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ORIGINAL RESEARCH ARTICLE

Patients With Bicuspid Aortic Stenosis Demonstrate Adverse Left Ventricular Remodeling and Impaired Cardiac Function Before Surgery With Increased Risk of Postoperative Heart Failure

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BACKGROUND: Differences in adverse cardiac remodeling between patients who have bicuspid (BAV) and tricuspid aortic valve (TAV) with severe isolated aortic stenosis (AS) and its prognostic impact after surgical aortic valve replacement remains unclear. We sought to investigate differences in preoperative diastolic and systolic function in patients with BAV and TAV who have severe isolated AS and the incidence of postoperative heart failure hospitalization and mortality.

METHODS: Two hundred seventy-one patients with BAV (n=152) or TAV (n=119) and severe isolated AS without coronary artery disease or other valvular heart disease, scheduled for surgical aortic valve replacement, were prospectively included. Comprehensive preoperative echocardiographic assessment of left ventricular (LV) diastolic and systolic function was performed. The heart failure events were registered during a mean prospective follow-up of 1260 days versus 1441 days for patients with BAV or TAV, respectively.

RESULTS: Patients with BAV had a more pronounced LV hypertrophy with significantly higher indexed LV mass ([LVMi] 134 g/m^2 versus 104 g/m^2, $P<0.001$), higher prevalence of LV diastolic dysfunction (72% versus 44%, $P<0.001$), reduced LV ejection fraction (55% versus 60%, $P<0.001$), significantly impaired global longitudinal strain ($P<0.001$), significantly higher NT-proBNP (N-terminal pro-brain natriuretic peptide) levels ($P=0.007$), and a higher prevalence of preoperative levosimendan treatment ($P<0.001$) than patients with TAV. LVMi was associated with diastolic dysfunction in both patients with BAV and TAV. There was a significant interaction between aortic valve morphology and LVMi on LV ejection fraction, which indicated a pronounced association between LVMi and LV ejection fraction for patients with BAV and lack of association between LVMi and LV ejection fraction for patients with TAV. Postoperatively, the patients with BAV required significantly more inotropic support ($P<0.001$). The patients with BAV had a higher cumulative incidence of postoperative heart failure admissions compared with patients with TAV (28.2% versus 10.6% at 6 years after aortic valve replacement, log-rank $P=0.004$). Survival was not different between patients with BAV and TAV (log-rank $P=0.165$).

CONCLUSIONS: Although they were significantly younger, patients with BAV who had isolated severe AS had worse preoperative LV function and an increased risk of postoperative heart failure hospitalization compared with patients who had TAV. Our findings suggest that patients who have BAV with AS might benefit from closer surveillance and possibly earlier intervention.

Key Words: aortic valve stenosis ■ bicuspid aortic valve disease ■ heart failure ■ heart failure, diastolic ■ tricuspid valve ■ ventricular dysfunction, left

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Clinical Perspective

What Is New?

- It is unknown whether the cardiac remodeling differs between patients with bicuspid (BAV) and tricuspid aortic valves with severe isolated aortic stenosis, and whether these differences affect the incidence of postoperative heart failure hospitalization and mortality.
- We prospectively investigated left ventricular function before surgical aortic valve replacement because of isolated severe aortic stenosis in 271 patients with a BAV or tricuspid aortic valve, without concomitant coronary artery disease or other valvular heart disease, and assessed the postoperative incidence of heart failure events.

What Are the Clinical Implications?

- Although significantly younger, patients with BAV had a more pronounced adverse left ventricular remodeling and a higher prevalence of preoperative left ventricular diastolic and systolic dysfunction.
- Patients with BAV had a higher cumulative incidence of postoperative heart failure admissions than patients with tricuspid aortic valves, whereas no difference in survival was observed.
- Patients with BAV with isolated severe aortic stenosis might benefit from closer surveillance of left ventricular function and possibly earlier intervention.

Nonstandard Abbreviations and Acronyms

AS	aortic stenosis
AVR	aortic valve replacement
BAV	bicuspid aortic valve
CK-MB	creatine kinase muscle-brain
DD	diastolic dysfunction
GLS	global longitudinal strain
HF	heart failure
LV	left ventricle
LVEF	left ventricular ejection fraction
LVMi	left ventricular mass index
TAV	tricuspid aortic valve

Aortic stenosis (AS) is one of the most common valvular heart diseases worldwide.[1] Degeneration of tricuspid aortic valve (TAV) or bicuspid aortic valve (BAV) represents the 2 most frequent causes of AS. Although TAV is commonly found in older patients with AS, BAV predominates in younger patients.[2] Although the prevalence of BAV is ≈1% to 2% in the general population,[3] patients with BAV constitute 50% of all patients that undergo surgical aortic valve replacement (AVR) for AS.[2]

The left ventricle (LV) adapts to the chronic pressure overload induced by the AS. Initially, this LV remodeling is beneficial but ultimately transits to a maladaptive state with irreversible systolic LV dysfunction. Diastolic dysfunction (DD) typically precedes systolic LV dysfunction and is associated with adverse outcomes in a variety of cardiovascular diseases, including severe AS.[4,5] LV global longitudinal strain (GLS) is a marker of subclinical systolic LV dysfunction, and an impaired GLS despite preserved LVEF is a powerful parameter of the outcome of AS.[6] Although DD and reduced GLS are common in patients with symptomatic severe AS, reduced LVEF is less frequently observed because of the compensatory mechanisms of the LV to maintain adequate stroke volume.[7–9] Surgical or interventional AVR reverses the excessive LV afterload and is the only effective treatment of severe AS.

Data from several cross-sectional studies suggest that adolescents and young adults with a BAV show early signs of adverse structural LV remodeling even in the absence of valvular dysfunction.[10] Consequently, impaired LV function is more common in individuals with BAV compared with age- and sex-matched TAV controls, and is probably related to a chronically elevated afterload attributable to eccentric aortic valve opening and decreased ascending aortic elasticity.[11,12] In longitudinal studies, it has been shown that individuals with BAV exhibit a higher risk of premature congestive heart failure (HF) than the general population.[13,14] In a recent retrospective study by Yang et al,[15] the progression of BAV and TAV AS was similar, but with higher mortality and cardiac damage in the TAV cohort. Coronary artery disease was significantly more common among patients with TAV AS, which might have affected the long-term outcome. The only echocardiographic study comparing preoperative LV systolic and diastolic function in a surgical cohort of patients with BAV and TAV also included concomitant coronary artery disease, which was more common among patients with TAV.[16] Thus, the effect of isolated AS on LV diastolic and systolic function in patients with BAV and TAV, and whether this affects postoperative outcome, remains unknown.

