but growing evidence suggests that the extent of AS-related cardiac damage has important prognostic implications independently of symptom status.[7,8] Furthermore, the adverse myocardial remodelling in AS generally appears before symptom onset,[8] and progression of myocardial fibrosis is accelerated in later stages of AS,[9] meaning that an only slightly delayed intervention can result in irreversible structural myocardial damage. Aligned with this evidence, several recent studies have demonstrated a benefit of early intervention in asymptomatic AS patients compared with a watchful waiting strategy. This was first suggested in observational studies,[10,11] and later also shown in randomized controlled trials.[12–14]

A congenital bicuspid aortic valve (BAV) demonstrates accelerated degeneration[15] and an increased risk of AS.[16] Although only 1% of the general population have a BAV,[17] approximately 50% of surgically excised stenotic valves during AVR are bicuspid, and the rest are tricuspid aortic valves (TAV).[18] At the time of AVR, there are important differences in clinical characteristics between BAV AS and TAV AS patients.[19–22] There is growing evidence supporting that BAV AS patients have worse myocardial function despite a significantly lower prevalence of cardiovascular risk factors.[20–23] Despite these differences, guidelines recommend similar timing for intervention in BAV and TAV patients with severe AS.

To date, no trial has investigated whether the timing of intervention has different prognostic implications for BAV AS and TAV AS patients. As such, this study aimed to investigate the impact of preoperative symptom severity and postoperative survival in patients with severe AS undergoing SAVR, stratified by aortic valve morphology. Understanding these interactions may help refine risk stratification, surgical timing, and individualized patient counselling.

Methods

Study design and study population

For the purpose of this observational study, patients who underwent surgical aortic valve replacement (SAVR) due to severe AS at our institution between 2005-01-01 and 2021-04-30 were eligible for inclusion. The patients were identified from the institutional Swedish Cardiac Surgery Registry, which contains prospectively collected data. We excluded patients with depressed left ventricular ejection fraction (LVEF), coronary artery disease (CAD, defined as previous percutaneous coronary intervention or coronary artery bypass grafting, or significant coronary stenoses evident on the preoperative diagnostic coronary angiogram), coexisting moderate to severe valvular stenosis or regurgitation, patients who previously underwent open-heart surgery, and patients scheduled for concomitant surgical procedures other than ascending aortic surgery or closure of the left atrial appendage. Patients were stratified according to aortic valve morphology

(BAV or TAV) as determined by direct visualization by the surgeon, and further by preoperative symptom status (mildly symptomatic, NYHA class I-II; highly symptomatic, NYHA class III-IV). The variables in the registry were completed and validated by reviewing all electronic patient charts. The investigators had full access to the database population from which the study population was derived, including access to all relevant variables and timepoints necessary to characterize the cohort. This study was approved by the Regional Ethics Review Committee (registration number 2017/221 and 2017/221/1), and the need for informed consent was waived. All procedures adhered to the Declaration of Helsinki. The study was conducted and reported in accordance with the Reporting of studies Conducted Using Observational Routinely-collected health Data (RECORD), which is an extension of the STROBE guidelines.

Outcome measures

All-cause mortality during follow-up after SAVR served as the primary outcome, stratified by aortic valve morphology and preoperative symptom status, which was assessed through interaction analysis. Relative survival was calculated to contextualize the observed mortality rates, comparing SAVR patients to the expected survival of the age- and sex-matched general Swedish population. Individual patient mortality data were obtained from the institutional Swedish Cardiac Surgery Registry via cross-linkage with the Swedish Population Registry. Index SAVR marked the beginning of the study period, with administrative censoring performed on 31 December 2023.

Statistical analysis

Continuous data are presented as means ± one standard deviation (SD), and categorical data are reported as frequencies with percentages. For comparison of continuous variables between BAV and TAV patients, and between highly and mildly symptomatic patients stratified by aortic valve morphology, an independent samples *T*-test was used. Corresponding comparisons of categorical variables were conducted with the χ^2 test or Fisher's exact test, as appropriate.

The crude survival probability for mildly symptomatic and highly symptomatic BAV AS and TAV AS during follow-up was compared with the log-rank test. Kaplan–Meier survival curves were used for graphical illustration of all-cause mortality for the respective groups. Association between preoperative symptom severity and postoperative survival was investigated in a multivariable Cox proportional hazards regression analysis, with inclusion of an interaction term between aortic valve morphology and symptom severity to assess whether symptom severity had different prognostic implications for BAV AS and TAV AS patients. A directed acyclic graph (DAG) was used to facilitate variable selection for the multivariable Cox proportional hazards regression analysis (Supplementary material). The final Cox proportional hazards regression model included the following variables: age ≥70 years, male sex, hypertension, diabetes mellitus, prior stroke, atrial fibrillation, peripheral artery disease, chronic obstructive pulmonary disease, BMI ≥30 kg/m^2, estimated glomerular filtration rate (eGFR) < 60 ml/min/1.73 m^2, mean pressure gradient ≥60 mmHg, type of prosthesis (biological or mechanical), NYHA class (NYHA I-II as reference) and aortic valve morphology (BAV as reference). All variables in the multivariable analysis met the assumptions of proportional hazards as assessed with the 2-sided Schoenfeld residuals test. Results are reported as adjusted hazard ratios (aHR) with their 95% confidence intervals (CI).

Relative survival was evaluated to contextualize the long-term prognosis of the study population relative to the background population. It is a method for estimating cause-specific survival without requiring information on recorded cause of death, thereby estimating excess mortality associated with severe AS and aortic valve replacement beyond the background mortality risk. Life tables for calculation of expected survival for the Swedish population matched for age, sex, and calendar year were obtained from the Human Mortality Database (www.mortality.org). Relative survival was calculated as the ratio of observed and expected survival using the Ederer II method.

Statistical analyses were performed in R Statistical Software (version 4.4.2). Relative survival was calculated in the 'relsurv' package.[24] We used the 'emmeans' package to derive estimated marginal means from the multivariable Cox proportional hazards model, to further assess the interaction between aortic valve morphology and preoperative symptom severity on all-cause mortality. Graphical illustrations were created in the 'ggplot2' package.[25] Two-tailed *P* values <.05 were considered statistically significant.

Sensitivity analyses

Sensitivity analyses were conducted to evaluate the robustness of the primary findings. These included Cox proportional hazards regression subgroup analysis stratified by aortic valve morphology, evaluation of the relationship between NYHA category and NT-proBNP levels (available in 56% of the cohort), assessment of the association between NT-proBNP and mortality, and calculation of E-values to estimate the minimum strength of association required for unmeasured confounding to explain away the observed associations.[26]

Results

Baseline characteristics

This study included 1054 patients, of which $n = 516$ (49.0%) had a bicuspid aortic valve and $n = 538$ (51.0%) had a tricuspid aortic valve. *Table 1* displays baseline characteristics for BAV AS and TAV AS patients in the whole cohort. In summary, BAV patients were different from TAV AS patients in terms of age (63.6 years vs 72.3 years, $P < .001$), male sex (64.9% vs TAV 51.3%, $P < .001$) and a lower prevalence of hypertension (53.5% vs 72.3%, $P < .001$), hypercholesterolaemia (32.0% vs. 41.5%, $P = .002$), diabetes mellitus (9.5% vs 19.9%, $P < .001$), chronic pulmonary disease (10.0% vs. 13.0%, $P = .006$), and chronic kidney disease (eGFR <60 mL/min/1.73 m^2: 5.8% vs 15.4%, $P < .001$). Severe HF symptoms were more common in TAV AS patients (69.0% vs 59.9%, $P = .003$).

