EuroIntervention 2022;18:193-202 published online ahead of print January 2022

Three-year outcomes of transcatheter aortic valve implantation for bicuspid versus tricuspid aortic stenosis

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This paper also includes supplementary data published online at: https://eurointervention.pcronline.com/doi/10.4244/EIJ-D-21-00734

KEYWORDS

- bicuspid aortic valve
- haemodynamics
- long-term outcomes
- reverse modelling
- transcatheter aortic valve implantation

Abstract

Background: Transcatheter aortic valve implantation (TAVI) might be a feasible treatment option for more patients with bicuspid aortic valve (BAV) stenosis. However, long-term follow-up data in this population are scarce.

Aims: The aim of this study was to evaluate three-year outcomes after TAVI in patients with BAV.

Methods: A total of 246 consecutive patients who underwent TAVI at a single centre in China between March 2013 and February 2018 were enrolled in this study. Clinical outcomes, health status and echocardiography were followed and recorded for three years.

Results: Among 109 (44.3%) BAV patients, 61.5% were Type 0 and 36.7% were Type 1 BAV patients. BAV patients were younger (75 vs 77 years, p=0.041) and had a lower Society of Thoracic Surgeons (STS) score (5.09 vs 6.00, p=0.026) compared to tricuspid aortic valve (TAV) patients. There were no differences in three-year survival rates between bicuspid and tricuspid patients (87.1% vs 79.5%, log-rank p=0.126). Multivariate Cox regression analysis adjusting for confounding factors revealed a similar risk of all-cause mortality in the BAV population (hazard ratio [HR] 0.86, 95% confidence interval [CI]: 0.44-1.70, p=0.666). Except for the rate of permanent pacemaker implantation that was lower in BAV patients (11.9% vs 21.9%, p=0.041), the incidence of other clinical adverse events was comparable between the two groups. Both BAV and TAV patients showed an obvious improvement in valve haemodynamics, which was sustained for three years. In addition, similar left ventricular reverse remodelling was found during follow-up.

Conclusions: BAV patients showed similar satisfactory three-year clinical outcomes, persistent valve haemodynamics improvement, and obvious cardiac reverse remodelling after TAVI compared to TAV patients.

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SUBMITTED ON 16/08/2021 - REVISION RECEIVED ON 09/10/2021 - ACCEPTED ON 07/12/2021

DOI: 10.4244/EIJ-D-21-00734

Abbreviations

AS	aortic stenosis
BAV	bicuspid aortic valve
NYHA	New York Heart Association
PPMI	permanent pacemaker implantation
SAVR	surgical aortic valve replacement
TAVI	transcatheter aortic valve implantation
TAV	tricuspid aortic valve

Introduction

Transcatheter aortic valve implantation (TAVI) was initially performed in inoperable patients or those at high risk for surgical aortic valve replacement (SAVR). The indication for TAVI gradually expanded to intermediate, even low-risk patients, and it was recommended for more patients with severe symptomatic aortic stenosis (AS) according to the updated guidelines[1-3]. An analysis of the Society of Thoracic Surgeons Adult Cardiac Surgery Database revealed that TAVI has rapidly evolved over the last decade, currently accounting for over half of all aortic valve interventions[4].

Bicuspid aortic valve (BAV) is the most common congenital valvular disease. In patients with BAV, aortic stenosis develops at an earlier age than in those with a tricuspid phenotype[5,6]. However, BAV patients have been systematically excluded from most randomised clinical trials because of unfavourable anatomical characteristics such as severe annular eccentricity, concomitant aortopathy, and severe calcification[7-10]. As the indications for TAVI are extending to low-risk patients, more patients with bicuspid aortic valve stenosis will become candidates for TAVI.

To date, several studies have confirmed the short-term efficacy and safety of TAVI in BAV[11-13]. However, long-term follow-up data in this population are scarce, which is particularly important when TAVI expands to younger patients with longer life expectancy. Therefore, this study was performed to compare the three-year outcomes of the TAVI procedure in bicuspid and tricuspid AS patients.

Editorial, see page 185

Methods

STUDY DESIGN AND PATIENT POPULATION

We retrospectively collected data from 257 consecutive patients who underwent TAVI at the Second Affiliated Hospital of Zhejiang University School of Medicine between March 2013 and February 2018. After excluding patients with quadricuspid aortic valves (n=2), pure aortic regurgitation (n=7), and those who underwent valve-in-valve procedures (n=2), the final study cohort enrolled 246 patients **(Supplementary Figure 1)**.

A multidisciplinary Heart Team discussed and decided all TAVI procedures. If the anatomical conditions of the artery were acceptable, transfemoral TAVI was performed. All procedures were performed in our hybrid operating room under general anaesthesia or local anaesthesia with sedation. Most patients were implanted with self-expanding valves such as the VenusA-Valve (Venus Medtech), CoreValve (Medtronic), VitaFlow (Microport), and TaurusOne Valve (Peijia Medical). The remaining participants were implanted with the balloon-expandable SAPIEN XT (Edwards Lifesciences) or the mechanically expandable Lotus Valve (Boston Scientific).

The study was approved by the medical ethics committee and complied with the Declaration of Helsinki. All patients provided written informed consent for the procedure and the use of anonymous data for research.

FOLLOW-UP AND DATA COLLECTION

The follow-up visits were performed 30 days after the procedure and then annually by our professional follow-up team. The majority of patients were followed up at our centre, while the rest were followed up via structured telephone interviews. All follow-up data were collected into our local database. Transthoracic echocardiography was required in the 30-day and annual follow-up. New York Heart Association (NYHA) status and clinical events were evaluated by a cardiologist. The complications were defined according to the Valve Academic Research Consortium-2 (VARC-2) consensus document[14]. Major adverse cardiovascular events (MACE) were defined as death, stroke, and myocardial infarction, as previously described[15].

IMAGING MEASUREMENT

Patients underwent a standard screening including echocardiography and contrast-enhanced multidetector computed tomography (MDCT) before procedures. Preoperative MDCT data were available for all patients. Anatomical structures measured on MDCT were evaluated in 3mensio software (Pie Medical Imaging). The type of aortic valve was distinguished based on full-phase MDCT by two professional cardiologists (Q.F. Zhu and Y.X. He) and was reconfirmed by the two authors (D. Zhou and Y.C. Guo) following the description by Sievers et al[16]. The calcium volume of the device landing zone was quantified in 3mensio software, using the threshold of 850 Hounsfield units, as previously described[17-19]. The implantation depth was measured by fluoroscopy in the non-coronary cusp direction, as previously described[20]. All echocardiograms were performed by experienced echocardiographers. Left ventricular (LV) mass was calculated using the Cube formula described in a previous study[21].

STATISTICAL ANALYSIS

Continuous variables were described as mean±standard deviation (SD) or median (interquartile range [IQR]) based on distributions. Normality tests were performed using the Shapiro-Wilk tests or Quartile-Quartile (Q-Q) plots. Continuous variables were compared between two groups using the unpaired Student's t-test or Mann-Whitney U-test according to their distributions. The comparison of echocardiographic data between baseline and different time points was performed using a paired samples t-test or Wilcoxon rank-sum test. Categorical variables were presented as percentages and were compared by the chi-square or Fisher's exact test. The McNemar chi-square test was used for paired samples. Cumulative survival rates were calculated using the Kaplan-Meier (K-M) survival analysis, and the log-rank test was

performed for comparison between two groups. Cox proportional hazard regression models were used to explore risk factors of three-year all-cause mortality. Variables with a p-value <0.10 in univariate Cox regression analysis were included in the multivariate model. In addition, logistic regression analysis was performed to identify potential confounding factors in bicuspid AS patients **(Supplementary Table 1)**. Next, a multivariate Cox regression analysis adjusted for these confounding factors was carried out to identify whether bicuspid AS was a risk factor of three-year all-cause mortality. A two-tailed p-value of <0.05 was considered statistically significant. Bonferroni correction was applied when multiple comparisons were performed. Statistical analysis was performed using SPSS Statistics software version 23.0 (IBM Corp.).