Because of the lack of evidence, combined with the prognostic relevance of LVEF,[17] GLS,[6] and DD[5] in severe AS, our aim was to perform a prospective comparative study of patients with BAV and TAV with isolated severe AS scheduled for AVR, with focus to investigate differences in (1) preoperative systolic LV function, (2) preoperative diastolic LV function, (3) mortality, and (4) postoperative rate of HF hospitalization.

METHODS

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

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Study Design and Patient Enrollment

In this prospective study, 271 consecutive patients with severe AS scheduled for AVR at a tertiary-level referral center (Uppsala University Hospital, Uppsala, Sweden) were included between January 1, 2014, and May 31, 2021. The diagnosis had been established before referral,[18,19] and the patients were accepted for AVR after evaluation by the Multidisciplinary Heart Valve Team. All patients had severe symptomatic AS or asymptomatic AS and depressed LVEF as indication for AVR. Baseline characteristics including demographic information, medical history, and clinical variables were collected at enrollment, at the time the patients received their preoperative information. Patients with a history of coronary artery disease (significant stenosis detected on preoperative coronary angiography, previous percutaneous coronary intervention, or coronary artery bypass grafting), previous other open-heart surgery, atrial fibrillation/flutter, concomitant moderate or severe aortic regurgitation, concomitant moderate or severe mitral regurgitation, significant mitral annular calcification, and patients scheduled for concomitant surgical procedures other than ascending aortic surgery (n=22 BAV and n=3 TAV, $P<0.001$) were not eligible for inclusion. No patient had a permanent pacemaker. The study was approved by the Ethics Review Board (registration number 2017/221 and 2017/221/1).

Determination of Aortic Valve Morphology

The aortic valve morphology (BAV or TAV) was determined perioperatively by the surgeon and documented directly in the operating room. A BAV was considered present in accordance with the classification system developed by Sievers and Schmidtke.[20]

Echocardiographic Imaging

All patients underwent a comprehensive preoperative transthoracic echocardiogram according to a standardized protocol before surgery. The same certified physician interpreted all examinations. The echocardiograms were obtained using machines from 3 different vendors, Philips EPIQ7 (Philips Medical Systems), GE Vivid E9 (General Electric Healthcare), and Siemens ACUSON SC2000 (Siemens). GLS was calculated off-line with a semiautomatic software (2D Cardiac Performance Analysis, TomTec Imaging System). Detailed description of the examination and interpretation of echocardiographic data are presented in the Supplemental Material.

In summary, the LV end-diastolic volume, LV end-systolic volume, and LVEF were obtained using the Simpson biplane method of discs. LV mass was calculated using the Devereux formula[21] and normalized to body surface area. Diastolic dysfunction was defined according to current guidelines in patients with normal or depressed LVEF.[22] DD was specifically considered present if the patient had depressed LVEF or if at least 3 of the following 4 criteria were present: E/e′ >14, septal e′ velocity <7 cm/s or lateral e′ velocity <10 cm/s, tricuspid regurgitation maximal velocity >2.8 m/s, and left atrial volume index >34 mL/m^2. Patients with 0 to 1 positive criteria had normal diastolic function, whereas patients with 2 positive criteria had indeterminate diastolic function. In patients with DD, the severity was categorized as grade I, grade II, or grade III, on the basis of the mitral inflow pattern (*E/A* ratio). Patients had grade I DD if *E/A* ≤0.8 and E ≤50 cm/s, and grade III DD if *E/A* ≥2. When *E/A* ≤0.8 and E >50 cm/s or *E/A* >0.8 to <2, the grading was based on the 3 criteria E/e′ (>14), tricuspid regurgitation maximal velocity (>2.8 m/s), and left atrial volume index (>34 mL/m^2). If 0 to 1 of 3 criteria was fulfilled, grade I DD was present. If 2 to 3 of 3 criteria were fulfilled, grade II DD was present. GLS was measured from apical 2-, 4-, and 3-chamber views according to recommendations.[23] The endocardial border was traced in the end-systolic frame, whereas the end-diastolic tracing was provided automatically by the software, allowing for manual correction if necessary.

Reproducibility

Inter- and intraobserver reproducibility for relevant parameters were analyzed in a random sample of 12 patients and presented in the Supplemental Material. Consistency of repeated measures was established with the use of Pearson correlation.

Outcome

We investigated the incidence of postoperative HF hospitalization in patients with BAV and TAV. HF was defined as the need for hospital management, either inpatient or outpatient care,[24] because of at least 1 sign or symptom corroborated by objective evidence of HF.[25] To avoid including episodes of HF related to the surgical procedure, we disregarded hospital readmissions attributable to HF within 30 days after the date of surgery. Only patients at risk 30 days after surgery were included (n=268). We did not differentiate between HF with reduced or preserved ejection fraction. Hospital management of complications clearly related to the AVR procedure (either early or late) were not considered HF events. Information on postoperative HF hospitalization was obtained from the electronic medical records. Follow-up was administratively censored on December 31, 2021.

Statistical Analysis

Continuous data are expressed as mean±SD and categorical variables are expressed as numbers (%). Differences in continuous variables between patients with BAV and TAV were analyzed using independent samples *t* test. For categorical tests, the χ^2 test or Fisher exact test was used when appropriate. Differences in HF hospitalization incidence between patients with BAV and TAV was displayed using cumulative incidence function to account for death as a competing risk. Logistic regression was used to investigate the association between LV hypertrophy (LV mass index, LVMi) and diastolic dysfunction, where patients with normal diastolic function were used as a reference category. In this analysis, patients with indeterminate diastolic function were considered to have DD, because indeterminate diastolic function is associated with worse prognosis.[26] Results are presented as odds ratio with 95% CI. An ordinary least-squares regression model was used to investigate the association between systolic function (LVEF) and LV hypertrophy (LVMi). Final models were adjusted for valve morphology, age, sex, diabetes, and hypertension. In the ordinary least-squares regression model, LVMi and age were modeled using restricted cubic splines with 4 knots at the 5th, 35th, 65th, and 95th percentiles, to allow for nonlinear associations. To assess whether the association differed according to valve

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morphology, a multiplicative interaction variable between aortic valve morphology and LVMi was included. The interaction was based only on the linear part of the spline for LVMi. Cox proportional hazard regression analysis was used to compare time to first HF event according to aortic valve morphology. The overall association between aortic valve morphology and increased incidence of HF was estimated in a Cox proportional hazards regression analysis. Given the relatively few HF events, adjustment was restricted to age, sex, and LVEF on the basis of a directed acyclic graph (Figure S1). Results are presented as adjusted hazard ratio with 95% CI. For covariates with a significant main effect in the adjusted Cox proportional hazards regression analysis, interaction with aortic valve morphology on HF hospitalization was tested by inclusion of a multiplicative interaction term in the model (eg, aortic valve morphology×LVEF). Statistical analyses were performed in SAS 9.4, SPSS for Windows 27.0 (SPSS Inc), and R 4.0 (R Core Team. R: a language and environment for statistical computing. 2018) using the rms-package.[27] A 2-tailed *P* value <0.05 was considered statistically significant.