Out of the BAV AS patients, 207 (40.1%) were mildly symptomatic and 309 (59.9%) were highly symptomatic. When comparing baseline characteristics between BAV AS patients in NYHA class I-II to those in NYHA class III-IV (*Table 2*), patients with more severe symptoms were older (64.6 years vs 62.1 years, $P = .011$), more often females (41.1% vs 26.1%, $P < .001$), had a higher body mass index (26.6 kg/m^2 vs 27.7 kg/m^2, $P = .006$) and more prevalent chronic pulmonary disease (2.9% vs 12.6%, $P < .001$) and atrial fibrillation (4.3% vs 12.3%, $P = .004$).

There were 167 (31.0%) mildly symptomatic and 371 (69.0%) highly symptomatic TAV AS patients (*Table 2*). TAV AS patients with more severe HF symptoms were older (73.3 years vs 70.1 years, $P < .001$), more often females (52.8% vs 39.5%, $P = .006$), had a higher body mass index (28.0 kg/m^2 vs 27.1 kg/m^2, $P = .030$), and a higher prevalence of hypertension (75.5% vs 65.3%, $P = .019$), diabetes mellitus (23.2% vs 12.6%, $P = .006$), atrial fibrillation (15.4% vs 6.0%, $P = .004$), and history of TIA/stroke (12.1% vs 4.2%, $P = .006$).

Observed survival

During a median follow-up of 8.6 years (range: 0.0–18.7 years), there were 364 deaths, of which 108 occurred in BAV AS patients and 256 in TAV AS patients. The majority of deaths in both the BAV AS group and TAV AS group occurred in highly symptomatic patients, with significant differences between mildly symptomatic and highly symptomatic in both groups (BAV AS log-rank $P < .001$ and TAV AS log-rank $P = .005$, *Figure 1*). The observed survival for BAV AS and TAV AS patients stratified by preoperative symptom severity is summarized in *Table 3*. For BAV AS patients in NYHA I-II and NYHA III-IV, the 1-, 5-, 10-, and 15-year observed survival rates were 99% vs 98%, 95% vs 91%, 90% vs 76% and 78% vs 54%, respectively. In contrast, for TAV AS patients in NYHA I-II and NYHA III-IV, the 1-, 5-, 10-, and 15-year observed survival were 95% vs 97%, 89% vs 82%, 69% vs 57% and 41% vs 26%, respectively.

In the multivariable Cox proportional hazards regression analysis, the association between preoperative symptom severity and mortality after SAVR differed according to aortic valve morphology, with

Table 1 Baseline characteristics of BAV AS and TAV AS patients undergoing SAVR

	Bicuspid aortic valve ($n = 516$)	Tricuspid aortic valve ($n = 538$)	*P* value
Age, years	63.6 (± 10.8)	72.3 (± 8.2)	<.001
Male sex, *n* (%)	335 (64.9)	276 (51.3)	<.001
Height, cm	172.5 (± 10.2)	169.5 (± 9.5)	<.001
Weight, kg	81.2(± 15.3)	79.9 (± 15.7)	.152
Body mass index, g/m^2	27.2 (± 4.3)	27.7 (± 4.6)	.094
Hypertension, *n* (%)	276 (53.5)	389 (72.3)	<.001
Diabetes mellitus, *n* (%)	49 (9.5)	107 (19.9)	<.001
Hypercholesterolemia, *n* (%)	165 (32.0)	223 (41.5)	.002
Chronic pulmonary disease, *n* (%)	45 (10.0)	77 (13.8)	.006
Atrial fibrillation, *n* (%)	47 (9.1)	67 (12.5)	.099
Peripheral artery disease, *n* (%)	20 (3.9)	35 (6.5)	.075
Prior TIA/stroke, *n* (%)	43 (8.3)	52 (9.7)	.517
Mean gradient >60 mmHg, *n* (%)	136 (26.4)	141 (26.2)	>.99
eGFR <60 ml/min/ 1.73 m^2, *n* (%)	30 (5.8)	83 (15.4)	<.001
Ascending aortic aneurysm, *n* (%)	85 (16.5)	14 (2.6)	<.001
NYHA class III-IV	309 (59.9)	371 (69.0)	.003
Angina pectoris, *n* (%)	168 (32.6)	189 (35.1)	.414
Presyncope, *n* (%)	118 (22.9)	114 (21.9)	.560
Syncope, *n* (%)	51 (9.9)	61 (11.3)	.505
Ventricular tachycardia/ fibrillation, *n* (%)	5 (1.0)	5 (1.0)	>.99
Type of prosthesis			<.001
Mechanical, *n* (%)	213 (41)	87 (16)	
Biological, *n* (%)	303 (59)	451 (84)	
Prosthesis size, mm	23.3 (± 1.7)	22.5 (± 1.7)	<.001

TIA, transient ischaemic attack; eGFR, estimated glomerular filtration rate.

evidence of a significant interaction (*P for interaction* =0.029). To facilitate interpretation, additional Cox proportional hazards regression analyses were performed stratified by aortic valve morphology as a sensitivity analysis. The adjusted hazard ratio for severe symptoms (NYHA III-IV) was 1.80 (95% CI 1.12–2.90) in BAV AS patients and 1.15 (95% CI 0.85–1.55) for TAV AS patients (*Figure 2*). These findings were consistent with the results of the primary interaction analysis. The results from the overall multivariable Cox proportional hazards regression analysis are provided in the Supplementary material. Neither angina pectoris nor syncope was associated with mortality after SAVR.

Relative survival

Here, we compared observed survival stratified by aortic valve morphology and preoperative symptom severity to the expected survival of the general population matched for age, sex, and calendar year (*Table 3*). Outcomes for mildly symptomatic BAV AS patients were excellent, with relative survival rates of 99%, 101%, 105%, and 105% at 1-, 5-, 10-, and 15-years of follow-up after SAVR. In contrast, BAV AS patients in NYHA III-IV had worse survival than expected, with relative survival rates of 99%, 98%, 94%, and 82% at 1-, 5-, 10-, and 15-years of follow-up after SAVR (*Figure 3*). TAV AS patients had worse survival than expected regardless of preoperative symptom severity, with highly symptomatic TAV AS patients having worse relative survival. Mildly symptomatic TAV AS patients had a relative survival of 95%, 89%, 69%, and 41% at 1-, 5-, 10-, and 15-year follow-up after SAVR. Highly symptomatic TAV AS patients had relative survival rates of 97%, 82%, 57%, and 26% at 1-, 5-, 10-, and 15-year follow-up after SAVR (*Figure 3*).

