European Journal of Cardio-Thoracic Surgery 59 (2021) 1191–1199
doi:10.1093/ejcts/ezaa474 Advance Access publication 26 January 2021

ORIGINAL ARTICLE

Cite this article as: Çelik M, Milojevic M, Durko AP, Oei FBS, Bogers AJJC, Mahtab EAF. Differences in baseline characteristics and outcomes of bicuspid and tricuspid aortic valves in surgical aortic valve replacement. Eur J Cardiothorac Surg 2021;59:1191–9.

Differences in baseline characteristics and outcomes of bicuspid and tricuspid aortic valves in surgical aortic valve replacement

Mevlüt Çelik, Milan Milojevic, Andras P. Durko, Frans B.S. Oei, Ad. J.J.C. Bogers and Edris A.F. Mahtab*

Department of Cardiothoracic Surgery, Erasmus University Medical Center, Rotterdam, Netherlands

* Corresponding author. Department of Cardiothoracic Surgery, Erasmus University Medical Center, Rotterdam, Netherlands. Tel: 0031 010 703 57 84; e-mail: e.mahtab@erasmusmc.nl (E.A.F. Mahtab).

Received 1 August 2020; received in revised form 14 November 2020; accepted 26 November 2020

CONVENTIONAL VALVE OPERATIONS

Key question

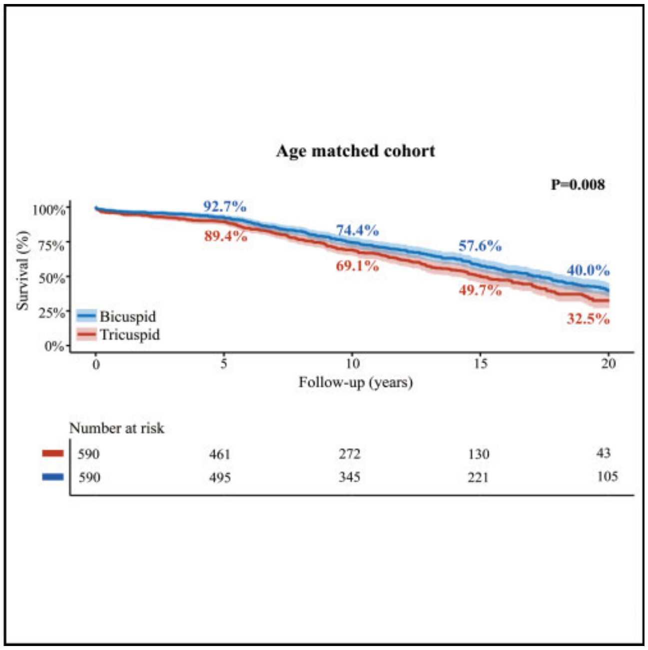
What are the long-term outcomes of patients with bicuspid aortic valve (BAV) undergoing surgical aortic valve replacement (SAVR)?

Key finding(s)

Patients with BAV undergoing SAVR have better survival than those in an age-matched cohort (p=0.008).

Take-home message

These satisfactory long-term results reinforce the role of SAVR in the BAV population.



Abstract

OBJECTIVES: Patients with bicuspid aortic valve (BAV) comprise a substantial portion of patients undergoing surgical aortic valve replacement (SAVR). Our goal was to quantify the prevalence of BAV in the current SAVR ± coronary artery bypass grafting (CABG) population, assess differences in cardiovascular risk profiles and assess differences in long-term survival in patients with BAV compared to patients with tricuspid aortic valve (TAV).

METHODS: Patients who underwent SAVR with or without concomitant CABG and who had a surgical report denoting the relevant valvular anatomy were eligible and included. Prevalence, predictors and outcomes for patients with BAV were analysed and compared to those patients with TAV. Matched patients with BAV and TAV were compared using a propensity score matching strategy and an age matching strategy.