Results

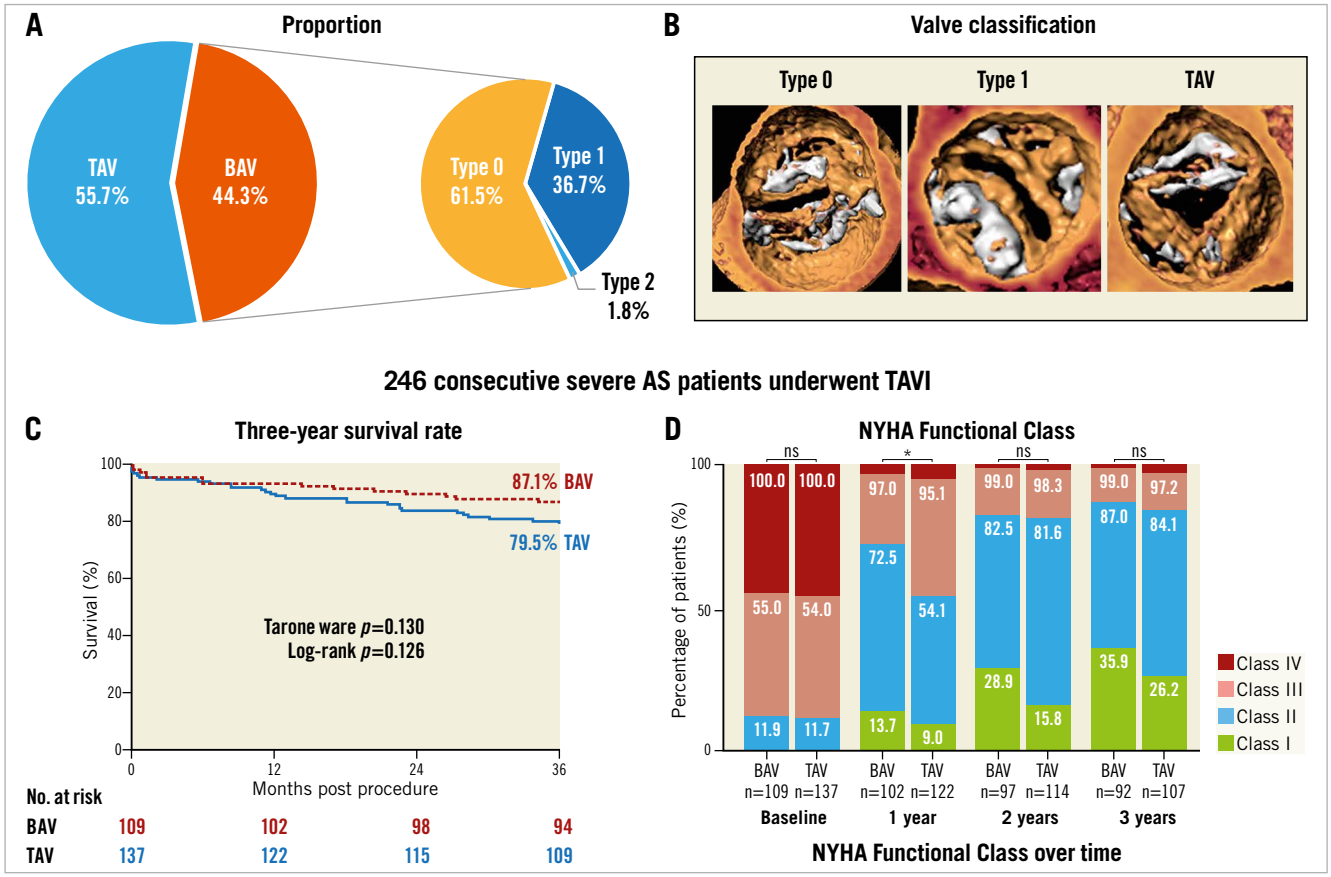
PATIENTS AND BASELINE CHARACTERISTICS

Among 246 consecutive patients who underwent TAVI between March 2013 and February 2018, 109 (44.3%) patients had BAV morphology, and the other 137 (55.7%) had TAV **(Central illustration)**. Population features, baseline echocardiography characteristics and CT analyses are shown in **Table 1** and **Table 2**. The median age was 77 years and 61% of the patients were male. The overall median Society of Thoracic Surgeons score was 5.56 (interquartile range [IQR]: 3.74-9.54).

Compared to tricuspid AS patients, BAV patients were younger (75 vs 77 years, p=0.041), had lower STS scores (5.09 vs 6.00, p=0.026), and had a lower proportion of patients with stroke history (1.8% vs 8.8%, p=0.020). According to echocardiography, bicuspid AS patients had less LV hypertrophy, and a smaller aortic valve area but a similar mean gradient and velocity. A more horizontal aorta, more severe calcification, and larger aortic root anatomy, including sinotubular and ascending aorta, were found in BAV patients.

PROCEDURAL CHARACTERISTICS AND OUTCOMES

Self-expanding valves were used most frequently (82.9%), followed by mechanically expandable valves (9.3%). Most patients underwent TAVI via the transfemoral access (96.7%). Transsubclavian, transaortic or transcarotid TAVI was performed in the remaining patients. Predilatation was routinely performed in 96.3% of patients, and 43.1% of patients received post-dilatation. No differences in these procedural factors were found between



Central illustration. *Population, three-year survival rate and NYHA Functional Class. A) Population proportion of BAV and TAV morphologies. B) Typical image of type 0, type 1 bicuspid aortic valve and tricuspid aortic valve. C) Kaplan-Meier estimates of the all-cause mortality. D) NYHA Functional Class at baseline and annual follow-up. BAV: bicuspid aortic valve; NYHA: New York Heart Association TAV: tricuspid aortic valve; TAVI: transcatheter aortic valve implantation*

Table 1. Baseline patient characteristics.

	Total (n=246)	BAV patients (n=109)	TAV patients (n=137)	*p*-value
Age, years	77 (72-81)	75 (71-80)	77 (73-81)	**0.041**
Male	150 (61.0%)	62 (56.9%)	88 (64.2%)	0.240
BMI, kg/m^2	22.64±3.57	22.47±3.19	22.78±3.84	0.499
STS score, %	5.56 (3.74-9.54)	5.09 (3.65-8.62)	6.00 (4.26-10.68)	**0.026**
Diabetes mellitus	53 (21.5%)	21 (19.3%)	32 (23.4%)	0.438
History of hypertension	141 (57.3%)	56 (51.4%)	85 (62.0%)	0.093
Smoker	29 (11.8%)	9 (8.3%)	20 (14.6%)	0.125
Dyslipidaemia	68 (27.6%)	26 (23.9%)	42 (30.7%)	0.236
Peripheral vascular disease	65 (26.4%)	25 (22.9%)	40 (29.2%)	0.269
Previous stroke	14 (5.7%)	2 (1.8%)	12 (8.8%)	**0.020**
Previous MI	6 (2.4%)	1 (0.9%)	5 (3.6%)	0.231
Previous PCI	33 (13.4%)	14 (12.8%)	19 (13.9%)	0.815
Previous CABG	1 (0.4%)	0 (0%)	1 (0.7%)	1.000
Atrial fibrillation/flutter	48 (19.5%)	22 (20.2%)	26 (19.0%)	0.813
Previous PPMI	6 (2.4%)	3 (2.8%)	3 (2.2%)	1.000
COPD	51 (20.7%)	21 (19.3%)	30 (21.9%)	0.613
History of cancer	10 (4.1%)	2 (1.8%)	8 (5.8%)	0.209
NYHA Class III or IV	217 (88.2%)	96 (88.1%)	121 (88.3%)	0.952
Dialysis	5 (2.0%)	1 (0.9%)	4 (2.9%)	0.386
Echocardiography				
LVEF, %	55.2 (43.1-63.7)	56.0 (40.6-64.3)	55.0 (44.4-62.1)	0.850
LVEF <55%	150 (61.0%)	52 (47.7%)	66 (48.2%)	0.700
Max velocity, m/s	4.81±0.72	4.89±0.74	4.74±0.69	0.100
Mean gradient, mmHg	55.7±16.6	58.2±18.2	53.6±15.0	**0.034**
Aortic valve area, cm^2	0.59±0.18	0.53±0.16	0.63±0.18	**<0.001**
Moderate/severe mitral regurgitation	62 (25.2%)	24 (22.0%)	38 (27.7%)	0.305
Moderate/severe tricuspid regurgitation	42 (17.1%)	18 (16.5%)	24 (17.5%)	0.835
LV mass, g	251.9 (212.1-306.5)	238.2 (204.0-287.5)	266.6 (221.6-326.2)	**0.003**
LV mass index, g/m^2	152.2 (128.8-188.9)	146.3 (122.5-181.9)	158.8 (135.8-192.6)	**0.011**

Data are presented as n (%) or mean±SD or median (interquartile range, IQR). *P*-values in bold are statistically significant. BAV: bicuspid aortic valve; BMI: body mass index; CABG: coronary artery bypass grafting; COPD: chronic obstructive pulmonary disease; LM: left main; LV: left ventricular; LVEF: left ventricular ejection fraction; MI: myocardial infarction; NYHA: New York Heart Association; PCI: percutaneous coronary intervention; PPMI: permanent pacemaker implantation; RCA: right coronary artery; STJ: sinotubular junction; STS: Society of Thoracic Surgeons; TAV: tricuspid aortic valve

BAV and TAV patients **(Table 3)**. Most in-hospital outcomes were comparable between the two groups, except that the BAV population suffered more aortic dissection (4.6% vs 0%, p=0.016) and fewer permanent pacemaker implantations (PPMI) (9.2% vs 19.7%, p=0.022). Detailed information on the patients converted to open SAVR is provided in **Supplementary Table 2**. The 30-day all-cause mortality rate was similar between the two groups (4.6% vs 4.4%, p=1.000).