Sensitivity analyses

NT-proBNP levels were available in 56% (597/1054) of the cohort. Patients with NYHA III-IV symptoms had higher log-transformed NT-proBNP levels than those with NYHA I–II symptoms (Wilcoxon rank-sum test, $P = .039$). In a logistic regression analysis, higher log-NT-proBNP was associated with increased odds of NYHA III-IV status (OR 1.16, 95% CI 1.01–1.35, $P = .044$), supporting concordance between biomarker-defined and symptom-defined disease severity. When adding NT-proBNP in the Cox proportional hazards regression model, the effect estimates remained largely unchanged, suggesting that NYHA category provides independent prognostic information. Furthermore, NT-proBNP was also independently associated with mortality. Importantly, there was a significant interaction between NT-proBNP and aortic valve morphology ($P = .016$), indicating effect modification. Specifically, the association between NT-proBNP and mortality was stronger in BAV AS patients compared with TAV AS patients. In TAV AS, the relationship was attenuated, although the direction of association remained positive (*Figure 4*).

To mitigate confounding in our Cox proportional hazards regression analysis, our adjustment strategy was guided by a prespecified DAG, which was used to identify a minimally sufficient set of covariates for adjustment based on causal relationships between exposure, outcome, and potential confounders. After adjusting for all variables suggested by the DAG, NYHA III-IV remained independently associated with all-cause mortality for BAV AS patients (HR = 1.80, 95% CI 1.12–2.90) but not for patients with TAV AS. We performed an E-value sensitivity analysis to assess the robustness of the observed association of unmeasured confounding. The E-value for the observed hazard ratio (HR = 1.80) was 3.00, indicating that an unmeasured confounder would need to be associated with both the exposure and outcome by a risk ratio of at least 3.00 each to fully explain away the observed association. The E-value for the lower bound of the 95% CI (1.12) was 1.51, indicating the minimal strength of association an unmeasured confounder would need to have with both exposure and outcome, beyond the measured covariates, to explain away the observed association and shift the confidence interval to include the null value.

Discussion

In this observational study, we investigated the influence of preoperative symptom severity on postoperative survival in BAV AS and TAV AS patients after SAVR. The key finding was that milder preoperative symptoms were associated with better long-term prognosis for BAV AS patients, and comparable to that of the general population up to 15 years after intervention. In contrast, highly symptomatic BAV AS

Table 2 Baseline characteristics of BAV AS and TAV AS patients stratified according to preoperative symptom status

	BAV NYHA I-II (*n* = 207)	BAV NYHA III-IV (*n* = 309)	*P* value	TAV NYHA I-II (*n* = 167)	TAV NYHA III-IV (*n* = 371)	*P* value
Age, years	62.1 (± 10.6)	64.6 (± 10.8)	.011	70.1 (± 9.1)	73.3 (± 7.6)	<.001
Male sex, *n* (%)	153 (73.9)	182 (58.9)	<.001	101 (60.5)	175 (47.2)	.006
Height, cm	174.6 (± 9.8)	171.1 (± 10.2)	<.001	171.1 (± 9.2)	168.8 (± 9.6)	.008
Weight, kg	81.2(± 13.8)	81.3 (± 16.2)	.957	79.5 (± 14.0)	80.0 (± 16.5)	.713
Body mass index, g/m^2	26.6 (± 4.0)	27.7 (± 4.4)	.006	27.1 (± 4.0)	28.0 (± 4.8)	.030
Hypertension, *n* (%)	103 (49.8)	173 (56.0)	.194	109 (65.3)	280 (75.5)	.019
Diabetes mellitus, *n* (%)	15 (7.2)	34 (11.0)	.203	21 (12.6)	86 (23.2)	.006
Hypercholesterolemia, *n* (%)	66 (31.9)	99 (32.0)	>.99	76 (45.5)	147 (39.6)	.235
Chronic pulmonary disease, *n* (%)	6 (2.9)	39 (12.6)	<.001	22 (13.2)	55 (14.8)	.709
Atrial fibrillation, *n* (%)	9 (4.3)	38 (12.3)	.004	10 (6.0)	57 (15.4)	.004
Peripheral artery disease, *n* (%)	5 (2.4)	15 (4.9)	.240	8 (4.8)	27 (7.3)	.372
Prior TIA/stroke, *n* (%)	12 (5.8)	31 (10.0)	.123	7 (4.2)	45 (12.1)	.006
Mean gradient ≥60 mmHg, *n* (%)	54 (26.1)	82 (26.5)	.991	51 (30.5)	90 (24.3)	.154
eGFR <60 ml/min/1.73 m^2, *n* (%)	7 (3.4)	23 (7.4)	.082	21 (12.6)	61 (16.4)	.271
Ascending aortic aneurysm, *n* (%)	29 (14.0)	56 (18.1)	.266	4 (2.4)	10 (2.7)	>.99
Type of prosthesis			.460			.058
Mechanical, *n* (%)	90 (42)	123 (58)		35 (40)	52 (60)	
Biological, *n* (%)	117 (39)	186 (61)		132 (29)	319 (71)	
Prosthesis size, mm	23.4 (±1.6)	23.2 (±1.7)	.251	22.6 (±1.8)	22.4 (±1.6)	.259

TIA, transient ischaemic attack; eGFR, estimated glomerular filtration rate; NT-proBNP, N-terminal pro-brain natriuretic peptide.

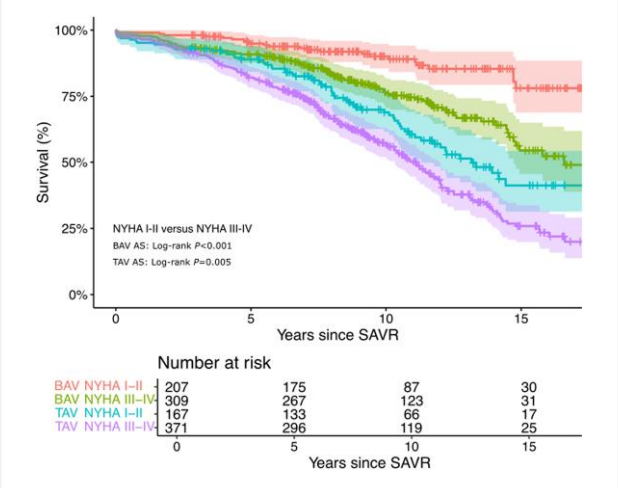


Figure 1 Survival after SAVR. Kaplan–Meier curves illustrating crude survival after SAVR stratified by aortic valve morphology and preoperative symptom severity

patients in NYHA class III or IV prior to SAVR had worse survival compared with the general population. For TAV AS patients, pre-operative symptom severity was not associated with post-operative prognosis, and both mildly symptomatic and highly symptomatic TAV AS patients had worse survival compared with the general population. Sensitivity analysis using NT-proBNP as a marker of disease severity yielded findings consistent with the primary interaction observed for NYHA category. This concordance supports the robustness of the effect modification by aortic valve morphology, suggesting that the relationship between disease severity and mortality after SAVR may differ between bicuspid and tricuspid aortic stenosis.