RESULTS: A total of 3723 patients, 3145 of whom (mean age 66.6 ± 11.4 years; 37.4% women) had an operative report describing their aortic valvular morphology, underwent SAVR ± CABG between 1987 and 2016. The overall prevalence of patients with BAV was 19.3% (607). Patients with BAV were younger than patients with TAV (60.6 ± 12.1 vs 68.0 ± 10.7, respectively). In the age-matched cohort, patients with BAV were less likely to have comorbidities, among others diabetes (*P* = 0.001), hypertension (*P* < 0.001) and hypercholesterolaemia (*P*

= 0.003), compared to patients with TAV. Twenty-year survival following the index procedure was higher in patients with BAV (14.8%) compared to those with TAV (12.9%) in the age-matched cohort (*P* = 0.015).

CONCLUSIONS: Substantial differences in the cardiovascular risk profile exist in patients with BAV and TAV. Long-term survival after SAVR in patients with BAV is satisfactory.

Keywords: Aortic valve replacement • Surgical • Coronary revascularization • Transcatheter aortic valve replacement • Transcatheter aortic valve implantation • High-volume centre • Bicuspid aortic valve • Incidence • Transcatheter

ABBREVIATIONS

AR	Aortic valve regurgitation
AS	Aortic valve stenosis
BAV	Bicuspid aortic valve
CABG	Coronary artery bypass grafting
LVEF	Left ventricular ejection fraction
SAVR	Surgical aortic valve replacement
TAV	Tricuspid aortic valve
TAVI	Transcatheter aortic valve implantation

INTRODUCTION

Bicuspid aortic valve (BAV) disease is the most prevalent congenital heart defect, with a prevalence between 0.5% and 2.0% in the general population [1, 2]. Compared to the patients with tricuspid aortic valve (TAV), patients with BAV are younger at the time of surgery [3]. Patients with a BAV present with a different cardiovascular risk profile than patients with a TAV and have a higher incidence of aortic stenosis (AS), aortic regurgitation (AR), aortopathy and related complications [4]. BAV and TAV both have anatomical and procedural differences at the time of surgical intervention [5].

Studies comparing the clinical profiles and outcomes of patients with BAV and TAV undergoing surgical aortic valve replacement (SAVR) are scarce, especially in an era where indications for transcatheter aortic valve implantation (TAVI) are expanding and becoming an alternative treatment for younger patients with low surgical risk and even for asymptomatic patients [6]. Therefore, the purpose of this study was to (i) describe the prevalence of BAV in the current SAVR population, (ii) describe similarities and differences in patients with BAV and TAV and (iii) compare the long-term survival and predictors of survival in patients with BAV and TAV.

METHODS

Study design

Adult (≥18 years) patients who underwent SAVR with or without a coronary artery bypass grafting (CABG) between 1987 and 2016 at the Erasmus Medical Centre, Rotterdam, Netherlands were included. Patients with concomitant surgical procedures other than CABG were excluded. Patients who did not receive a biological or mechanical aorta valve prosthesis were excluded. Patients with previous aortic valve replacement were likewise excluded. Baseline patient and procedural characteristics were collected from electronic medical records. Survival status was obtained through the National Civil Registry. Patients were classified according to the number of cusps treated during the operation. Valvular morphology was defined by the surgeon in the operative report. Functional BAV, such as having an obstructed or incomplete commissure in an originally tricuspid valve, was classified as TAV.

This study was conducted according to the privacy policy of the Erasmus Medical Centre and the Erasmus Medical Centre regulations for the appropriate use of data in patient-oriented research, which are based on international regulations, including the Declaration of Helsinki (MEC-2020-0454). All the authors vouch for the validity of the data and adherence to the protocol.