LONG-TERM CLINICAL OUTCOME

The clinical data of 245 patients were available at three years **(Supplementary Figure 1)** (one BAV patient could not be contacted after the second-year follow-up). Long-term clinical outcomes are shown in **Table 4**. No significant differences in all-cause mortality (12.8% vs 20.4%, p=0.116) or cardiovascular mortality (5.5% vs 10.9%, p=0.129) were found between the BAV and TAV populations during three years of follow-up. The three-year survival rates were similar in bicuspid (87.1%, 95% confidence interval [CI]: 83.9-90.3) and tricuspid (79.5%, 95% CI: 76.0-83.0) AS patients (log-rank p=0.126) according to Kaplan-Meier estimates **(Central illustration)**. Furthermore, the incidence of MACE, stroke, myocardial infarction and aortic valve reintervention was also comparable between the two groups. Nevertheless, the rate of permanent pacemaker implantation was consistently lower in bicuspid AS patients. Moreover, fewer BAV patients suffered NYHA Class III or IV symptoms at one-year follow-up, although the difference disappeared over the next two years **(Central illustration)**.

Table 2. Baseline CT findings.

	Total (n=246)	BAV patients (n=109)	TAV patients (n=137)	*p*-value
Average diameter, mm	24.7 (22.9-26.2)	24.5 (23.2-26.2)	24.8 (22.6-26.6)	0.847
Area, mm^2	468.1 (408.0-537.4)	463.1 (414.9-531.8)	471.0 (401.8-546.5)	0.935
Area derived diameter, mm	24.4 (22.8-26.2)	24.3 (23.0-26.0)	24.5 (22.6-26.4)	0.977
Perimeter, mm	78.6 (73.1-83.7)	78.1 (73.8-83.7)	78.7 (72.3-84.6)	0.833
Perimeter derived diameter, mm	25.0 (23.3-26.6)	24.9 (23.5-26.6)	25.1 (23.0-26.9)	0.803
Average STJ diameter, mm	30.4 (27.4-33.2)	31.1 (28.5-34.1)	30.0(26.8-32.7)	**0.004**
STJ height, mm	22.5 (20.3-25.4)	23.7 (20.0-26.2)	21.9 (20.3-24.7)	0.056
Ascending aorta diameter at 4 cm, mm	37.51±4.37	39.42±4.06	35.99±4.01	**<0.001**
Max ascending aorta diameter, mm	40.60±5.31	43.17±4.70	38.55±4.88	**<0.001**
RCA height, mm	16.1 (14.3-18.6)	16.0 (14.3-18.8)	16.2 (14.0-18.4)	0.578
LM height, mm	14.6 (12.3-17.4)	16.1 (13.6-18.6)	13.7 (12.0-16.6)	**<0.001**
Aortic root angle, degree	53.0 (46.0-59.0)	55.0 (48.0-60.5)	50.2 (45.0-58.0)	**0.014**
Device landing zone calcification, mm^3	467.6 (203.0-806.6)	519.7 (303.4-818.0)	435.2 (149.9-788.4)	**0.025**

Data are presented as n (%) or mean±SD or median (interquartile range, IQR). *P*-values in bold are statistically significant. BAV: bicuspid aortic valve; CT: computed tomography; LM: left main; RCA: right coronary artery; STJ: sinotubular junction; TAV: tricuspid aortic valve

Table 3. Procedural characteristics and outcomes.

		BAV patients (n=109)	TAV patients (n=137)	*p*-value
Valve type	Self-expanding valve	91 (83.5%)	113 (82.5%)	0.143
	Balloon-expandable valve	5 (4.6%)	14 (10.2%)	
	Mechanically expandable valve	13 (11.9%)	10 (7.3%)	
Transfemoral access		105 (96.3%)	133 (97.1%)	0.735
Predilatation		106 (97.2%)	131 (95.6%)	0.739
Post-dilatation		50 (45.9%)	56 (40.9%)	0.432
Oversizing by annulus perimeter, %		6.52 (1.05-13.33)	9.72 (4.31-15.13)	**0.014**
Implantation depth*, mm		4.5 (1.7-8.0)	6.0 (3.9-11.0)	**<0.001**
Conversion to SAVR		4 (3.7%)	1 (0.7%)	0.174
Cardiopulmonary resuscitation		5 (4.6%)	3 (2.2%)	0.472
Coronary obstruction		1 (0.9%)	1 (0.7%)	1.000
Myocardial infarction		1 (0.9%)	0 (0%)	0.443
Bleeding¶		10 (9.2%)	10 (7.3%)	0.593
Aortic dissection		5 (4.6%)	0 (0%)	**0.016**
Stroke		1 (0.9%)	1 (0.7%)	1.000
Tamponade		2 (1.8%)	1 (0.7%)	0.586
Acute kidney injury		6 (5.5%)	5 (3.6%)	0.697
PPMI		10 (9.2%)	27 (19.7%)	**0.022**
New atrial fibrillation		3 (2.8%)	8 (5.8%)	0.394
Blood transfusion		14 (12.8%)	22 (16.1%)	0.479
Severe patient-prosthesis mismatch		3 (2.9%)	4 (3.0%)	1.000
Echocardiography before discharge				
LVEF, %		59.7 (52.0-64.8)	58.8 (52.1-64.2)	0.563
Max velocity, m/s		2.44±0.51	2.40±0.46	0.531
Mean gradient, mmHg		12.89±5.34	12.35±5.01	0.423
Aortic valve area, cm^2		1.57±0.29	1.61±0.33	0.332
Moderate/severe PVL		7 (6.5%)	16 (11.9%)	0.162

Data are presented as n (%) or mean±SD or median (interquartile range, IQR). *P*-values in bold are statistically significant. * Implantation depth was measured by fluoroscopy on the non-coronary cusp direction. ¶ Life-threatening bleeding. BAV: bicuspid aortic valve; LVEF: left ventricular ejection fraction; PPMI: permanent pacemaker implantation; PVL: paravalvular leakage; SAVR: surgical aortic valve replacement; TAV: tricuspid aortic valve

Additionally, some subgroup analyses were performed. The comparisons of BAV and TAV patients when considering only the patients treated with a self-expanding valve, balloon-expandable valve or mechanically expandable valve are shown in **Supplementary Table 3** and **Supplementary Table 4**, respectively. In a subgroup analysis of BAV patients, no difference of three-year clinical outcomes was found between type 0 and type 1 patients **(Supplementary Table 5)**.

ECHOCARDIOGRAPHIC FINDINGS

Both bicuspid and tricuspid AS patients had a distinct decrease in mean gradient and had an increased area of the aortic valve after the procedure, and this improvement was sustained for three years **(Figure 1A, Figure 1B)**. The moderate or severe paravalvular leakage rate was similar after TAVI (6.5% vs 11.9%, p=0.162). There was also no difference in PVL between the two groups in the first year (8.3% vs 8.7%, p=0.925), second year (6.6% vs 13.4%, p=0.198) and third year (3.9% vs 6.5%, p=0.668) on echocardiographic examination. Although BAV patients had a lower LV mass at baseline **(Figure 1C)**, a similar decrease of LV mass was found between BAV and TAV patients **(Table 4, Figure 1D)**. This improvement mainly occurred during the first year after the TAVI procedure **(Figure 1D, Supplementary Figure 2)**. The detailed annual quantification of left heart chamber size is shown in **Supplementary Table 6**. A comparison between baseline echocardiography and the echo data at different time points is provided in **Supplementary Table 7**.

UNIVARIATE AND MULTIVARIATE ANALYSIS

According to the univariate Cox regression analysis, bicuspid AS was not differentially associated with the all-cause mortality (hazard ratio [HR] 0.61, 95% CI: 0.32-1.16). After adjusting for potential confounding factors, including age, STS score, prior stroke, and LV mass, bicuspid AS was not associated with risk of all-cause

Table 4. Three-year outcomes.