A loss in life expectancy after SAVR has previously been reported, and this survival penalty is most pronounced among younger patients,[27,28] where a larger proportion presumably have a BAV. Comparative studies that have investigated outcomes for BAV AS and TAV AS patients after SAVR have systematically reported worse prognosis for TAV AS patients. However, we believe that this comparison is not relevant because, even in age- and sex-matched cohorts, TAV AS patients have significantly more prevalent comorbidities.[19] Therefore, TAV AS patients will not only be at higher surgical risk they will also be more likely to encounter events related to their comorbidities rather than what can be related to the aortic valve disease. This is likely the reason why preoperative symptom status was not associated with postoperative survival in TAV AS patients in the present study, and that both mildly symptomatic and highly symptomatic TAV AS patients demonstrated worse survival compared with an age- and sex-matched population.

Due to the different patient characteristics of BAV and TAV patients with severe AS, some studies have investigated prognosis exclusively in BAV patients undergoing SAVR, and contextualized it to the expected survival of the general population. To date, two studies have reported

Table 3 Relative survival in BAV AS and TAV AS patients

	Bicuspid aortic valve					
	NYHA I-II			NYHA III-IV		
	Patients (*n*)	Observed survival, %	Relative survival, %	Patients (*n*)	Observed survival, %	Relative survival, %
1 year	205	99 (98–100)	99 (98–100)	302	98 (96–99)	99 (98–101)
5 years	175	95 (92–98)	101 (98–104)	267	91 (88–94)	98 (95–102)
10 years	87	90 (86–95)	105 (100–111)	123	76 (71–82)	94 (87–101)
15 years	30	78 (69–86)	105 (93–119)	31	54 (46–65)	82 (69–97)
	Tricuspid aortic valve					
	NYHA I-II			NYHA III-IV		
	Patients (*n*)	Observed survival, %	Relative survival, %	Patients (*n*)	Observed survival, %	Relative survival, %
1 year	159	95 (92–99)	97 (98–101)	358	97 (95–98)	99 (97–101)
5 years	133	89 (84–94)	100 (96–102)	296	82 (78–86)	97 (95–101)
10 years	66	69 (61–77)	95 (88–105)	119	57 (52–63)	88 (80–97)
15 years	17	41 (31–54)	72 (55–95)	25	26 (20–34)	60 (46–78)

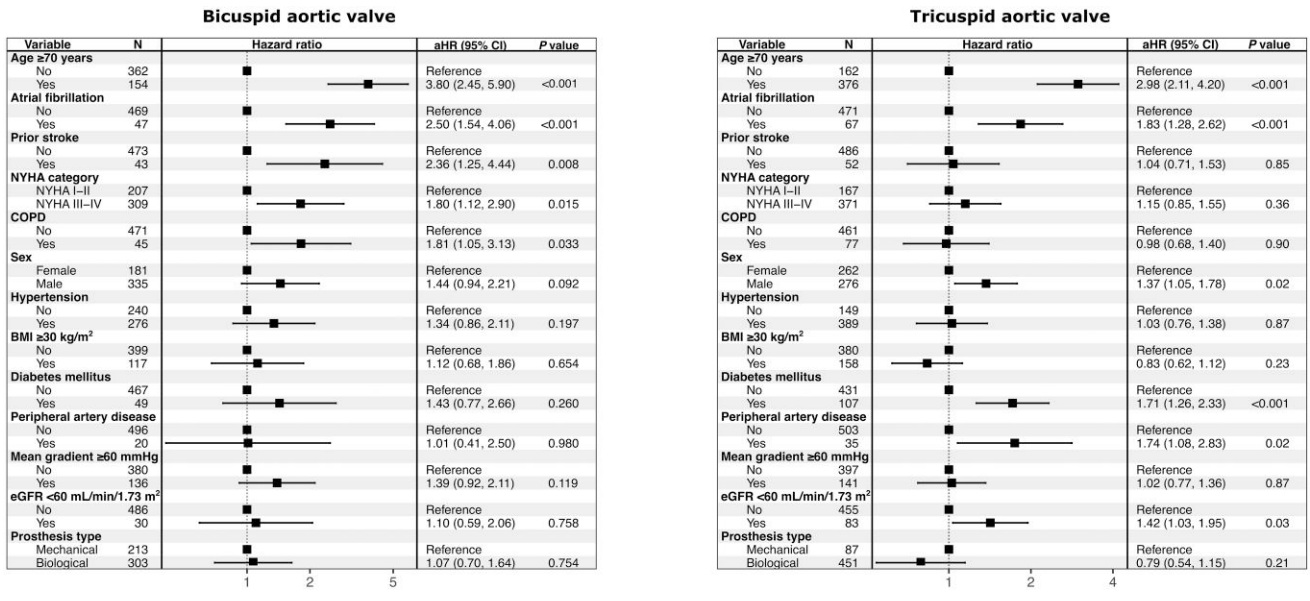


Figure 2 Forest plot showing multivariable associations with mortality after SAVR stratified by aortic valve morphology. A multivariable Cox proportional hazards regression analysis was conducted to investigate the association between baseline characteristics and all-cause mortality after SAVR. Among patients with BAV AS, preoperative NYHA III-IV was independently associated with mortality, whereas this association was not observed in patients with TAV AS

that the observed survival of BAV patients after SAVR is excellent and comparable to that of the general population.[29,30] Several important differences between these studies and the present study may explain the discrepancies in the results. First of all, we stratified patients according to preoperative symptom status to investigate whether symptom severity was associated with postoperative survival or not. Among the BAV AS cohort in our study, 40% were classified as mildly symptomatic, whereas the majority of patients in the study by Glaser *et al.* were mildly symptomatic (77% in NYHA I-II).[30] In the study by Holmgren *et al.*, 50% of the BAV cohort was in NYHA I-II.[29] This could