RESULTS

Patient Characteristics

Baseline characteristics of the whole cohort (n=271) and differences between patients with BAV and TAV are summarized in Table 1. Compared with patients who have TAV, patients with BAV were younger (65 years versus 71 years, *P*<0.001) and had less hypertension, type 2 diabetes, hyperlipidemia, and lower body mass index. The prevalence of chronic obstructive pulmonary disease, obstructive sleep apnea, and peripheral artery disease was similar. Systolic blood pressure immediately before AVR was significantly lower in patients with BAV (135 mm Hg versus 141 mm Hg, *P*=0.004), whereas diastolic blood pressure did not differ between groups. Patients with BAV had a significantly higher heart rate than patients with TAV (76 beats/min versus 69 beats/min, *P*<0.001). Patients with BAV had significantly higher NT-proBNP (N-terminal pro-brain natriuretic peptide) levels (1683 ng/L versus 689 ng/L, *P*=0.007) immediately before AVR, despite being equally symptomatic as patients with TAV according to the New York Heart Association classification (*P*=0.329). Preoperative creatinine levels were lower in the BAV cohort (78 µg/L versus 83 µg/L, *P*=0.019). Approximately 9% (14/152) of the patients with BAV received preoperative levosimendan treatment, although none of the patients with TAV required preoperative levosimendan treatment (*P*<0.001).

Echocardiographic Parameters

Echocardiographic parameters for the whole cohort, and differences between patients with BAV and TAV, as well, are shown in Table 2. Inter- and intraobserver intraclass correlation were excellent (>0.9) for all parameters (Supplemental Material). All patients had severe AS and there were no differences in maximal transvalvular velocities, maximal or mean transvalvular gradients, or aortic valve area, but the calculated aortic valve area was significantly smaller in patients with BAV (0.80 cm versus 0.89 cm, *P*=0.007; aortic valve area index, 0.41 cm/m^2 versus 0.45 cm/m^2, *P*=0.002). The diameters at the level of the aortic sinus, sinotubular junction, and ascending aorta were significantly larger in patients with BAV (*P*<0.001). Pressure recovery, measured at the sinotubular junction level, was significantly higher in patients with TAV (*P*<0.001).

LV Diastolic Function

Diastolic function could be analyzed in 227 of 271 (84%) patients, including 130 of 152 (86%) patients with BAV and 97 of 119 (82%) patients with TAV. Diastolic dysfunction was present in 60% (137/227) of these patients, whereas 26% (58/227) had normal diastolic function and 14% (32/117) had indeterminate diastolic function. Grade I DD was found in 15% (34/227), grade II DD in 37% (85/227), and grade III DD in 9% (21/227). The prevalence of DD was significantly higher in patients with BAV than in patients with TAV (72% versus 44%, *P*<0.001) with the following distribution: Grade I DD 20% versus 8% (*P*=0.013); grade II DD 40% versus 34% (*P*=0.334); grade III DD 15% versus 2% (*P*=0.001). Diastolic function was indeterminate in 11% (14/130) of patients with BAV and in 20% (19/97) of patients TAV (*P*=0.066), respectively (Figure S2). Looking at individual diastolic parameters, patients with BAV had larger left atrial volume index, higher tricuspid regurgitation maximal velocity, lower A-wave velocity, higher E/A ratio, and shorter mitral E wave deceleration time than patients with TAV. The septal e′ velocity, lateral e′ velocity, and E/e′ ratio were not different between the groups. There was an association between LVMi and diastolic dysfunction (odds ratio, 1.04 [95% CI, 1.01–1.06]; *P*=0.002), but no significant interaction ($P_{interaction}$=0.708) between LVMi and aortic valve morphology (BAV or TAV) on DD was observed.

LV Size and Systolic Function

LV systolic and diastolic volumes were larger in patients who have BAV with a significantly lower LVEF than patients with TAV (55% versus 60%, *P*<0.001). The intraventricular septum and posterior LV wall were thicker, and LV end-diastolic linear diameter was bigger in patients with BAV. Accordingly, the indexed LV mass was significantly higher in patients with BAV (134 g/m^2 versus 104 g/m^2, *P*<0.001), but there was no difference in relative wall thickness, probably because of the higher frequency of eccentric remodeling in patients with BAV. The difference in LV hypertrophy and remodeling

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Table 1. Baseline Characteristics

Characteristics	All (n=271)	Bicuspid aortic valve (n=152)	Tricuspid aortic valve (n=119)	*P* value
Demographic data				
Age, y	68±8.7	65±9.1	71±6.7	<0.001
Male sex, n (%)	167 (62)	100 (66)	67 (56)	0.111
Body mass index, kg/m^2	27.9±4.5	27.2±4.6	28.7±4.3	0.011
Body surface area, m^2	1.95±0.21	1.95±0.22	1.94±0.21	0.907
Physiological data				
Systolic blood pressure, mm Hg	137±16	135±18	141±13	0.004
Diastolic blood pressure, mm Hg	77±11	77±12	78±9	0.592
Heart rate, beats/min	73±16	76±18	69±11	<0.001
Clinical data, n (%)				
Diabetes	38 (14)	13 (9)	25 (28)	0.003
Arterial hypertension	185 (68)	89 (59)	96 (81)	<0.001
Hypercholesterolemia	122 (45)	55 (36)	67 (56)	<0.001
Chronic obstructive pulmonary disease	20 (7)	9 (6)	11 (9)	0.299
Peripheral artery disease	20 (7)	11 (7)	9 (8)	0.919
Obstructive sleep apnea	8 (3.0)	4 (2.9)	4 (3.6)	0.733
Smoking (previous or current)	104 (38)	58 (38)	46 (38)	0.933
Antihypertensive medication				
Angiotensin-converting enzyme inhibitor/ angiotensin receptor II blocker	142 (52)	76 (50)	66 (55)	0.296
β-blocker	120 (44)	54 (36)	66 (55)	<0.001
Calcium channel blocker	54 (20)	21 (13)	33 (28)	0.003
Diuretics	67 (25)	31 (20)	36 (30)	0.051
NYHA class				0.329
NYHA I	19 (7)	9 (6)	10 (8)	
NYHA II	105 (39)	61 (40)	44 (37)	
NYHA III	140 (52)	76 (50)	64 (54)	
NYHA IV	7 (2)	6 (4)	1 (1)	
Preoperative levosimendan	14 (5)	14 (9)	0 (0)	<0.001
Laboratory data				
Hemoglobin, g/L	139±12	140±12	138±13	0.265
NT-proBNP, ng/L	1247±2843	1683±3622	689±1069	0.007
Creatinine, µg/L	80±17	78±15	83±18	0.019