	At 1 year			At 2 years			At 3 years		
	BAV patients (n=109)	TAV patients (n=137)	*p*-value	BAV patients (n=109)	TAV patients (n=137)	*p*-value	BAV patients (n=109)	TAV patients (n=137)	*p*-value
All-cause mortality	7 (6.4%)	15 (10.9%)	0.216	11 (10.1%)	22 (16.1%)	0.173	14 (12.8%)	28 (20.4%)	0.116
Cardiovascular mortality	4 (3.7%)	10 (7.3%)	0.222	5 (4.6%)	12 (8.8%)	0.200	6 (5.5%)	15 (10.9%)	0.129
MACE*	12 (11%)	16 (11.7%)	0.870	16 (14.7%)	25 (18.2%)	0.456	22 (20.2%)	31 (22.6%)	0.643
All stroke	5 (4.6%)	3 (2.2%)	0.472	5 (4.6%)	6 (4.4%)	1.000	8 (7.3%)	6 (4.4%)	0.320
Disabling stroke	2 (1.8%)	2 (1.5%)	1.000	2 (1.8%)	4 (2.9%)	0.696	3 (2.8%)	4 (2.9%)	1.000
Myocardial infarction	2 (1.8%)	1 (0.7%)	0.586	2 (1.8%)	1 (0.7%)	0.586	2 (1.8%)	2 (1.5%)	1.000
Aortic valve re-intervention	0 (0%)	2 (1.5%)	0.504	0 (0%)	2 (1.5%)	0.504	0 (0%)	2 (1.5%)	0.504
Life-threatening bleeding bleeding	11 (10.1%)	10 (7.3%)	0.436	11 (10.1%)	11 (8%)	0.573	11 (10.1%)	11 (8.0%)	0.573
Pacemaker implantation	12 (11%)	30 (21.9%)	**0.024**	13 (11.9%)	30 (21.9%)	**0.041**	13 (11.9%)	30 (21.9%)	**0.041**
New atrial fibrillation	5 (4.6%)	14 (10.2%)	0.100	5 (4.6%)	15 (10.9%)	0.070	6 (5.5%)	15 (10.9%)	0.129
NYHA Class III/IV	28 (27.5%)	56 (45.9%)	**0.005**	17 (17.5%)	21 (18.4%)	0.866	12 (13.0%)	17 (15.9%)	0.571
Echocardiography findings	**n=96**	**n=115**		**n=61**	**n=68**		**n=51**	**n=63**	
LVEF, %	64.7 (60.4-68.9)	63.2 (56.8-67.1)	**0.023**	63.6 (60.0-67.0)	64.1 (58.0-67.7)	0.865	63.0 (57.6-68.0)	60.4 (56.9-65.4)	0.149
Max velocity, m/s	2.32±0.54	2.21±0.49	0.122	2.35±0.51	2.17±0.53	0.056	2.25±0.52	2.22±0.52	0.772
Mean gradient, mmHg	11.40±5.82	10.43±4.44	0.177	11.84±5.74	9.88±4.73	**0.037**	10.76±5.15	10.33±4.74	0.640
Aortic valve area, cm^2	1.56±0.35	1.63±0.37	0.195	1.54±0.48	1.64±0.39	0.208	1.54±0.35	1.61±0.35	0.348
Moderate/severe PVL	8 (8.3%)	10 (8.7%)	0.925	4 (6.6%)	9 (13.4%)	0.198	2 (3.9%)	4 (6.5%)	0.688
LV mass, g	175.2 (152.1-212.1)	195.2 (158.5-241.2)	**0.014**	171.0 (144.9-221.7)	189.4 (159.8-245.2)	0.061	167.2 (131.5-202.8)	190.4 (140.1-237.7)	0.066
Decrease of LV mass, g	62.7 (30.2-99.6)	62.3 (12.9-100.8)	0.650	60.7 (16.4-109.4)	46.7 (15.4-106.6)	0.847	72.2 (42.0-120.5)	69.1 (29.9-125.2)	0.705
Moderate/severe MR	7 (7.3%)	11 (9.6%)	0.556	9 (14.8%)	9 (13.4%)	0.830	3 (5.9%)	8 (12.7%)	0.365
Moderate/severe TR	9 (9.4%)	11 (9.6%)	0.963	12 (19.7%)	7 (10.4%)	0.143	7 (13.7%)	11 (17.5%)	0.587

Data are presented as n (%) or mean±SD or median (interquartile range, IQR). *P*-values in bold are statistically significant. MACE*: major adverse cardiovascular events, including all-cause mortality, stroke and myocardial infarction. BAV: bicuspid aortic valve; LV: left ventricular; LVEF: left ventricular ejection fraction; MR: mitral regurgitation; NYHA: New York Heart Association; PVL: paravalvular leakage; TAV: tricuspid aortic valve; TR: tricuspid regurgitation

mortality (HR 0.86, 95% CI: 0.44-1.70) **(Table 5)**. In multivariate Cox regression analysis using a forward Likelihood Ratio method, higher STS score, history of stroke, prior pacemaker implantation, dialysis, and combination of moderate or severe mitral regurgitation were found to be the independent predictors of three-year all-cause mortality **(Supplementary Table 8)**.

Table 5. Multivariate Cox regression analyses of three-year mortality adjusted for confounding variables.

	Multivariate regression model 01		Multivariate regression model 02		Multivariate regression model 03	
	p-value	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value	HR (95% CI)
Bicuspid AS	0.151	0.62 (0.33-1.19)	0.398	0.75 (0.39-1.46)	0.666	0.86 (0.44-1.70)
Age, years	0.600	1.01 (0.96-1.07)	0.380	0.98 (0.92-1.03)	0.373	0.97 (0.92-1.03)
STS score, per 1%	–	–	<0.001	1.09 (1.06-1.12)	<0.001	1.09 (1.06-1.13)
Previous stroke	–	–	–	–	0.025	3.01 (1.15-7.91)
Left ventricular mass, per 1 g	–	–	–	–	0.372	1.00 (1.00-1.01)

Multivariate regression model 01: multivariate Cox regression model adjusted for age. Multivariate regression model 02: multivariate Cox regression model adjusted for age and STS score. Multivariate regression model 03: multivariate Cox regression model adjusted for age, STS score, previous stroke and left ventricular mass. CI: confidence interval; HR: hazard ratio; STS: Society of Thoracic Surgeons