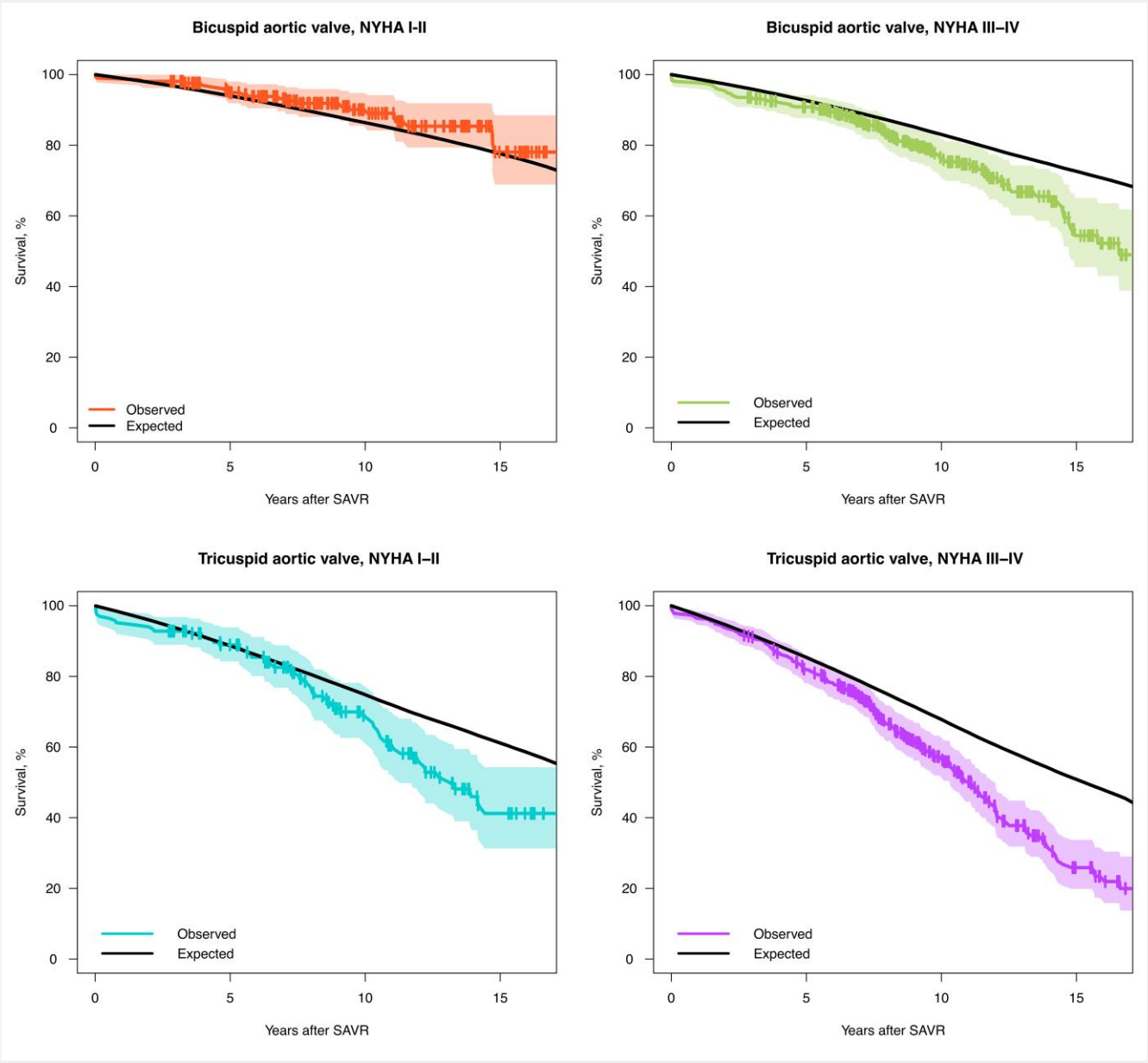


Figure 3 Observed and expected survival. Kaplan-Meier curves illustrating observed survival and 95% confidence intervals stratified according to aortic valve morphology and preoperative symptom severity, compared with the expected survival of the general population matched for age, sex and calendar year

explain their excellent outcomes, which are also in line with the excellent survival of our mildly symptomatic BAV AS cohort. Furthermore, while we excluded patients with isolated aortic regurgitation (AR), they constituted 22% and 10% of the total study populations in the respective studies.[29,30] Aortic regurgitation causes volume overload rather than pressure overload and is therefore associated with a different pattern of cardiac remodelling (eccentric vs concentric) and less fibrosis, which in turn is associated with better capacity of left ventricular recovery after intervention. BAV AR patients are also younger at the time of intervention,[31] with an overall longer life-expectancy. In patients with heart failure, AR is associated with better prognosis than AS, regardless of ejection fraction category.[32] The inclusion of AR patients could also partly explain the overall excellent outcomes in the studies by Glaser *et al.* and Holmgren *et al.*[29,30] Moreover, the median follow-up time after SAVR for the BAV AS patients in our cohort was 9.5 years. In contrast, Holmgren *et al.*[29] had a median follow-up time of 4.9 years, and Glaser *et al.*[30] had a mean follow-up time of 6.3 years. Altogether, we had longer overall follow-up for BAV AS patients, which gives a better estimate of the long-term survival in this patient group.

The optimal timing for AVR for patients with severe AS remains under discussion. The potential benefit of early intervention to arrest or even reverse AS-induced cardiac damage needs to be balanced to the risk associated with a prosthetic aortic valve (thromboembolism, bleeding, endocarditis, and valve failure necessitating reintervention).[33] Recent randomized trials have therefore investigated the potential benefit of early intervention in asymptomatic AS patients as compared with a watchful waiting strategy. To date, survival benefit from early intervention of asymptomatic AS patients has been demonstrated in

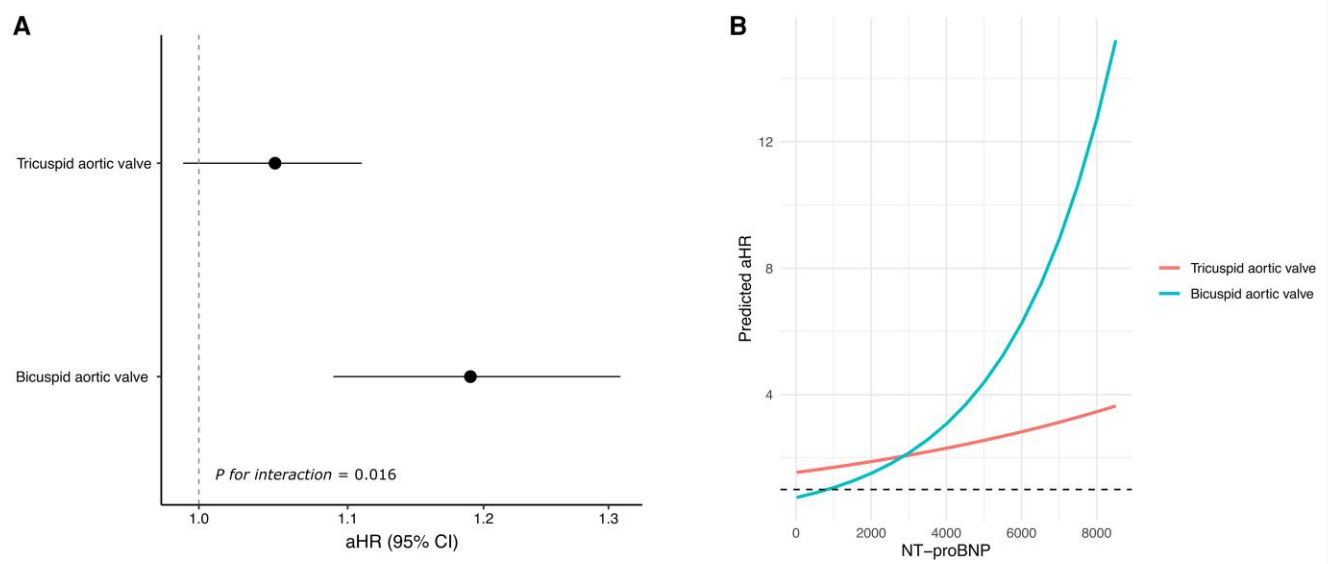


Figure 4 Interaction between NT-proBNP and aortic valve morphology on all-cause mortality. (*A*) Adjusted HR for all-cause mortality after SAVR per 500 ng/l increase in NT-proBNP, stratified by aortic valve morphology in the sensitivity analysis. This panel provides the primary statistical quantification of effect modification by aortic valve morphology. (*B*) Predicted aHR for all-cause mortality across NT-proBNP levels (per 500 ng/l increase) stratified by aortic valve morphology, estimated from the multivariable Cox proportional hazards regression analysis adjusted for baseline covariates as specified in the Methods. This panel visualizes the clinical range of interaction. The concordance between the stratified effect estimates (*A*) and the model-derived risk gradients (*B*) provides evidence of effect modification by aortic valve morphology