Data are presented as mean±SD for continuous variables and n (%) for categorical variables. NT-proBNP indicates N-terminal pro-brain natriuretic peptide; and NYHA, New York Heart Association.

patterns for patients with BAV and TAV are visualized in Figure 1 and Figure S3, respectively. There was a negative association between LVEF and LVMi (β=−0.451, *P*<0.001) with reduced LVEF in patients with LV hypertrophy. Visualizing this association according to aortic valve morphology indicated a pronounced association in patients with BAV and lack of association for patients with TAV (Figure 2). Formal interaction analysis verified a significant interaction between LVMi and aortic valve morphology on LVEF ($P_{interaction}$=0.0049). Global longitudinal strain, adequately analyzed in 203 patients (n=116 BAV and n=87 TAV, *P*=0.546), was significantly impaired for patients with BAV (−14.3% versus −18.1%, *P*<0.001).

Peroperative Characteristics

The peroperative characteristics are summarized in Table 3. The extracorporeal circulation and aortic cross-clamp times were significantly longer for patients with BAV (118.4 minutes versus 106.8 minutes, *P*<0.001; 86.3 minutes versus 75.2 minutes, *P*<0.001, respectively), even after excluding patients who underwent concomitant ascending aortic surgery (114.2 minutes

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Table 2. Preoperative Echocardiographic Characteristics

Characteristics	All (n=271)	Bicuspid aortic valve (n=152)	Tricuspid aortic valve (n=119)	*P* value
LV size and systolic parameters				
LV ejection fraction, %	57±9	55±11	60±6	<0.001
Global longitudinal strain (n=203), %	−15.9±4.9	−14.3±4.0	−18.1±5.2	<0.001
LV end-diastolic volume index, mL/m^2	71±32	76±37	64±20	0.003
LV end-systolic volume index, mL/m^2	32±17	36±20	26±9	<0.001
Interventricular septum thickness, mm	12.5±1.9	12.9±1.9	11.8±1.9	<0.001
Posterior wall thickness, mm	11.5±1.8	12.0±1.7	10.9±1.7	<0.001
LV mass index, g/m^2	121±36	134±37	104±24	<0.001
Relative wall thickness	0.47±0.09	0.48±0.09	0.46±0.09	0.091
AV parameters				
AV maximal velocity, m/s	4.60±0.53	4.60±0.56	4.59±0.50	0.616
AV maximal gradient, mm Hg	86±21	87±22	85±19	0.634
AV mean gradient, mm Hg	54±14	55±15	53±12	0.231
AV area, cm^2	0.83±0.24	0.80±0.24	0.89±0.23	0.007
AV area index, cm^2/m^2	0.42±0.11	0.41±0.11	0.45±0.10	0.002
Pressure recovery, mm Hg	2.30±0.11	2.11±0.75	2.58±0.74	<0.001
Aortic diameters				
Aortic sinus, mm	35±4.7	36±4.7	33±4.2	<0.001
Sinotubular junction, mm	30±5.0	32±5.1	28±4.2	<0.001
Ascending aorta, mm	37±6.3	39±6.5	34±5.0	<0.001
LV diastolic parameters				
Left atrial volume index, mL/m^2	38±10	40±10	36±10	<0.001
E wave, cm/s	0.83±0.22	0.84±0.23	0.82±0.21	0.437
A wave, cm/s	0.87±0.27	0.79±0.26	0.99±0.25	<0.001
E/A ratio	1.09±0.75	1.24±0.90	0.90±0.39	<0.001
Septal e′, cm/s	5.7±1.5	5.5±1.5	5.9±1.4	0.084
Lateral e′, cm/s	7.0±1.9	7.0±1.9	7.0±1.9	0.961
E/e′	14.3±5.0	14.8±5.6	13.8±4.0	0.160
Tricuspid regurgitation maximal velocity, m/s	2.63±0.40	2.72±0.44	2.51±0.31	0.002
Deceleration time, ms	225±74	204±69	251±73	<0.001
Diastolic dysfunction (n=227), n (%)	137 (60)	94 (72)	43 (44)	<0.001
Grade I, n (%)	34 (15)	26 (20)	8 (8)	0.013
Grade II, n (%)	85 (37)	52 (40)	33 (34)	0.334
Grade III, n (%)	21 (9)	19 (15)	2 (2)	0.001
Indeterminate, n (%)	33 (15)	14 (11)	19 (20)	0.066

Data are presented as mean±SD for continuous variables and n (%) for categorical variables. AV indicates aortic valve; and LV, left ventricular.

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versus 106.5 minutes, *P*=0.0036; 82.7 minutes versus 74.8 minutes, *P*=0.043, respectively). Peak levels of the postoperative myocardial damage markers (troponin I and CK-MB [creatine kinase muscle-brain]) were not different between patients with BAV and TAV. Patients with BAV required more postoperative inotropic support (29.6% versus 16.0%), whereas patients with TAV required more postoperative intravenous antihypertensive treatment (26.9% versus 23.0%, *P*=0.017). Preoperative LVEF was associated with postoperative need for inotropic support (odds ratio per 10-U LVEF decrease, 1.58 [95% CI, 1.22–2.09], *P*=0.001). Patients with BAV had a longer stay in the intensive care unit, although this difference was not statistically significant (2.18 days versus 1.71 days, *P*=0.072). Only 2 patients required postoperative dialysis (n=1 patient with BAV and n=1 patient with TAV, *P*>0.99), and the frequency of reoperation attributable to bleeding was not different for patients with BAV and TAV (5.9% versus 1.7%, *P*=0.120).