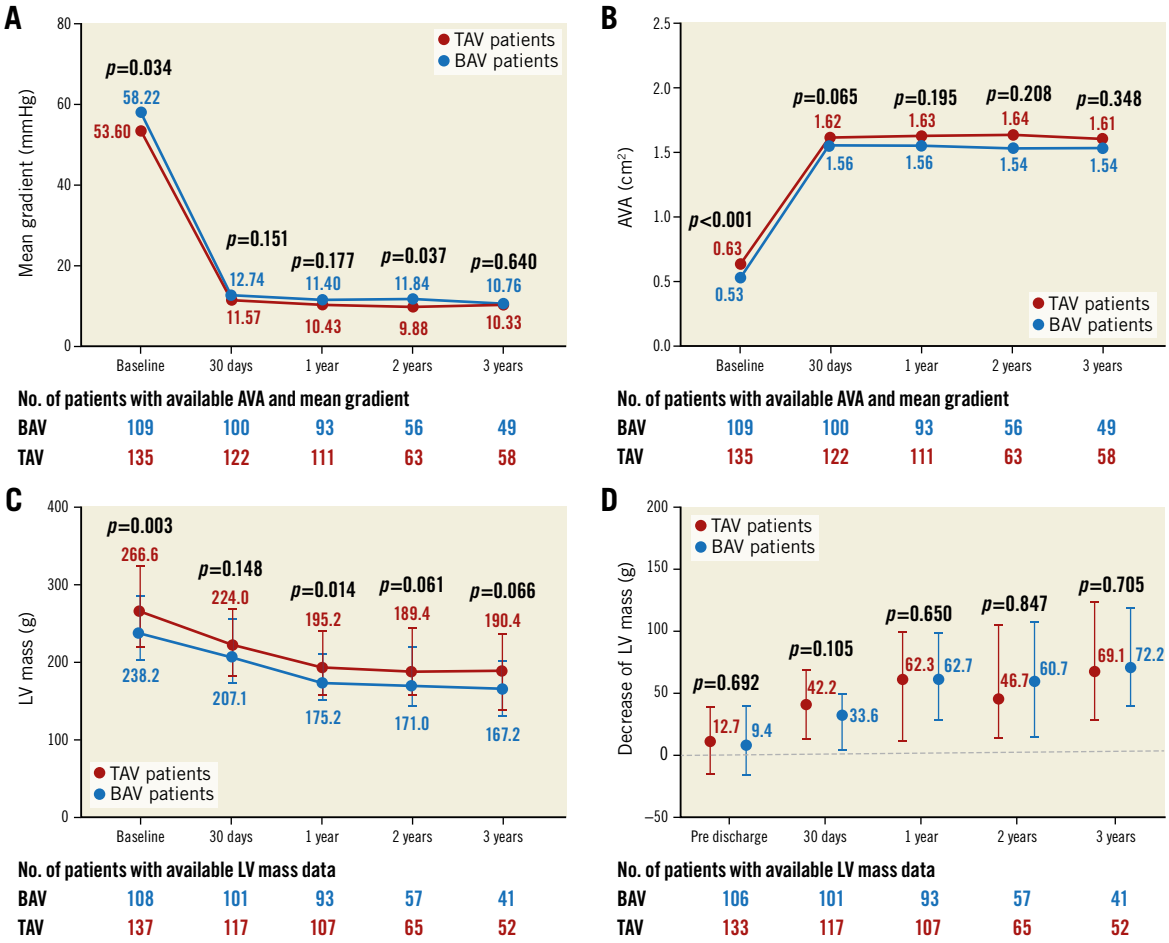


Figure 1. *Echocardiographic findings up to three years. Changes in mean gradient (A), AVA (B), and LV mass (C) from baseline to 30 days, 1 year, 2 years, and 3 years in the BAV patients and TAV patients. D) Comparison of decrease in LV mass between TAV patients and BAV patients at pre-discharge, 30 days, 1 year, 2 years, and 3 years. The bars in (C) and (D) represent interquartile range. AVA: aortic valve area; BAV: bicuspid aortic valve; LV: left ventricle; TAV: tricuspid aortic valve*

Discussion

To the best of our knowledge, this is the first study that has compared the long-term outcomes of TAVI for BAV versus TAV up to three years. The main findings of the study are: 1) except for the lower incidence of permanent pacemaker implantation that was observed in BAV patients, three-year clinical outcomes were comparable between bicuspid and tricuspid AS patients; 2) the bicuspid AS patients had a lower percentage of NYHA Class III/IV in the first year after the TAVI procedure while the percentage was similar between the BAV and TAV groups in the second and third year of follow-up; 3) BAV patients showed consistent valve haemodynamic improvement, which was similar to TAV patients; and 4) both TAV and BAV patients experienced significant LV reverse remodelling after TAVI.

Because of its anatomical characteristics, bicuspid aortic stenosis used to be considered a contraindication for TAVI.

However, recent studies have suggested the satisfactory short-term efficacy and safety of TAVI in BAV patients[11,12]. In addition, a national database analysis, which included 1,055 BAV patients who underwent TAVI and 30,840 BAV patients who received SAVR, revealed similar in-hospital outcomes between the two groups[22]. According to the 2020 ACC/AHA guidelines for valvular heart disease, TAVI is recommended in BAV patients as an alternative to SAVR after careful and comprehensive assessment[2]. Furthermore, a previous study demonstrated a high frequency (47.5%) of bicuspid AS in the Chinese population, thus suggesting many bicuspid TAVI candidates[23]. In our study, the proportion of BAV was 44.3%, 61.5% of whom were BAV Type 0. This revealed completely different population characteristics from those in the West[11,24]. Therefore, the study is warranted to evaluate long-term clinical outcomes in the Chinese BAV population.

According to the K-M survival analysis, the three-year survival rates were comparable between BAV and TAV patients (p=0.126) **(Central illustration)**. Although it showed a numerically higher three-year survival rate in the BAV population, this may be related to the younger age, lower STS score, and fewer baseline comorbidities. Consequently, three multivariate Cox analyses were performed to adjust for confounding factors,

revealing that bicuspid AS was not associated with a different risk of three-year all-cause mortality **(Table 5)**. Moreover, 5.5% of BAV patients suffered cardiovascular mortality during the three years of follow-up, which was comparable to TAV patients (p=0.129). In a subgroup analysis of patients treated with a self-expanding valve, a similar incidence of all-cause mortality, cardiovascular mortality and MACE was found in the two groups **(Supplementary Table 3)**. Similar results could also be found in patients who underwent TAVI using balloon-expandable valves and mechanically expandable valves **(Supplementary Table 4)**. The satisfactory clinical results provide long-term evidence for TAVI in bicuspid AS. A valuable basis was provided for large-scale randomised controlled trials to explore further the feasibility and effectiveness of TAVI for BAV. It could be assumed that, with the accumulation of evidence[6,9,25], TAVI might be gradually applied to the BAV population in the future.

Nearly 90% of the patients in our study suffered from NYHA Class III or IV symptoms at baseline. After the TAVI procedure, a significant decrease of NYHA stage could be found in both the bicuspid and tricuspid AS population. Nevertheless, the proportion of patients with NYHA Class I/II functional status was larger in BAV patients at one-year follow-up, which might be due to the worse baseline health status and more severe LV remodelling in tricuspid AS patients. The observed difference disappeared in the second and third years of follow-up, suggesting it took longer for the heart function to recover in TAV patients. Nevertheless, although TAV patients suffered more severe LV remodelling before the procedure, tricuspid and bicuspid AS patients experienced similar and notable reverse remodelling after TAVI. This recovery predominantly occurred in the first year after the procedure and remained stable at follow-up **(Supplementary Figure 2)**.

Unfortunately, as some echocardiography data were not available during follow-up, the findings need to be verified by further studies.

Aortic dissection is a devastating and potentially life-threatening complication. Notably, there was a significantly higher incidence of aortic dissection (4.6%) in BAV patients. It should be noted that the study presented here was a real-world study, which means that it includes some patients with hostile aortic anatomy for whom TAVI was performed to save their lives. According to previous studies, ascending aorta dilatation is a basic feature of bicuspid valve abnormality that can contribute to a higher risk of aortic dissection and rupture[9,26]. In addition to this, the more severe calcification and larger aortic angulation could also increase the risk of aortic dissection. Therefore, preprocedural anatomy should be carefully assessed to identify patients at high risk of these complications.

The adverse clinical effect of permanent pacemaker implantation after a TAVI procedure was highlighted in a recent pooled analysis[27]. In our study, most patients underwent TAVI using a first-generation self-expanding prosthesis, which was thought to have a higher risk of PPMI[28]. According to previous studies, bicuspid AS patients are thought to have a similar or higher risk of PPMI[11,29]. Nevertheless, our study revealed a lower incidence of PPMI in bicuspid AS patients in three years of follow-up (11.9% vs 21.9%, p=0.041). Since bicuspid AS patients had more severe valve calcification (519.7 mm^3 vs 435.2 mm^3, p=0.025), which could provide radial force for anchoring, the higher prosthesis implantation depth (4.5 mm vs 6.0 mm, p<0.001) and different valve size selection strategy based on supra-annular structure might have contributed to the difference between the two groups, as described in previous studies[25,30]. Accordingly, further exploration of different strategies for minimising pacemaker implantation in bicuspid AS patients is warranted.

In our multivariate Cox regression analysis, prior stroke and higher STS score were independent predictors of three-year all-cause mortality. As the BAV patients had a lower proportion of stroke history and lower STS scores, these two factors should be highlighted since they could contribute to the numerically higher three-year survival rate. Moreover, we found that poor health status (dialysis) and more cardiac comorbidities (with a prior pacemaker and moderate or severe mitral regurgitation) were associated with worse long-term prognosis.

Limitations

This study has some limitations that should be considered when interpreting our findings. First, the data in this study were retrospectively collected from our TAVI database. However, some patients (40.2%) were in our prospective cohort registry (the Transcatheter Aortic Valve Replacement Single Center Registry in Chinese Population [TORCH] registry, NCT02803294), which was initiated in June 2016. A prospective, multicentre, randomised controlled study for bicuspid AS patients is also ongoing (NCT04722796). Secondly, although only one patient was lost to follow-up within three years after the procedure, the non-randomised design and small sample size made it difficult to match baseline characteristics precisely. Even though similar results could be found in multivariate regression analysis adjusted for confounding factors, the finding that bicuspid and tricuspid AS patients had a similar long-term prognosis should be further verified by large-scale and longer follow-up (e.g., five- or 10-year follow-up) studies. Furthermore, echocardiographic data were not available for all patients during follow-up, which might have led to bias.

Conclusions

Except for a lower incidence of permanent pacemaker implantation, bicuspid AS patients had comparable three-year outcomes to tricuspid AS patients after the TAVI procedure. Both the BAV and TAV populations showed significant improvement in valve haemodynamics, which could be sustained for three years. Similar LV reverse remodelling was also found during follow-up. This study suggests satisfactory long-term outcomes of TAVI in BAV patients; however, these findings need to be further confirmed by large-scale and randomised studies.