two trials. In the Randomized Comparison of Early Surgery vs Conventional Treatment in Very Severe Aortic Stenosis (RECOVERY) trial,[12] asymptomatic AS patients referred for early SAVR had lower operative mortality as well as a lower cumulative incidence of cardiovascular death during an 8-year follow-up. These benefits were sustained and further reinforced at 10 years, with persistent separation of event curves showing continued reductions in all-cause and cardiovascular mortality and fewer late sudden deaths in the early surgery group compared with conservative management.[34] In the aortic valve replacement vs conservative treatment in asymptomatic aortic stenosis (AVATAR) trial,[13] early intervention was associated with lower all-cause mortality at 5 years, although the effect on cardiovascular death was non-significant. In contrast, the transcatheter aortic-valve replacement for asymptomatic severe aortic stenosis (EARLY TAVR) showed no effect of early intervention on hard endpoints.[14] Similarly, in the early intervention in patients with asymptomatic severe aortic stenosis and myocardial fibrosis (EVOLVED) trial,[35] early intervention of asymptomatic patients with evidence of myocardial fibrosis had no effect on all-cause mortality after 5 years of follow-up. Interestingly, RECOVERY was the only trial to demonstrate an effect of early intervention on cardiovascular mortality. Although it should be acknowledged that the RECOVERY trial investigated the benefit of early SAVR in very severe asymptomatic AS, meaning that some patients already fulfilled a relative indication for SAVR, this is the only trial that included a majority of BAV AS patients. In fact, 67% of the patients randomized to early SAVR had a BAV. In contrast, only a minority of BAV AS patients were included in the AVATAR (14%),[13] EVOLVED (29%)[35] and EARLY TAVR (8%) trials that demonstrated no effect of early intervention on postoperative survival.

We have previously demonstrated that BAV AS patients have worse LV remodelling and LV function compared with TAV counterparts, which translates into a higher risk of several postoperative complications.[20–22] BAV AS patients have a higher incidence of postoperative heart failure events,[20] persisting postoperative atrial fibrillation,[21] and severe conduction disturbances including new-onset complete atrioventricular block and left bundle branch block (LBBB).[22] Interestingly, new-onset LBBB was associated with worse survival for BAV AS but not TAV AS patients. Because BAV AS patients tend to show more pronounced adverse LV remodelling before SAVR than TAV AS patients, a new-onset LBBB is likely to be less well tolerated in this group. Earlier intervention in BAV AS patients may help reduce the incidence of postoperative complications and lessen their associated consequences. In our sensitivity analysis, we observed a significant interaction between NT-proBNP and aortic valve morphology. Specifically, the association between NT-proBNP and mortality was stronger in BAV AS patients compared with TAV AS patients, where the relationship was attenuated. This further supports our conclusion that mortality in BAV AS patients is primarily driven by adverse LV remodelling, and that earlier intervention might be beneficial in these patients. Several others have also demonstrated the prognostic significance of adverse cardiac remodelling on prognosis after AVR,[7,36–38] with a notably greater impact observed in younger patients.[39] Furthermore, patients with AS and coexisting CAD report more severe symptoms with less severe AS and AS-related adverse myocardial remodelling.[39] It is therefore important to study prognosis in AS patients without coexisting CAD, especially since CAD is significantly more frequent in TAV AS patients.[19] Since the development of irreversible myocardial fibrosis progresses nonlinearly,[9] with an accelerating rate as the AS severity increases, a majority of patients will likely develop symptoms in the near future. In the EARLY TAVR study, almost 30% developed symptoms and underwent intervention within 6 months from randomization. In the RECOVERY trial, the median time from randomization to intervention in the conservative care group was just under 2 years. This indicates that the time from asymptomatic status to symptom onset is relatively short, and the exposure to prosthetic valve-related complications is not significantly longer with an early interventional strategy. This

perspective is important to consider when discussing the risks of earlier intervention.

Clinical perspectives

The findings of this study reinforce that BAV and TAV patients with severe AS should not be assessed as one entity when being considered for SAVR, as the groups are heterogeneous with regard to age and cardiovascular risk factors, and BAV patients generally have a longer expected survival after surgery. Our results further support previous conclusions that mildly symptomatic patients with severe AS may benefit from early SAVR, adding the important aspect that this effect may be primarily driven by BAV AS patients. A randomized controlled trial assessing outcomes in asymptomatic BAV AS after SAVR, where early intervention is compared to watchful waiting, is needed to verify if asymptomatic BAV AS patients would benefit from early surgery.

Limitations

First, although we did all measures to adjust for potential confounders, the observational design of the study infers a risk of residual confounding. The *E*-value for the observed hazard ratio (HR = 1.80) was 3.00, indicating that an unmeasured confounder would need to be associated with both the exposure and outcome by a risk ratio of at least 3.00 each to fully explain away the observed association, implying that only a strong unmeasured confounder could account for the observed effect. While weaker confounding (RR = 1.51) could shift the confidence interval to include the null, such an effect would need to act independently of the comprehensive set of covariates already included. Together, these findings suggest that the results of the present study are reasonably robust to unmeasured confounding, although modest residual bias cannot be excluded. Second, this was a single-centre study and the results might not be generalized to the overall BAV AS and TAV AS populations. Third, we did not investigate cause-specific survival. However, cause-of-death reports are often unavailable or subject to misclassification, and relative survival is an established surrogate measure of cause-specific survival that does not rely on the recorded cause of death. By comparing observed survival in the study population with expected survival in the general population matched on age, sex, and calendar year, relative survival estimates the excess mortality attributable to the disease or intervention. Fourth, echocardiographic data beyond LVEF were not readily available for all patients in this retrospective cohort and were therefore not included in the present analysis, which may limit the ability to fully account for structural LV remodelling. However, both NYHA functional class and NT-proBNP remained independently associated with mortality in the multivariable analyses, supporting their role as robust markers of disease severity and prognosis in this cohort. Fifth, our study cohort was limited to patients undergoing surgical AVR, and therefore the findings may not be generalized to patients treated with transcatheter AVR, who may differ with respect to baseline characteristics and risk profiles. Finally, although survival was most likely not majorly influenced by prosthetic valve-related complications, as evident by the excellent survival in the mildly symptomatic BAV AS patients, we did not investigate other morbidity measures such as structural valve deterioration, prosthetic valve endocarditis or valve thrombosis requiring treatment or reintervention, severe bleeding events, and so on. These are also important factors to consider when discussing early intervention.