End points and definitions

The primary end point was to assess the prevalence of BAV and the differences in patient characteristics between BAV and TAV in the SAVR population. An additional end point was the difference in survival between patients with BAV and TAV. To assess for the prevalence of BAV within the surgical cohort, patients were classified across 6 age groups (group 1: patients younger than 40; group 2: patients between 40 and 49; group 3: patients between 50 and 59; group 4: patients between 60 and 69; group 5: patients between 70 and 79; and group 6: patients aged or older than 80). The primary indication for an operation (AS, AR or combined AS and AR) was determined based on the initial echocardiogram and on the clinical guidelines in use at the time of the operation, corresponding to the current European and American valvular guidelines [7, 8]. In general, SAVR within 24 h of establishing the indication was classified as an emergency procedure. Renal failure was defined as a creatinine level ≥2.0 mg/dl. Left ventricular function was classified as normal if the left ventricular ejection fraction (LVEF) was >50%, as mildly reduced if the LVEF was 40–49%, as moderately reduced if the LVEF was 30–39% and as severely reduced if the LVEF was less than 30%, as assessed by a trained echocardiographer [9].

Statistical analyses

Discrete variables are presented as numbers, percentages or proportions and compared with either the χ^2 test or the Fisher's exact test, where appropriate. Continuous variables are presented as means ± standard deviation or median with the interquartile range if there was evidence of skewed data according to the Kolmogorov–Smirnov test and compared with either the two-sample *t*-test or the Wilcoxon rank-sum test, where appropriate.

Non-parsimonious logistic regression was used to estimate each patient's probability of being in the BAV group. Propensity scores were calculated for each group with the following covariates: age, gender, previous cardiac operation, atrial fibrillation, diabetes mellitus, decompensation, hypercholesterolaemia, hypertension, myocardial infarction, previous percutaneous coronary intervention, chronic obstructive pulmonary disease,

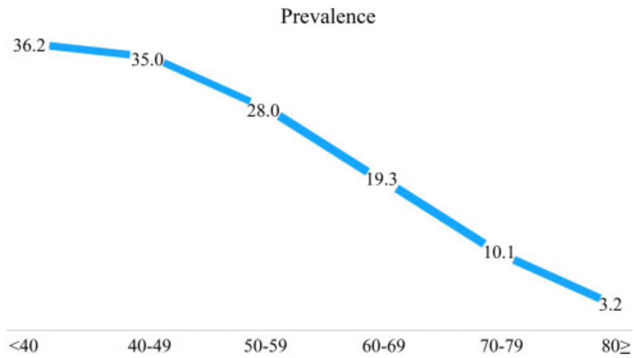


Figure 1: Prevalence of bicuspid aortic valve. The percentage of patients with bicuspid aortic valves decreases considerably with increasing age. Results are reported as percentages.

endocarditis, history of cancer, stroke/transient ischaemic attack, arterial disease, indication for surgery, concomitant CABG and size and type of valve implanted. The balance between treatment groups was assessed with the use of standardized mean differences. A standardized mean difference of 0.1 or less was deemed to be the ideal balance, and a standardized difference of 0.2 or less was deemed to be an acceptable balance [10]. The relative survival can be used as an estimate of cause-specific mortality. It is defined as the ratio between the observed survival rates and the expected survival rates in the general population [11]. Furthermore, the proportional hazard assumption for the overall group was assessed with the corresponding test for correlation of the Schoenfeld residuals over time. Nonetheless, the restricted mean survival time at 10 years of follow-up was calculated to substantiate the overall between-group treatment effect in the overall cohort, the propensity score-matched cohort and the age-matched cohort.

The Human Mortality Database is used to obtain the age-, sex- and calendar year-matched expected survival data of the general population in the Netherlands [12]. The Human Mortality Database is continuously updated and includes mortality data from Netherlands through 2016. Relative survival is estimated using the Ederer II method [13, 14]. Predictors of mortality were identified in a Cox proportional hazards model. Significant variables on univariable analyses were included in a multivariable Cox proportional hazards model. Sensitivity analysis was performed for isolated SAVR. Two-sided *P*-values <0.05 were considered to be statistically significant. Data analyses were done using SPSS 25.0 (SPSS Inc., Chicago, IL, USA) and R software, version 3.5 (R Foundation, Vienna, Austria). Figures were generated using Microsoft Excel (Microsoft, Redmond, WA, USA) and R software, version 3.5 (R Foundation).