Impact on daily practice

Based on the accumulated evidence, the indications for TAVI are expanding rapidly to low-risk patients. Furthermore, the NOTION 2 trial (NCT02825134) is exploring the effectiveness of TAVI in a young population. As patients with BAV are more likely to develop severe AS at a young age, it can be assumed that more BAV patients will be candidates for TAVI. However, no evidence on the long-term outcomes of TAVI exist in this population. In our study, we found that BAV patients had similar satisfactory three-year clinical outcomes, persistent valve haemodynamic improvement, and obvious cardiac reverse remodelling compared with TAV patients. The study provides evidence for clinical practice and further exploration of TAVI for bicuspid aortic stenosis.

Funding

This work was supported by the National Key R&D Program of China (2019YFA0110400 for JA. Wang, 2016YFC13010204 for JA. Wang). The National Natural Science Foundation of China (No. 81870292 for JA. Wang, No. 81570233, 81770252 for XB. Liu). The Key Social Development Program of Major Science and Technology Projects in Zhejiang Province (No. 2015C03028 for JA. Wang).

Conflict of interest statement

The authors have no conflicts of interest to declare.

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Supplementary data

Supplementary Table 1. Univariate logistic regression analyses of bicuspid aortic stenosis.

Supplementary Table 2. Characteristics of patients converted to open SAVR.

Supplementary Table 3. Three-year outcomes of patients treated with a self-expanding valve.

Supplementary Table 4. Three-year outcomes of patients treated with a balloon-expandable or mechanically expandable valve.

Supplementary Table 5. Baseline characteristics and outcomes of Type 0 and Type 1 BAV.

Supplementary Table 6. Left chamber size on echocardiography.

Supplementary Table 7. Comparisons between baseline echocardiography and different time points.

Supplementary Table 8. Univariate and multivariate Cox regression analysis of three-year all-cause mortality.

Supplementary Figure 1. Flow chart of the study population.

Supplementary Figure 2. Comparisons of LV mass between different time points.

The supplementary data are published online at: https://eurointervention.pcronline.com/doi/10.4244/EIJ-D-21-00734

Supplementary data

Table 1. Univariate logistic regression analyses of bicuspid aortic stenosis.

	Univariate logistic regression	
	p-value	OR (95% CI)
Age, years	**0.043**	0.96 (0.92-1.00)
STS score, per 1%	**0.018**	0.94 (0.89-0.99)
Previous stroke	**0.035**	0.20 (0.04-0.89)
Left ventricular mass, g	**0.004**	1.00 (0.99-1.00)

CI: confidence interval; OR: odds ratio; STS: Society of Thoracic Surgeons

Supplementary Table 2. Characteristics of patients converted to open SAVR.

Patient no.	Age	Valve type	Prosthesis	Major complications during procedure	Surgical valve	PVL after procedure	Clinical outcomes
1	77	Type 1	SEV	Tamponade; circulation collapse; aortic dissection.	21# Epic	NA	Died after procedure
2	74	Type 1	SEV	Aortic dissection; circulation collapse.	19# Regent	NA	Died after procedure
3	69	TAV	SEV	Left coronary obstruction after second valve implantation.	19# Regent	None	NYHA I at the third-year follow-up
4	84	Type 1	SEV	Valve embolisation.	21# Regent	None	NYHA I at the third-year follow-up
5	82	Type 1	BEV	Severe PVL after second valve implantation.	21# Biocor	Trace	NYHA I at the third-year follow-up

BEV: balloon-expandable valve; NYHA: New York Heart Association; PVL: paravalvular leakage; SAVR: surgical aortic valve replacement; SEV: self-expanding valve; TAV: tricuspid aortic valve; Type 1 represents type 1 bicuspid aortic valve

Supplementary Table 3. Three-year outcomes of patients treated with self-expanding valve.

	BAV patients (n=91)	**TAV patients (n=113)**	***p*-value**
All-cause mortality	14 (15.4%)	21 (18.6%)	0.547
Cardiovascular mortality	6 (6.6%)	12 (10.6%)	0.314
MACE*	21 (23.1%)	24 (21.2%)	0.753
All stroke	7 (7.7%)	4 (3.5%)	0.320
Disabling stroke	3 (3.3%)	1 (0.9%)	0.326
Myocardial infarction	2 (2.2%)	2 (1.8%)	1.000
Bleeding†	10 (11%)	10 (8.8%)	0.609
Permanent pacemaker implantation	9 (9.9%)	27 (23.9%)	**0.009**
New atrial fibrillation	6 (6.6%)	13 (11.5%)	0.230
NYHA Class III/IV	9 (12.2%)	14 (15.6%)	0.533
3-year echocardiography			
LVEF, %	64.0 (60.1-69.0)	61.9 (58.0-65.7)	0.124
Max velocity, m/s	2.11±0.45	2.15±0.49	0.651
Mean gradient, mmHg	9.41±4.17	9.72±4.47	0.734
Aortic valve area, cm^2	1.60±0.34	1.63±0.34	0.727
Moderate/severe PVL	2 (5.1%)	4 (7.7%)	0.697

Data are presented as n (%) or mean±SD or median (interquartile range, IQR). P-values in bold are statistically significant.

MACE*: major adverse cardiovascular events, including all-cause mortality, stroke and myocardial infarction. Bleeding†: life-threatening bleeding.

BAV: bicuspid aortic valve; LVEF: left ventricular ejection fraction; NYHA: New York Heart Association; PVL: paravalvular leakage; TAV: tricuspid aortic valve

Supplementary Table 4. Three-year outcomes of patients treated with balloon-expandable or mechanically expandable valve.

	Mechanically expandable valve			Balloon-expandable valve		
	BAV (n=13)	**TAV (n=10)**	***p*-value**	**BAV (n=5)**	**TAV (n=14)**	***p*-value**
All-cause mortality	0 (0.0%)	3 (30.0%)	0.068	0 (0.0%)	4 (28.6%)	0.530
Cardiovascular Mortality	0 (0.0%)	1 (10.0%)	0.435	0 (0.0%)	2 (14.3%)	1.000
MACE*	1 (7.7%)	3 (30.0%)	0.281	0 (0.0%)	4 (28.6%)	0.530
All stroke	1 (7.7%)	0 (0.0%)	1.000	0 (0.0%)	2 (14.3%)	1.000
Disabling stroke	0 (0.0%)	0 (0.0%)	-	0 (0.0%)	2 (14.3%)	1.000
Myocardial infarction	0 (0.0%)	0 (0.0%)	-	0 (0.0%)	0 (0.0%)	-
Bleeding†	0 (0.0%)	0 (0.0%)	-	1 (20.0%)	1 (7.1%)	0.468
PPMI	3 (21.3%)	3 (30.0%)	1.000	1 (20.0%)	0 (0.0%)	0.263
New atrial fibrillation	0 (0.0%)	0 (0.0%)	-	0 (0.0%)	2 (14.3%)	1.000
NYHA Class III/IV	1 (7.7%)	1 (14.3%)	1.000	2 (40.0%)	2 (20.0%)	0.560
3-year echocardiography						
LVEF, %	59.0±5.0	57.8±5.5	0.666	61.7±5.7	57.0±3.0	0.208
Max velocity, m/s	2.73±0.48	2.74±0.52	0.958	2.70±0.50	2.38±0.56	0.479
Mean gradient, mmHg	16.44±6.11	15.50±5.01	0.759	11.33±1.15	10.67±3.79	0.785
Aortic valve area, cm^2	1.29±0.26	1.56±0.18	0.168	1.51±0.52	1.32±0.06	0.706
Moderate/severe PVL	0 (0.0%)	0 (0.0%)	-	0 (0.0%)	0 (0.0%)	-

Data are presented as n (%) or mean±SD or median (interquartile range [IQR]).

MACE*: major adverse cardiovascular events, including all-cause mortality, stroke and myocardial infarction. Bleeding†: life threatening bleeding.

BAV: bicuspid aortic valve; LVEF: left ventricular ejection fraction; NYHA: New York Heart Association; PPMI: permanent pacemaker implantation; PVL: paravalvular leakage

Supplementary Table 5. Baseline characteristics and outcomes of Type 0 and Type 1 BAV.