Conclusions

Mildly symptomatic BAV AS patients had a survival comparable to that of the general population up to 15 years after intervention. In contrast, highly symptomatic BAV AS patients had significantly worse outcomes. Among TAV AS patients, preoperative symptom severity had a limited effect on postoperative survival, which was more strongly influenced by the presence of severe comorbidities. The results suggest that BAV AS patients could benefit from earlier intervention before development of severe symptoms. Our findings are hypothesis generating and should be confirmed in a prospective randomized controlled trial investigating early AVR compared with watchful waiting exclusively in BAV AS patients.

Author contributions

Johan O. Wedin (Conceptualization, Formal analysis, Funding acquisition, Investigation, Methodology, Software, Visualization, Writing—original draft [lead], Data curation, Project administration, Resources, Writing—review & editing [equal]), Nathalie Hjert (Investigation, Methodology, Visualization, Writing—original draft, Writing—review & editing [supporting]), Sergey Rodin (Conceptualization, Investigation, Methodology, Project administration, Supervision, Validation, Writing—original draft, Writing—review & editing [supporting]), Oscar E. Simonson (Conceptualization, Data curation, Investigation, Methodology, Project administration, Resources, Supervision, Writing—review & editing [supporting]), Frank A. Flachskampf (Conceptualization, Investigation, Resources, Supervision, Validation, Writing—review & editing [supporting]), Stefan K. James (Conceptualization, Methodology, Resources, Validation, Writing—review & editing [supporting], Supervision [equal]), Elisabeth Ståhle (Conceptualization, Data curation, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Writing—review & editing [equal]), and Karl-Henrik Grinnemo (Conceptualization, Formal analysis, Investigation, Methodology, Validation [equal], Data curation, Project administration, Resources, Supervision, Writing—review & editing [lead], Funding acquisition, Software, Visualization, Writing—original draft [supporting])

Supplementary data

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

Declarations

Data availability

The analysed dataset and programming codes underlying this manuscript will be shared on reasonable request to the corresponding author.

Disclosure of Interest

Drs Grinnemo, Rodin and Simonson are shareholders of the company AVulotion AB. All other authors have nothing to disclose.

Funding

This study was supported by the following grants: Lennander's foundation; Erik, Karin and Gösta Selander's foundation; Royal Society of Arts and Scientists; Uppsala County Association Against Heart and Lung Diseases; The Swedish Heart and Lung Association; The Swedish Heart and Lung Foundation (Application number 20241226); Uppsala County Council; Åke Senning's memory. The sponsors had no role in study design or writing of the manuscript.

Ethical Approval

Ethical Approval was not required.

Pre-registered Clinical Trial Number

None supplied.