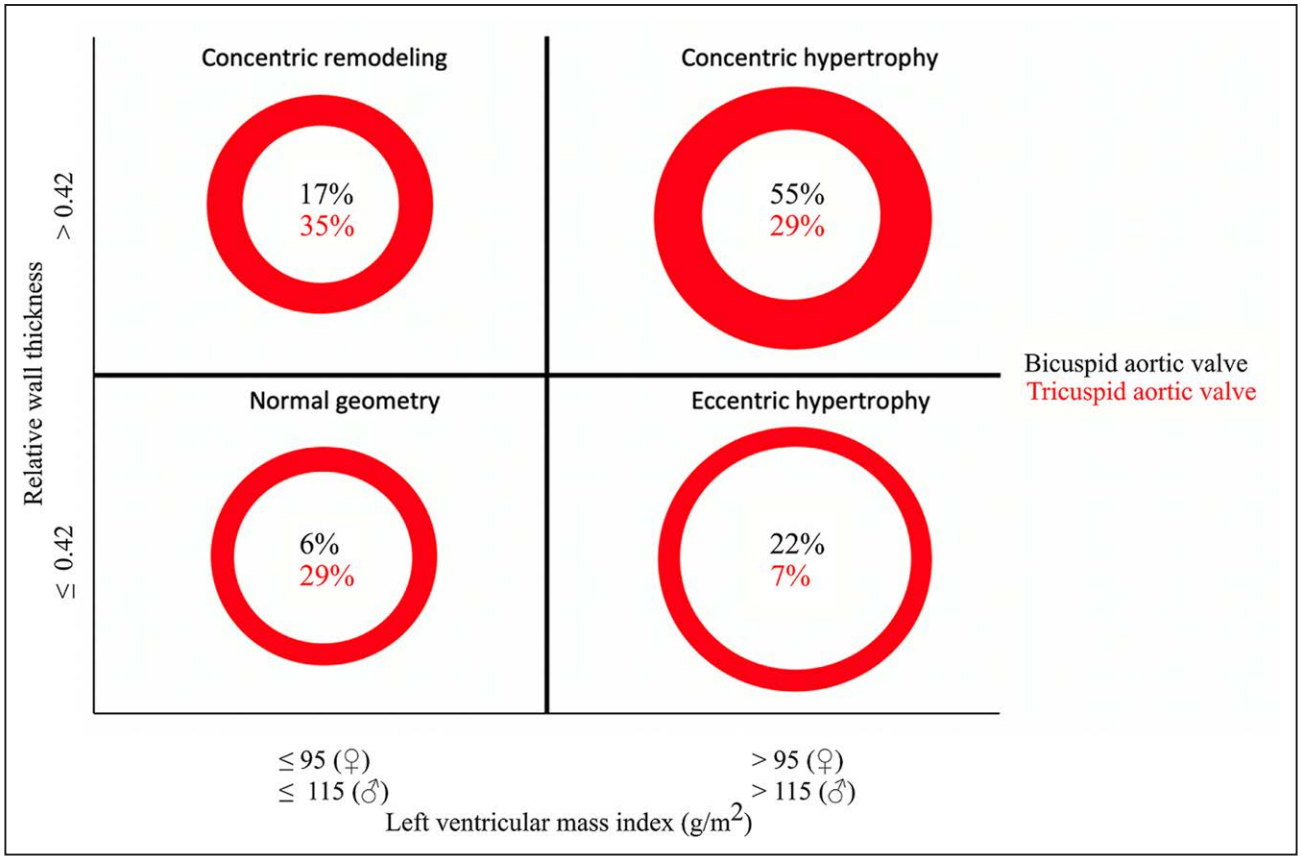

Figure 1. Left ventricular remodeling patterns.
The distribution of different left ventricular remodeling patterns (normal geometry, concentric remodeling, concentric hypertrophy, and eccentric hypertrophy) in patients with bicuspid and tricuspid aortic valve with isolated severe aortic stenosis.

Outcome

Mean follow-up after AVR was similar between the groups but tended to be shorter for patients with BAV (1260 days versus 1441 days, *P*=0.052). There were 17 deaths in total (n=6 BAV and n=11 TAV). Of those, 3 patients (2 BAV and 1 TAV) died in-hospital deaths in association with the index surgery. Because these 3 patients were not at risk for HF during follow-up, they were excluded from analysis of HF. The survival was comparable for patients with BAV and TAV (log-rank *P*=0.165; Figure 3). Overall, 31 patients (11.6%) were hospitalized because of HF during follow-up, of which 24 were patients with BAV and 7 were patients with TAV. The cumulative incidence function for HF is depicted according to aortic valve morphology and death as a competing risk for HF (BAV 28.2% versus TAV 10.6% at 6 years after AVR, log-rank *P*=0.004; Figure 4). In an adjusted Cox proportional hazards model (adjusted for age, sex, and LVEF), summarized in Table 4, BAV morphology was independently associated with time to HF hospitalization (adjusted hazard ratio, 2.77 [95% CI, 1.14–6.77], *P*=0.019). LVEF was also associated with HF hospitalization (adjusted hazard ratio per 10-U decrease, 1.35 [95% CI, 1.01–1.82], *P*=0.044). There was no interaction between aortic valve morphology and LVEF regarding HF hospitalization ($P_{interaction}$=0.868).

DISCUSSION

We prospectively investigated diastolic and systolic function and postoperative outcome in a well-characterized cohort of patients with BAV and TAV with severe isolated AS scheduled for AVR. Our main findings were that patients with BAV had worse preoperative diastolic and systolic LV function and a higher cumulative incidence of postoperative HF hospitalization. Survival was not statistically different between patients with BAV and TAV after AVR.

Chronically elevated afterload caused by AS leads to adverse remodeling with concentric hypertrophy, reduced compliance, increased LV stiffness, and eventually DD.[28] In the present study, the overall prevalence of DD was similar to what has been previously reported in AS cohorts.[29] It is surprising that patients with BAV had more prevalent and more severe DD than patients with TAV. Patients with BAV also had higher indexed LV mass. Logistic regression revealed an association between LVMi and DD, and LV hypertrophy seems to be the main mechanism behind DD in both patients with BAV and