RESULTS

Characteristics of patients with bicuspid aortic valves

A total of 3723 patients underwent SAVR with or without CABG, 3145 of whom had a surgeon's report on the valvular anatomy, with 607 BAV (19.3%) and 2538 TAV (80.7%). A total of 48 patients with BAV were excluded due to concomitant aortic surgery; differences in characteristics between included and excluded patients are shown in Supplementary Material, Table S1. The prevalence of bicuspid aortic morphology according to age group was 36.2%, 35.0%, 28.0%, 19.3%, 10.1% and 3.2% in patients aged <40, 40–49, 50–59, 60–69, 70–79 and 80≥ years, respectively (Fig. 1). The prevalence of bicuspid aortic morphology for those operated after the year 2000 is shown in Supplementary Material, Fig. S1. Patients with BAV were younger than patients with TAV at the time of the operation (mean age 60.6 ± 12.1 years vs 68.0 ± 10.7 years; *P* < 0.001) and were less often women (32.9% vs 38.5%; *P* = 0.013). The prevalence of BAV decreased from 43.8% to 16.2% between 1987 and 2016. The prevalence of hypertension (24.7% vs 39.6%), hypercholesterolaemia (10.0% vs 18.6%) and diabetes (7.7% vs 17.2%) was lower in patients with BAV than in those with TAV (all *P*-values <0.001) (Table 1). These differences persisted after age matching. Further characteristics in the overall cohort, the propensity score-matched cohort and the age-matched cohort are shown in Table 1. Subanalyses on the characteristics of patients operated on after 2000 are shown in Supplementary Material, Table S2 and Fig. S2.

Procedural characteristics

The indication for surgery was mainly AS (75.0%), followed by AR (7.7%) or AS and AR combined (17.1%). Concomitant CABG surgery was performed in 21.9% of the patients, less often in patients with BAV compared to those with TAV (*P* < 0.001); this difference persisted after age matching (*P* = 0.004). The incidence of mechanical valve implantation was higher in the BAV group compared to the TAV group in the overall cohort (61.4% vs 39.2%; *P* < 0.001) and in the age-matched cohort (63.1% vs 57.5%; *P* = 0.05). The diameter of the implanted prosthesis was higher in patients with BAV than in those with TAV in the overall cohort (24.4 ± 2.4 vs 23.4 ± 2.3; *P* < 0.001) and in the age-matched cohort (24.4 ± 2.4 vs 23.7 ± 2.4; *P* < 0.001).

Long-term outcomes after surgery

A total of 1728 patients died during the follow-up period (309 patients with BAV and 1419 patients with TAV; *P* = 0.03). Survival was 75.1% vs 57.4% and 40.5% vs 17.8% at 10 and 20 years of follow-up in the overall cohort for patients with BAV and TAV, respectively (*P* < 0.001) (Fig. 2A). The survival was 75.1% vs 69.9% and 40.0% vs 33.7% at 10 and 20 years of follow-up in the propensity score-matched cohort for patients with BAV and TAV, respectively (*P* = 0.02) (Fig. 2B). The survival was 74.4% vs 69.1% and 40.0% vs 32.5% at 10 and 20 years of follow-up in the age-matched cohort for patients with BAV and TAV, respectively (*P* = 0.015) (Fig. 2C). Similar results have been noted for patients operated on after 2000 (Supplementary Material, Fig. S3). In age-, sex- and year-matched Dutch controls, the relative survival in patients with BAV was 102.6%, 98.6%, 95.5% and 89.0%, at 5, 10, 15 and 20 years of follow-up, respectively (Fig. 3A). The relative survival in patients with TAV was 97.0%, 87.5%, 70.2% and 52.9%, at 5, 10, 15 and 20 years of follow-up, respectively (Fig. 3B). Patients with BAV had 7 months survival benefit compared to those with TAV at 20 years of follow-up in the overall cohort (Table 2), which diminished after propensity score matching. Further survival benefits according to different matching methods and age groups are shown in Table 2.