References

1. Iung B, Delgado V, Rosenhek R, Price S, Prendergast B, Wendler O, *et al.* Contemporary presentation and management of valvular heart disease. *Circulation* 2019;**140**:1156–69. https://doi.org/10.1161/CIRCULATIONAHA.119.041080
2. Baumgartner H, Iung B, Otto CM. Timing of intervention in asymptomatic patients with valvular heart disease. *Eur Heart J* 2020;**41**:4349–56. https://doi.org/10.1093/eurheartj/ehaa485
3. Maznyczka A, Prendergast B, Dweck M, Windecker S, Généreux P, Hildick-Smith D, *et al.* Timing of aortic valve intervention in the management of aortic stenosis. *JACC Cardiovasc Interv* 2024;**17**:2502–14. https://doi.org/10.1016/j.jcin.2024.08.046
4. Otto CM. timing of aortic valve surgery. *Heart* 2000;**84**:211–8. https://doi.org/10.1136/heart.84.2.211
5. Otto CM, Nishimura RA, Bonow RO, Carabello BA, Erwin JP, Gentile F, *et al.* 2020 ACC/AHA guideline for the management of patients with valvular heart disease: executive summary: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *Circulation* 2021;**143**:e35–71. https://doi.org/10.1161/CIR.0000000000000932
6. 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
7. 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
8. Everett RJ, Treibel TA, Fukui M, Lee H, Rigolli M, Singh A, *et al.* Extracellular myocardial volume in patients with aortic stenosis. *J Am Coll Cardiol* 2020;**75**:304–16. https://doi.org/10.1016/j.jacc.2019.11.032
9. Everett RJ, Tastet L, Clavel M-A, Chin CWL, Capoulade R, Vassiliou VS, *et al.* Progression of hypertrophy and myocardial fibrosis in aortic stenosis: a multicenter cardiac magnetic resonance study. *Circ Cardiovasc Imaging* 2018;**11**:e007451. https://doi.org/10.1161/CIRCIMAGING.117.007451
10. Kang D-H, Park S-J, Rim JH, Yun S-C, Kim D-H, Song J-M, *et al.* Early surgery vs conventional treatment in asymptomatic very severe aortic stenosis. *Circulation* 2010;**121**:1502–9. https://doi.org/10.1161/CIRCULATIONAHA.109.909903
11. Taniguchi T, Morimoto T, Shiomi H, Ando K, Kanamori N, Murata K, *et al.* Initial surgical vs conservative strategies in patients with asymptomatic severe aortic stenosis. *J Am Coll Cardiol* 2015;**66**:2827–38. https://doi.org/10.1016/j.jacc.2015.10.001
12. Kang D-H, Park S-J, Lee S-A, Lee S, Kim D-H, Kim H-K, *et al.* Early surgery or conservative care for asymptomatic aortic stenosis. *N Engl J Med* 2020;**382**:111–9. https://doi.org/10.1056/NEJMoa1912846
13. Banovic M, Putnik S, Da Costa BR, Penicka M, Deja MA, Kotrc M, *et al.* Aortic valve replacement vs. Conservative treatment in asymptomatic severe aortic stenosis: long-term follow-up of the AVATAR trial. *Eur Heart J* 2024;**45**:4526–35. https://doi.org/10.1093/eurheartj/ehae585
14. Généreux P, Schwartz A, Oldemeyer JB, Pibarot P, Cohen DJ, Blanke P, *et al.* Transcatheter aortic-valve replacement for asymptomatic severe aortic stenosis. *N Engl J Med* 2025;**392**:217–27. https://doi.org/10.1056/NEJMoa2405880
15. Beusch CM, Simonson OE, Wedin JO, Sabatier P, Felldin U, Kadekar S, *et al.* Analysis of local extracellular matrix identifies different aetiologies behind bicuspid and tricuspid aortic valve degeneration and suggests therapies. *Cell Mol Life Sci* 2023;**80**:268. https://doi.org/10.1007/s00018-023-04926-1
16. Yang L-T, Ye Z, Wajih Ullah M, Maleszewski JJ, Scott CG, Padang R, *et al.* Bicuspid aortic valve: long-term morbidity and mortality. *Eur Heart J* 2023;**44**:4549–62. https://doi.org/10.1093/eurheartj/ehad477
17. Sillesen A-S, Vøgg O, Pihl C, Raja AA, Sundberg K, Vedel C, *et al.* Prevalence of bicuspid aortic valve and associated aortopathy in newborns in Copenhagen, Denmark. *JAMA* 2021;**325**:561–7. https://doi.org/10.1001/jama.2020.27205
18. Roberts WC, Ko JM. Frequency by decades of unicuspid, bicuspid, and tricuspid aortic valves in adults having isolated aortic valve replacement for aortic stenosis, with or without associated aortic regurgitation. *Circulation* 2005;**111**:920–5. https://doi.org/10.1161/01.CIR.0000155623.48408.C5
19. Huntley GD, Thaden JJ, Alsidawi S, Michelena HI, Maleszewski JJ, Edwards WD, *et al.* Comparative study of bicuspid vs. tricuspid aortic valve stenosis. *Eur Heart J Cardiovasc Imaging* 2018;**19**:3–8. https://doi.org/10.1093/ehjci/jex211
20. Wedin JO, Vedin O, Rodin S, Simonson OE, Hörsne Malmborg J, Pallin J, *et al.* Patients with bicuspid aortic stenosis demonstrate adverse left ventricular remodeling and impaired cardiac function before surgery with increased risk of postoperative heart failure. *Circulation* 2022;**146**:1310–22. https://doi.org/10.1161/CIRCULATIONAHA.122.060125
21. Wedin JO, Rodin S, Flachskampf FA, Simonson OE, Pallin J, Hörsne Malmborg J, *et al.* Left atrial dysfunction in bicuspid aortic valve patients with severe aortic stenosis is associated with post-operative atrial fibrillation following aortic valve replacement. *Eur Heart J Open* 2024;**4**:oeae020. https://doi.org/10.1093/ehjopen/oeae020
22. Wedin JO, Näslund V, Rodin S, Simonson OE, Flachskampf FA, James SK, *et al.* Conduction disturbances and outcome after surgical aortic valve replacement in patients with bicuspid and tricuspid aortic stenosis. *Circulation* 2025;**151**:288–98. https://doi.org/10.1161/CIRCULATIONAHA.124.070753
23. Louca A, Petursson P, Sundström J, Rawshani A, Hagström H, Settergren M, *et al.* Comparative outcomes of transcatheter aortic valve replacement in bicuspid vs. tricuspid aortic valve stenosis patients: insights from the SWEDEHEART registry. *IJC Heart Vasc* 2025;**59**:101705. https://doi.org/10.1016/j.ijcha.2025.101705
24. Perme MP, Pavlic K. Nonparametric relative survival analysis with the *R* package relsurv. *J Stat Softw* 2018;**87**:1–27. https://doi.org/10.18637/jss.v087.i08
25. Wickham H. *ggplot2*. Cham: Springer International Publishing. 2016. http://link.springer.com/10.1007/978-3-319-24277-4 (29 May 2025, date last accessed).
26. VanderWeele TJ, Ding P. Sensitivity analysis in observational research: introducing the E-value. *Ann Intern Med* 2017;**167**:268–74. https://doi.org/10.7326/M16-2607
27. Enger TB, Pleym H, Stenseth R, Greiff G, Wahba A, Videm V. Reduced long-term relative survival in females and younger adults undergoing cardiac surgery: a prospective cohort study. *PLoS One* 2016;**11**:e0163754. https://doi.org/10.1371/journal.pone.0163754
28. Glaser N, Persson M, Jackson V, Holzmann MJ, Franco -Cereceda A, Sartipy U. Loss in life expectancy after surgical aortic valve replacement. *J Am Coll Cardiol* 2019;**74**:26–33. https://doi.org/10.1016/j.jacc.2019.04.053
29. Holmgren A, Enger TB, Näslund U, Videm V, Valle S, Evjemo KJD, *et al.* Long-term results after aortic valve replacement for bicuspid or tricuspid valve morphology in a Swedish population. *Eur J Cardiothorac Surg* 2020;**59**:570–6. https://doi.org/10.1093/ejcts/ezaa348
30. Glaser N, Jackson V, Eriksson P, Sartipy U, Franco-Cereceda A. Relative survival after aortic valve surgery in patients with bicuspid aortic valves. *Heart* 2021;**107**:1167–72. https://doi.org/10.1136/heartjnl-2020-318733
31. Yotsumoto G, Moriyama Y, Toyohira H, Shimokawa S, Iguro Y, Watanabe S, *et al.* Congenital bicuspid aortic valve: analysis of 63 surgical cases. *J Heart Valve Dis* 1998;**7**:500–3.
32. Shahim B, Shahim A, Adamo M, Chioncel O, Benson L, Crespo-Leiro MG, *et al.* Prevalence, characteristics and prognostic impact of aortic valve disease in patients with heart failure and reduced, mildly reduced, and preserved ejection fraction: an analysis of the ESC heart failure long-term registry. *Eur J Heart Fail* 2023;**25**:1049–60. https://doi.org/10.1002/ejhf.2908
33. Vesey JM, Otto CM. Complications of prosthetic heart valves. *Curr Cardiol Rep* 2004;**6**:106–11. https://doi.org/10.1007/s11886-004-0007-x
34. Kang D-H, Park S-J, Kim GY, Lee S, Sun BJ, Kim JB, *et al.* Early surgery or conservative care for asymptomatic aortic stenosis at 10 years. *N Engl J Med* 2026;**394**:1167–74. https://doi.org/10.1056/NEJMoa2511920
35. 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. *JAMA* 2025;**333**:213–21. https://doi.org/10.1001/jama.2024.22730
36. Vollema EM, Amanullah MR, Ng ACT, Van Der Bijl P, Prevedello F, Sin YK, *et al.* Staging cardiac damage in patients with symptomatic aortic valve stenosis. *J Am Coll Cardiol* 2019;**74**:538–49. https://doi.org/10.1016/j.jacc.2019.05.048
37. Yang L-T, Boler A, Medina-Inojosa JR, Scott CG, Maurer MJ, Eleid MF, *et al.* Aortic stenosis progression, cardiac damage, and survival: comparison between bicuspid and tricuspid aortic valves. *JACC Cardiovasc Imaging* 2021;**14**:1113–26. https://doi.org/10.1016/j.jcmg.2021.01.017
38. Généreux P, Pibarot P, Redfors B, Bax JJ, Zhao Y, Makkar RR, *et al.* Evolution and prognostic impact of cardiac damage after aortic valve replacement. *J Am Coll Cardiol* 2022;**80**:783–800. https://doi.org/10.1016/j.jacc.2022.05.006
39. Beach JM, Mihaljevic T, Svensson LG, Rajeswaran J, Marwick T, Griffin B, *et al.* Coronary artery disease and outcomes of aortic valve replacement for severe aortic stenosis. *J Am Coll Cardiol* 2013;**61**:837–48. https://doi.org/10.1016/j.jacc.2012.10.049