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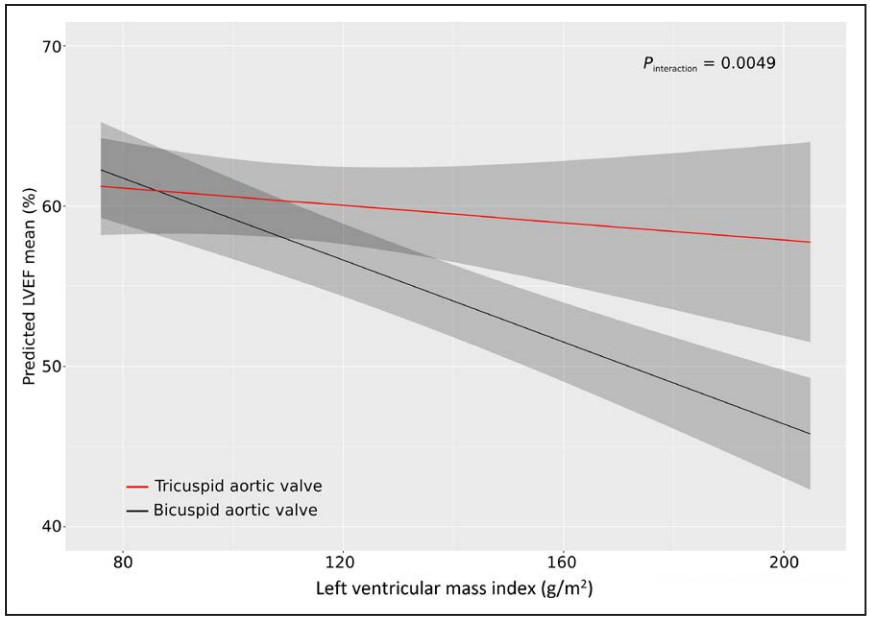

Figure 2. Interaction between aortic valve morphology and left ventricular mass index on left ventricular ejection fraction with 95% CIs.
The graph shows the association between left ventricular mass index (*x* axis) and left ventricular ejection fraction (LVEF; *y* axis) according to aortic valve morphology (bicuspid aortic valve=black line; tricuspid aortic valve=red line).

patients with TAV. The increased LV mass observed in patients with BAV may result from a chronically elevated transvalvular gradient already present from birth.[30] In contrast, hypertension, with debut later in life, probably contributes to the LV hypertrophy in patients with TAV. Elevated transvalvular gradients in young patients with BAV most probably originate from abnormal rheology attributable to the unequal size and eccentric opening of the leaflets.[12,31] Increased ascending aortic stiffness also contributes to a chronically elevated afterload in young patients with BAV.[11,32–34] In line with the findings of the present study, several others have found a higher LV mass and subclinical LV dysfunction in young patients with BAV, suggesting that the compensatory concentric remodeling process begins early in life.[10,35] A future large longitudinal study that follows patients with BAV from an early age and forward might give us information about when adverse LV remodeling is initiated and how it is affected by aortic valve degeneration. Furthermore, analyzing LV structure and function in different age groups of patients with BAV referred for AVR could also potentially support the concept of an age-dependent adverse LV remodeling. This subgroup analysis could not be performed in the present study because of the relatively small BAV sample size.

Surgical or interventional AVR is the only treatment of severe AS.[18] In advanced cases, LV mass recovery is incomplete after surgery with associated increased morbidity and mortality.[36] The likelihood of recovering DD postoperatively is decreasing with an increasing preoperative LV mass, where the final stage of the adverse remodeling process is irreversible myocardial fibrosis.[37] Deciphering the age-dependent remodeling of the LV in patients with BAV is therefore of utmost importance.

LV GLS is a marker of subclinical LV dysfunction and has been proven a robust predictor of adverse cardiovascular outcome in a variety of cardiac conditions,[38] including after AVR.[6] We found a significantly impaired GLS in patients with BAV, suggesting that myocardial contractility was affected to a greater extent before AVR compared with patients with TAV. Because this is an early marker of deteriorating systolic LV function, it could provide valuable information, especially in patients with pronounced LV hypertrophy, predominately patients with BAV.

The impaired LV function of patients with BAV was also reflected in a significantly higher pre- and postoperative use of levosimendan and inotropic support, respectively, than in TAV counterparts. There was no difference in postoperative CK-MB and Troponin I levels, which indicates that the longer extracorporeal circulation and aortic cross-clamp times in patients with BAV did not cause any further damage to the myocardium and should therefore have a minor impact on postoperative myocardial function. Therefore, the increased need of postoperative inotropic support in the patients with BAV is most certainly a reflection of the impaired preoperative LV function, as supported by the association between preoperative LVEF and postoperative inotropic support.

In severe AS, cardiac output is maintained through compensatory concentric hypertrophy, which makes the estimation of systolic LV function in terms of LVEF problematic, because it is highly influenced by loading conditions.[9] This means that LVEF can be maintained, despite reduced myocardial contractility, through concentric remodeling. On the contrary, an afterload mismatch may cause a depressed LVEF even in patients with preserved myocardial contractility. However, LVEF is the only parameter that guides intervention in asymptomatic patients with AS. It has recently become increasingly evident that adhering to the proposed LVEF cutoff (<50%) results in an excessive postoperative mortality.[7,17] Therefore, the most recent American guidelines suggest that AVR may

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Table 3. Peroperative Characteristics

Characteristics	All (n=271)	Bicuspid aortic valve (n=152)	Tricuspid aortic valve (n=119)	*P* value
Extracorporeal circulation time, min	113.3±32.1	118.4±30.9	106.8±32.5	<0.001
Aortic cross-clamp time, min	81.4±22.9	86.3±21.5	75.2±23.1	<0.001
Peak troponin I, ng/L	3494±5451	3736±5749	3182±5050	0.430
Peak creatine kinase muscle-brain, µg/L	32±103	30±67	36±137	0.617
Intensive care unit stay, days	2.0±2.1	2.2±2.4	1.7±1.7	0.072
Inotropic support, n (%)	64 (23.6)	45 (29.6)	19 (16.0)	0.009
Intravenous antihypertensive treatment, n (%)	55 (20.3)	23 (15.1)	32 (26.9)	0.017
Dialysis, n (%)	2 (0.7)	1 (0.7)	1 (0.8)	>0.99
Reoperation attributable to bleeding, n (%)	11 (4.1)	9 (5.9)	2 (1.7)	0.120

Data are presented as mean±SD for continuous variables and n (%) for categorical variables.

be considered in asymptomatic patients with a progressive decline in LVEF to <60% on serial imaging.[39] In the present study, patients with BAV had significantly lower LVEF than patients with TAV at the time of AVR. We suggest that the higher LV mass in patients with BAV could explain the significant difference in LVEF, because there was a significant interaction between LV mass and aortic valve morphology. Again, this is probably related to the chronicity of the BAV disorder, affecting the afterload already from birth. A higher proportion of the patients with BAV (22% versus 74%) had eccentric LV hypertrophy, which is the final stage of maladaptive LV remodeling observed late in the disease process.[40] Concentric hypertrophy induces DD, but maintains LVEF through a preserved contractile function, which explains why LV mass was equally associated with DD in patients with BAV and TAV in our study. When the compensated concentric hypertrophy eventually progresses to an eccentric hypertrophy, LV function deteriorates as the preload reserve is lost.[41] This is probably why LV mass had an impact on systolic LV function in patients with BAV, but not in patients with TAV.