Factors associated with survival during follow-up in the age-matched population

In multivariable analyses, the presence of cardiovascular risk factors such as increasing age (*P* < 0.001), atrial fibrillation (*P*

Table 1: Baseline and procedural characteristics stratified according to the overall cohort, propensity score-matched cohort and age-matched cohort

	TAV (2538)	BAV (607)	*P*-value	SMD	PSM-TAV (593)	PSM-BAV (593)	*P*-value	SMD	AM-TAV (590)	AM-BAV (590)	*P*-value	SMD
Age at operation, mean ± SD	68.0 ± 10.7	60.6 ± 12.1	<0.001	0.647	61.6 ± 12.5	61.0 ± 11.7	0.40	0.049	61.3 ± 11.5	61.3 ± 11.5	>0.999	<0.001
Gender (female), *n* (%)	977 (38.5)	200 (32.9)	0.01	0.116	193 (32.5)	198 (33.4)	0.81	0.018	188 (31.9)	198 (33.6)	0.58	0.036
Indication, *n* (%)	1843 (72.6)	455 (75.0)	0.02	0.149	452 (76.2)	445 (75.0)	0.77	0.062	382 (64.7)	447 (75.8)	<0.001	0.353
AS	306 (12.1)	47 (7.7)	0.24	0.053	50 (8.4)	47 (7.9)	0.64	0.027	110 (18.6)	42 (7.1)	<0.001	0.243
AI	385 (15.2)	104 (17.1)	0.002	0.145	89 (15.0)	100 (16.9)	0.75	0.018	97 (16.4)	100 (16.9)	<0.001	0.349
Combined			0.23	0.053			0.38	0.051			0.81	0.014
Previous cardiac operation, *n* (%)	161 (6.3)	31 (5.1)	0.29	0.053	29 (4.9)	30 (5.1)	>0.999	0.008	41 (6.9)	29 (4.9)	0.18	0.086
Creatinine level, median (IQR)	0.98 (0.84–1.16)	0.95 (0.82–1.10)	0.001	0.095	0.95 (0.81–1.10)	0.95 (0.81–1.10)	0.86	0.087	0.96 (0.83–1.13)	0.95 (0.81–1.10)	0.19	0.089
≥2 mg/dl, *n* (%)	67 (2.7)	10 (1.7)	0.20	0.069	9 (1.5)	9 (1.5)	>0.999	<0.001	13 (2.2)	9 (1.5)	0.51	0.051
Atrial fibrillation, *n* (%)	350 (13.8)	54 (8.9)	0.002	0.155	61 (10.3)	54 (9.1)	0.56	0.040	66 (11.2)	54 (9.2)	0.29	0.067
Diabetes mellitus, *n* (%)	436 (17.2)	47 (7.7)	<0.001	0.289	50 (8.4)	47 (7.9)	0.83	0.018	85 (14.4)	47 (8.0)	0.001	0.205
Decompensation cordis, *n* (%)	397 (15.6)	64 (10.5)	0.002	0.152	54 (9.1)	63 (10.6)	0.44	0.051	97 (16.4)	62 (10.5)	0.004	0.174
Hypertension, *n* (%)	1004 (39.6)	150 (24.7)	<0.001	0.322	158 (26.6)	150 (25.3)	0.64	0.031	213 (36.1)	149 (25.3)	<0.001	0.237
Hypercholesterolaemia, *n* (%)	473 (18.6)	61 (10.0)	<0.001	0.247	60 (10.1)	61 (10.3)	>0.999	0.006	97 (16.4)	61 (10.3)	0.003	0.180
Previous myocardial infarction, *n* (%)	312 (12.3)	48 (7.9)	0.003	0.146	54 (9.1)	47 (7.9)	0.53	0.042	68 (11.5)	4 (8.1)	0.06	0.114
Previous PCI, *n* (%)	201 (7.9)	21 (3.5)	<0.001	0.193	25 (4.2)	21 (3.5)	0.65	0.035	40 (6.8)	21 (3.6)	0.018	0.146