	Type 0 BAV patients (n=67)	Type 1 BAV patients (n=40)	*p*-value
Ages, years	74 (70-79)	77 (74-82)	**0.014**
Male	30 (44.8%)	30 (75.0%)	**0.002**
STS score, %	4.47 (3.54-8.50)	5.83 (3.89-8.75)	0.172
NYHA Class III or IV	58 (86.6%)	36 (90.0%)	0.826
Baseline echocardiography			
LVEF, %	56.0 (45.0-63.8)	54.7 (40.0-64.7)	0.792
Max velocity, m/s	4.94±0.81	4.82±0.64	0.434
Mean gradient, mmHg	59.93±20.08	55.55±15.06	0.204
Aortic valve area, cm^2	0.52±0.17	0.57±0.15	0.098
LV mass, g	233.1 (197.4-283.6)	258.4 (215.4-300.7)	0.063
LV mass index, g/m^2	142.4 (120.3-180.8)	152.1 (125.8-187.5)	0.316
3-year outcomes			
All-cause mortality	8 (11.9%)	6 (15.0%)	0.650
Cardiovascular mortality	5 (7.5%)	1 (2.5%)	0.407
MACE*	12 (17.9%)	10 (25.0%)	0.380
All stroke	4 (6.0%)	4 (10.0%)	0.699
Disabling stroke	2 (3.0%)	1 (2.5%)	1.000
Myocardial infarction	1 (1.5%)	1 (2.5%)	1.000
Bleeding†	4 (6.0%)	7 (17.5%)	0.116
PPMI	4 (6.0%)	8 (20.0%)	0.056
New atrial fibrillation	5 (7.5%)	1 (2.5%)	0.407
NYHA Class III/IV	7 (12.1%)	5 (15.6%)	0.880
3-year echocardiography			
LVEF, %	66.6 (58.6-69.1)	60.3 (55.9-65.2)	**0.043**
Max velocity, m/s	2.20±0.45	2.29±0.59	0.530
Mean gradient, mmHg	10.37±4.73	10.85±5.46	0.741
Aortic valve area, cm^2	1.55±0.31	1.56±0.39	0.961
Moderate/severe PVL	1(3.3%)	1(5.0%)	1.000
LV mass, g	154.2 (133.5-186.4)	200.6 (135.6-240.5)	0.213
Decrease of LV mass, g	67.8 (36.8-126.0)	75.5 (51.3-117.2)	0.444

Data are presented as n (%) or mean±SD or median (interquartile range [IQR]). P-values in bold are statistically significant.

MACE*: major adverse cardiovascular events, including all-cause mortality, stroke and myocardial infarction.

Bleeding†: life threatening bleeding.

BAV: bicuspid aortic valve; LV: left ventricular; LVEF: left ventricular ejection fraction; NYHA: New York Heart Association; PPMI: permanent pacemaker implantation; PVL: paravalvular leakage; STS: Society of Thoracic Surgeons

Supplementary Table 6. Left chamber size on echocardiography.

	BAV patients (n=109)	TAV patients (n=137)	*p*-value
Baseline echocardiography			
IVSd, cm	1.29±0.21	1.28±0.20	0.759
LVIDd, cm	4.89±0.70	5.26±0.78	**<0.001**
LVPWd, cm	1.24 (1.14-1.33)	1.23 (1.15-1.35)	0.775
LA, cm	4.12±0.66	4.37±0.64	**0.004**
1-year echocardiography			
IVSd, cm	1.17±0.21	1.22±0.20	0.096
LVIDd, cm	4.44±0.56	4.60±0.75	0.092
LVPWd, cm	1.09 (1.01-1.21)	1.16 (1.03-1.27)	**0.021**
LA, cm	3.97±0.65	4.27±0.72	**0.002**
2-year echocardiography			
IVSd, cm	1.17±0.26	1.20±0.19	0.515
LVIDd, cm	4.50±0.74	4.65±0.81	0.281
LVPWd, cm	1.08 (0.99-1.22)	1.14 (1.01-1.23)	0.212
LA, cm	4.02±0.59	4.18±0.59	0.130
3-year echocardiography			
IVSd, cm	1.19±0.28	1.20±0.21	0.908
LVIDd, cm	4.21±0.58	4.59±0.85	**0.016**
LVPWd, cm	1.08 (0.97-1.26)	1.13 (1.02-1.19)	0.518
LA, cm	4.06±0.89	4.37±0.63	0.060

Data are presented as mean±SD or median (interquartile range [IQR]). P-values in bold are statistically significant.

IVSd: interventricular septal thickness at diastole; LA: left atrial; LVIDd: left ventricular internal diameter at end-diastole; LVPWd: left ventricular posterior wall thickness at diastole

Supplementary Table 7. Comparisons between baseline echocardiography and different time points.

		Baseline	At 30 days	At 1 year	At 2 years	At 3 years
All patients	LVEF, %	55.2 (43.1-63.7)	61.5 (56.0-65.1)*	64.1 (58.2-67.9)*	64.0 (59.1-67.5)*	61.6 (57.5-67.4)*
	Mean gradient, mmHg	55.7±16.6	12.1±6.1*	10.9±5.1*	10.8±5.3*	10.5±4.9*
	Aortic valve area, cm^2	0.59±0.18	1.59±0.27*	1.60±0.36*	1.59±0.44*	1.58±0.35*
	Left ventricular mass, g	251.9 (212.1-306.5)	215.5 (181.3-259.0)*	187.8 (156.7-229.7)*	180.4 (154.5-234.6)*	183.0 (136.9-214.2)*
	Moderate/severe MR	62 (25.2%)	30 (13.3%)*	18 (8.5%)*	18 (14.1%)	11 (9.6%)
	Moderate/severe TR	42 (17.1%)	22 (9.7%)	20 (9.5%)	19 (14.8%)	18 (15.8%)
BAV patients	LVEF, %	56.0 (40.6-64.3)	62.2 (58.6-65.1)*	64.7 (60.4-68.9)*	63.6 (60.0-67.0)*	63.0 (57.6-68.0)*
	Mean gradient, mmHg	58.2±18.2	12.7±7.4*	11.40±5.82*	11.84±5.74*	10.76±5.15*
	Aortic valve area, cm^2	0.53±0.16	1.56±0.27*	1.56±0.35*	1.54±0.48*	1.54±0.35*
	Left ventricular mass, g	238.2 (204.0-287.5)	207.1 (174.5-256.0)*	175.2 (152.1-212.1)*	171.0 (144.9-221.7)*	167.2 (131.5-202.8)*
	Moderate/severe MR	24 (22.0%)	12 (11.8%)†	7 (7.3%)	9 (14.8%)	3 (5.9%)
	Moderate/severe TR	18 (16.5%)	8 (7.8%)	9 (9.4%)	12 (19.7%)	7 (13.7%)

Echocardiographic data at different time points were compared with data at baseline.

Continuous variables were compared using the Wilcoxon rank-sum test or paired samples t-test. Categorical variables were compared using the McNemar chi-square test. Multiple tests were corrected by Bonferroni correction ($p<0.013$). * Represents $p<0.001$. † Represents $p<0.013$.

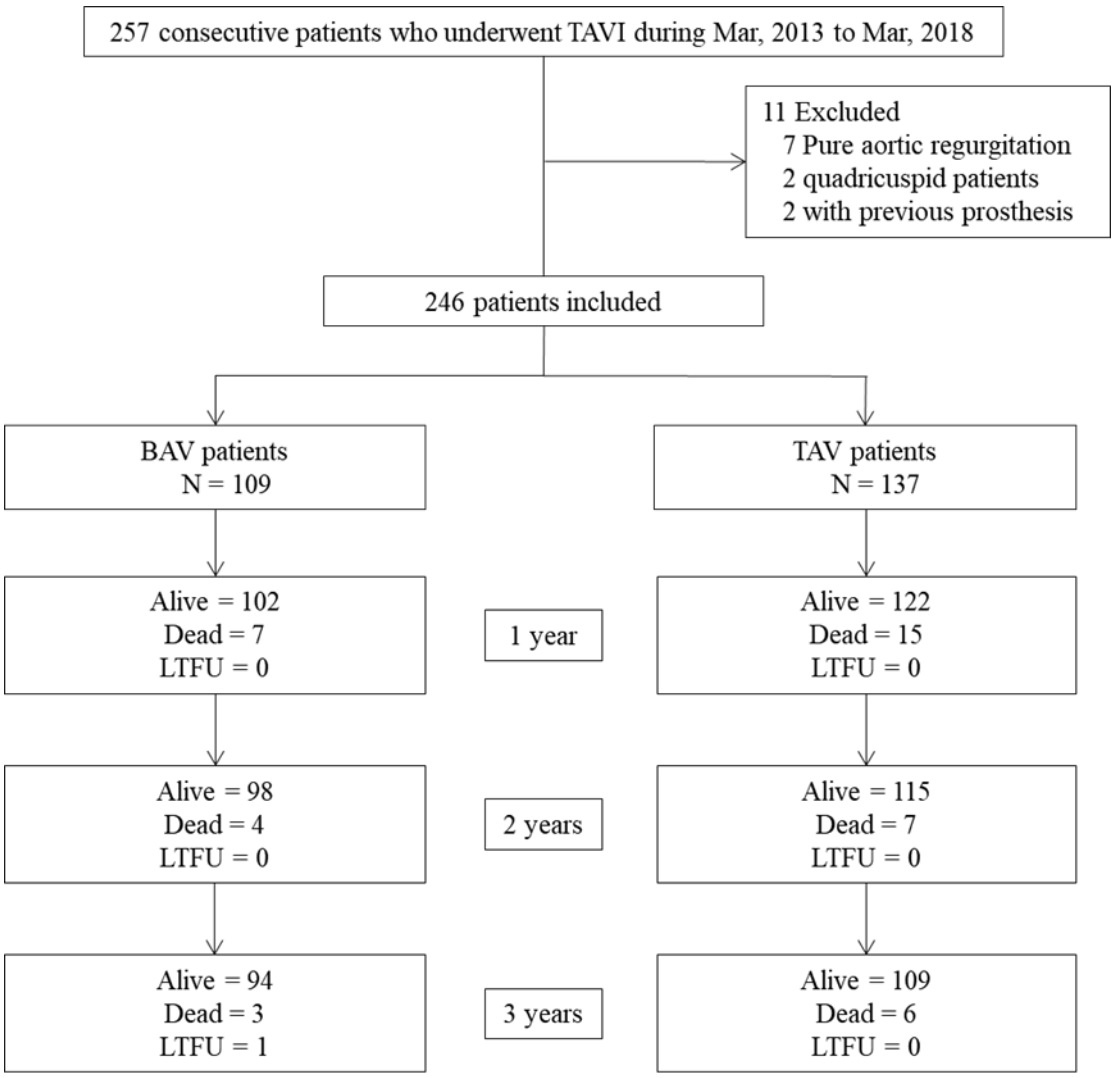
BAV: bicuspid aortic valve; LVEF: left ventricular ejection fraction; MR: mitral regurgitation; TR: tricuspid regurgitation