Another important finding was the difference of pressure recovery in patients with BAV and TAV. Pressure recovery is a phenomenon frequently observed in patients with AS and is more prevalent in patients with

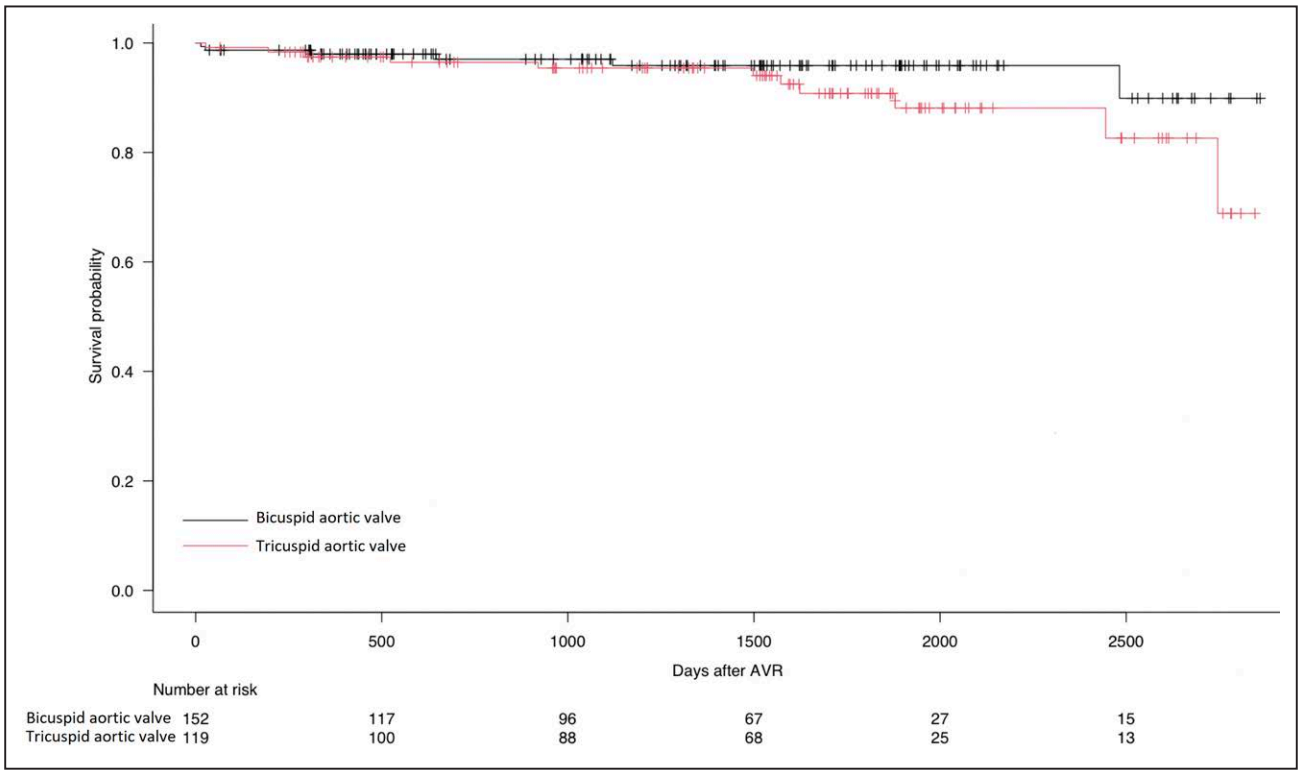

Figure 3. Survival after aortic valve replacement.
Kaplan-Meier curve illustrating all-cause mortality in patients with bicuspid (black line) and tricuspid aortic valve (red line) after aortic valve replacement (AVR) attributable to isolated severe aortic stenosis.

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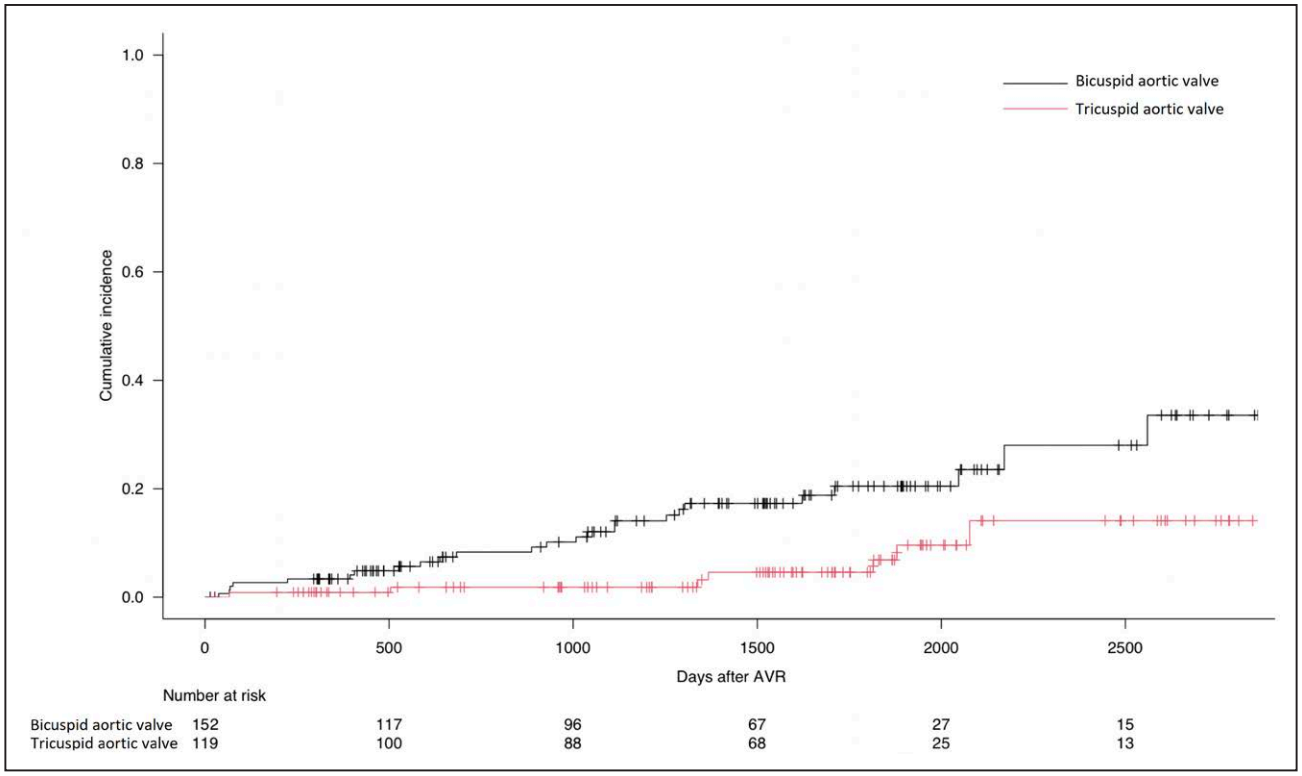

Figure 4. Heart failure hospitalization after aortic valve replacement.
Cumulative incidence function of postoperative heart failure hospitalization by aortic valve morphology (bicuspid aortic valve=black line; tricuspid aortic valve=red line), with all-cause death as competing risk. AVR indicates aortic valve replacement.

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small ascending aortas, that is, predominately patients with TAV.[42,43] Although several studies have shown the importance of adjusting for pressure recovery, it has not been implemented in clinical routine. This can potentially lead to a systematic overestimation of AS severity in patients with TAV, resulting in referral for intervention early in the disease process with less adverse cardiac remodeling. The opposite was observed for patients with BAV, where the aortic diameters were larger than for patients with TAV. At the same time, an eccentric jet is more frequently observed in patients with BAV, which together with the lower pressure recovery might lead to a potential underestimation of the AS severity.[31,44] This could explain why patients with BAV are referred late in the disease process when diastolic and systolic dysfunction already has developed.

Timing of aortic valve intervention in patients with AS has been discussed extensively during the past 2 decades.[45,46] Nevertheless, the optimal timing remains unclear, and current guidelines are mostly based on observational data and expert opinion.[47] Young patients, where presumably a higher proportion of the patients have a BAV, have a substantial loss in life expectancy after AVR compared with older patients.[48] In 2015, Taniguchi et al[49] reported a favorable outcome for asymptomatic patients with AS who underwent early AVR compared with those managed conservatively. The proportion of patients with BAV was significantly higher in the early AVR group, where depressed LVEF was also more common. These results were confirmed in the recent prospective RECOVERY trial (Randomized Comparison of Early Surgery Versus Conventional Treatment in Very Severe Aortic Stenosis).[50] Asymptomatic patients with severe AS had a lower incidence of cardiovascular death when assigned to early AVR instead of conservative care, and BAV was more common in the early AVR cohort. Very recently, Glaser et al[51] found that patients with BAV had a survival rate after AVR similar to that of the general population. This was despite the very high prevalence of preoperative LV dysfunction, where 23% of the patients with BAV had LVEF <50% (which is in line with the findings of the present study, where 21.5% of the patients with BAV had LVEF <50%). A mixed BAV cohort was included in the study by Glaser et al,[51] where 22% had severe aortic regurgitation as the primary indication for AVR, and why the results cannot be generalized to patients with BAV AS. Randomized controlled trials are needed to confirm whether patients with BAV AS benefit from early intervention. In our view, one logical way of optimizing timing of AVR is to investigate patients with BAV and TAV separately in future studies.

Clinical Perspectives

The results of our present study indicate that patients with BAV with isolated AS have more advanced cardiac

Table 4. Multivariate Cox Proportional Hazards Regression Analysis

Characteristic	Hazard ratio (95% CI)	*P* value	Heart failure incidence rate/100 person-years
Bicuspid aortic valve	2.77 (1.14–6.77)	0.019	4.8 (3.2–7.1)
Female sex	1.34 (0.65–2.74)	0.425	3.4 (2.0–5.7)
Age, per 10-y increase	1.08 (0.72–1.61)	0.708	
Age <63 y	1.12 (0.51–2.43)		4.5 (2.5–8.2)
Age 63–73 y	0.64 (0.30–1.36)		2.3 (1.2–4.5)
Age >73 y	1.57 (0.71–3.49)		3.3 (1.9–5.8)
LVEF, per 10-U decrease	1.35 (1.01–1.82)	0.044	
LVEF≤40%	0.98 (0.29–3.35)		4.1 (1.3–12.7)
LVEF 41%–59%	2.70 (1.23–5.92)		4.9 (3.2–7.4)
LVEF≥60%	0.32 (0.13–0.79)		1.3 (0.1–2.9)

LVEF is included as a linear variable. LVEF indicates left ventricular ejection fraction.

pathology than patients with TAV AS at the time of AVR. This was further strengthened by the finding that patients with BAV were subjected to significantly earlier readmission because of HF after surgery compared with patients with TAV. Therefore, patients with BAV might benefit from closer surveillance of LV function and possibly earlier intervention. Our findings are possibly explained by a chronically elevated afterload from a young age, in combination with a systematic overestimation of AS severity in patients with TAV because of the pressure recovery phenomenon. This hypothesis remains speculative, and the underlying mechanisms must be further elucidated. It is therefore of importance to investigate and expand the clinical implications of our findings in future studies, where patients with isolated AS are studied with no interference of coronary artery disease, which otherwise might mask the differences in AS-related adverse LV remodeling between patients with TAV and BAV.

Study Limitations

This study has some limitations to consider. First, the study population was recruited from a single center, which might bias the results. Complementary studies are needed to confirm our findings. Second, the algorithm for determination of diastolic function should be interpreted cautiously because it does not directly measure the LV filling pressure. However, this is a prospective study with a well-characterized cohort. Third, we did not consider pressure recovery and adjusted aortic valve area as a confounder in the present study. However, the current guidelines do not recommend that this should be performed in the clinical routine. Accordingly, pressure recovery was not considered during the Multidisciplinary Heart Team conference where the patients in the present study were accepted for AVR. Thus, this study is representative of everyday clinical practice.

Conclusions

At the time of AVR, patients with BAV with isolated severe AS have worse preoperative LV function and a higher incidence of postoperative HF hospitalization than their TAV counterparts. Patients with BAV and TAV with isolated severe AS should not be regarded as one entity. Our findings suggest that the contemporary guidelines are appropriate for patients with TAV, whereas patients with BAV might benefit from closer surveillance and possibly earlier intervention before developing adverse LV remodeling and deteriorating LV function.

ARTICLE INFORMATION

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Disclosures

Drs Grinnemo, Rodin, and Simonson are cofounders of the company AVulotion AB. Dr Vedin is an employee of Boehringer Ingelheim AB, Stockholm, Sweden. All authors have approved the final article. The other authors report no conflicts.

Supplemental Material

Expanded Methods
Table S1
Figures S1–S3
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