Supplementary Table 8. Univariate and multivariate Cox regression analyses of three years all-cause mortality.

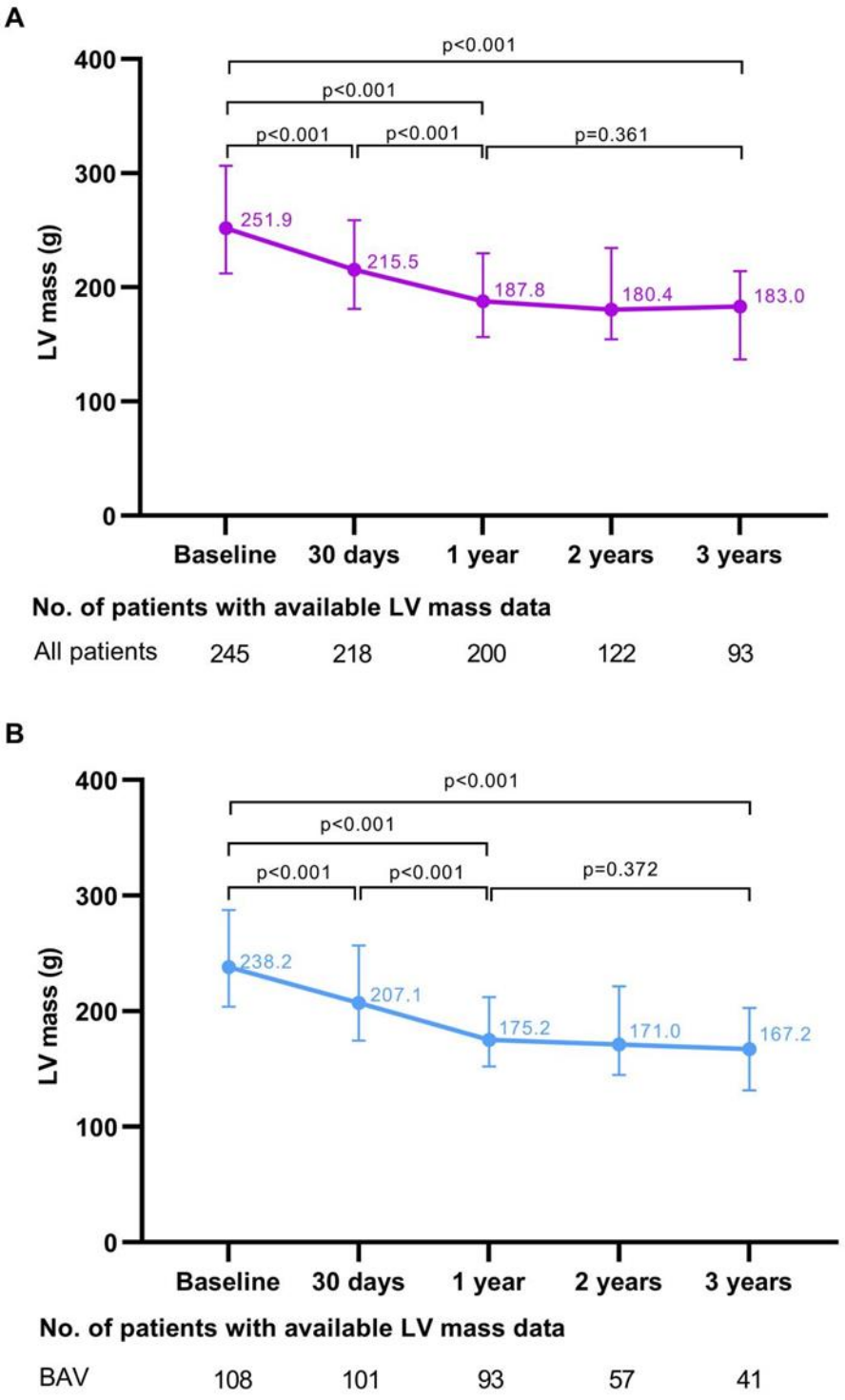
	Univariate regression		Multivariate regression	
	p-value	HR (95% CI)	*p*-value	HR (95% CI)
Bicuspid aortic stenosis	0.130	0.61 (0.32-1.16)	-	-
Ages, per 1 year	0.473	1.02 (0.97-1.07)	-	-
Male	0.464	1.27 (0.67-2.41)	-	-
Body mass index, per 1 kg/m^2	0.288	0.95 (0.87-1.04)	-	-
STS score, per 1%	**<0.001**	1.09 (1.06-1.12)	**<0.001**	1.07 (1.04-1.11)
Diabetes mellitus	0.963	0.98 (0.47-2.05)	-	-
History of hypertension	0.705	1.13 (0.61-2.09)	-	-
Smoker	0.152	0.35 (0.09-1.47)	-	-
Dyslipidaemia	0.914	1.04 (0.53-2.03)	-	-
Chronic obstructive pulmonary disease	0.875	1.06 (0.51-2.22)	-	-
History of cancer	0.532	0.53 (0.07-3.86)	-	-
Peripheral vascular disease	0.127	1.64 (0.87-3.07)	-	-
Previous stroke	0.064	2.42 (0.95-6.16)	**0.021**	3.05 (1.18-7.90)
Previous MI	0.476	0.05 (0.00-206.25)	-	-
Previous PCI	0.418	1.40 (0.62-3.15)	-	-
Previous atrial fibrillation/flutter	**0.034**	2.03 (1.05-3.90)	-	-
Previous PPMI	**0.026**	3.81 (1.18-12.35)	**0.016**	4.76 (1.35-16.83)
NYHA	0.827	1.05 (0.66-1.67)	-	-
Dialysis	**<0.001**	8.46 (3.00-23.86)	**0.006**	6.78 (1.73-26.62)
LVEF <55%	**0.027**	2.04 (1.09-3.84)	-	-
Moderate/severe MR	**0.004**	2.44 (1.32-4.49)	**0.001**	3.09 (1.60-5.97)
Moderate/severe TR	**0.001**	3.07 (1.63-5.77)	-	-
DLZ calcification score, per 1 mm^3	0.402	1.00 (1.00-1.00)	-	-
LVMI, per 1 g/m^2	0.465	1.00 (1.00-1.01)	-	-

The variables with a p-value <0.10 in univariate analysis were entered in multivariate Cox regression analysis using a forward Likelihood Ratio method.

DLZ: device landing zone; LVEF: left ventricular ejection fraction; LVMI: left ventricular mass index; MI: myocardial infarction; MR: mitral regurgitation; NYHA: New York Heart Association; PCI: percutaneous coronary intervention; PPMI: permanent pacemaker implantation; STS: Society of Thoracic Surgeons; TR: tricuspid regurgitation



Supplementary Figure 1. Flow chart of the study population.
BAV: bicuspid aortic valve; LTFU: lost to follow-up; TAV: tricuspid aortic valve; TAVI: transcatheter aortic valve implantation



Supplementary Figure 2. Comparisons of LV mass between different time points.

LV mass were compared between different time points in all patients (A) or BAV patients (B) using the Wilcoxon rank-sum test. The bars represent the interquartile range. P-values were corrected by Bonferroni correction (p<0.010). LV: left ventricular