COPD, *n* (%)	292 (11.5)	44 (7.2)	0.003	0.146	37 (6.2)	44 (7.4)	0.49	0.047	67 (11.4)	44 (7.5)	0.028	0.134
Endocarditis, *n* (%)	99 (3.9)	26 (4.3)	0.75	0.019	21 (3.5)	23 (3.9)	0.88	0.018	35 (5.9)	24 (4.1)	0.18	0.086
History of cancer, *n* (%)	190 (7.5)	26 (4.3)	0.007	0.136	24 (4.0)	26 (4.4)	0.89	0.017	37 (6.3)	26 (4.4)	0.20	0.083
Stroke/TIA, *n* (%)	240 (9.5)	35 (5.8)	0.005	0.139	27 (4.6)	35 (5.9)	0.36	0.061	55 (9.3)	35 (5.9)	0.037	0.128
Stroke	106 (4.2)	17 (2.8)	0.15	0.075	15 (2.5)	17 (2.9)	0.86	0.021	23 (3.9)	17 (2.9)	0.42	0.056
TIA	155 (6.1)	21 (3.5)	0.014	0.124	13 (2.2)	21 (3.5)	0.22	0.081	35 (5.9)	21 (3.6)	0.08	0.112
Arterial disease, *n* (%)	131 (5.2)	14 (2.3)	0.004	0.151	11 (1.9)	14 (2.4)	0.69	0.035	23 (3.9)	14 (2.4)	0.18	0.088
Carotid	22 (0.9)	1 (0.2)	0.12	0.098	1 (0.2)	1 (0.2)	>0.999	<0.001	5 (0.8)	1 (0.2)	0.22	0.095
Peripheral	114 (4.5)	13 (2.1)	0.011	0.132	10 (1.7)	13 (2.2)	0.67	0.037	19 (3.2)	13 (2.2)	0.37	0.063
Concomitant CABG, *n* (%)	914 (36.0)	133 (21.9)	<0.001	0.307	133 (22.4)	132 (22.3)	>0.999	0.004	177 (30.0)	133 (22.5)	0.004	0.170
Valve size, mean ± SD	23.4 ± 2.3	24.4 ± 2.4	<0.001	0.466	24.4 ± 2.4	24.4 ± 2.4	0.86	0.010	23.7 ± 2.4	24.4 ± 2.4	<0.001	0.296
Urgency, *n* (%)	28 (1.2)	6 (1.2)	0.09	0.138	4 (0.8)	6 (1.2)	0.69	0.094	7 (1.3)	5 (1.0)	0.34	0.134
Emergency	2252 (98.8)	490 (98.8)			525 (99.2)	478 (98.8)			522 (98.7)	475 (99.0)		
Not an emergency												
LVEF, *n* (%)	1880 (79.9)	445 (81.8)	0.65	0.062	447 (82.2)	437 (81.7)	0.78	0.063	416 (76.3)	433 (81.9)	0.09	0.156
Preserved	164 (7.0)	31 (5.7)			25 (4.6)	31 (5.8)			43 (7.9)	29 (5.5)		
Mildly reduced	227 (9.6)	48 (8.8)			49 (9.0)	48 (9.0)			54 (9.9)	48 (9.1)		
Moderately reduced	82 (3.5)	20 (3.7)			23 (4.2)	19 (3.6)			32 (5.9)	19 (3.6)		
Severely reduced												
Valve (mechanical), *n* (%)	996 (39.2)	389 (64.1)	<0.001	0.513	356 (60.0)	376 (63.4)	0.26	0.069	339 (57.5)	372 (63.1)	0.050	0.114

AI: aortic insufficiency; AM: age-matched; AS: aortic stenosis; BAV: bicuspid aortic valve; CABG: coronary artery bypass grafting; COPD: chronic obstructive pulmonary disease; IQR: interquartile range; LVEF: left ventricular ejection fraction; PCI: percutaneous coronary intervention; PSM: propensity score matched; SD: standard deviation; SMD: standardized mean difference; TAV: tricuspid aortic valve; TIA: transient ischaemic attack.

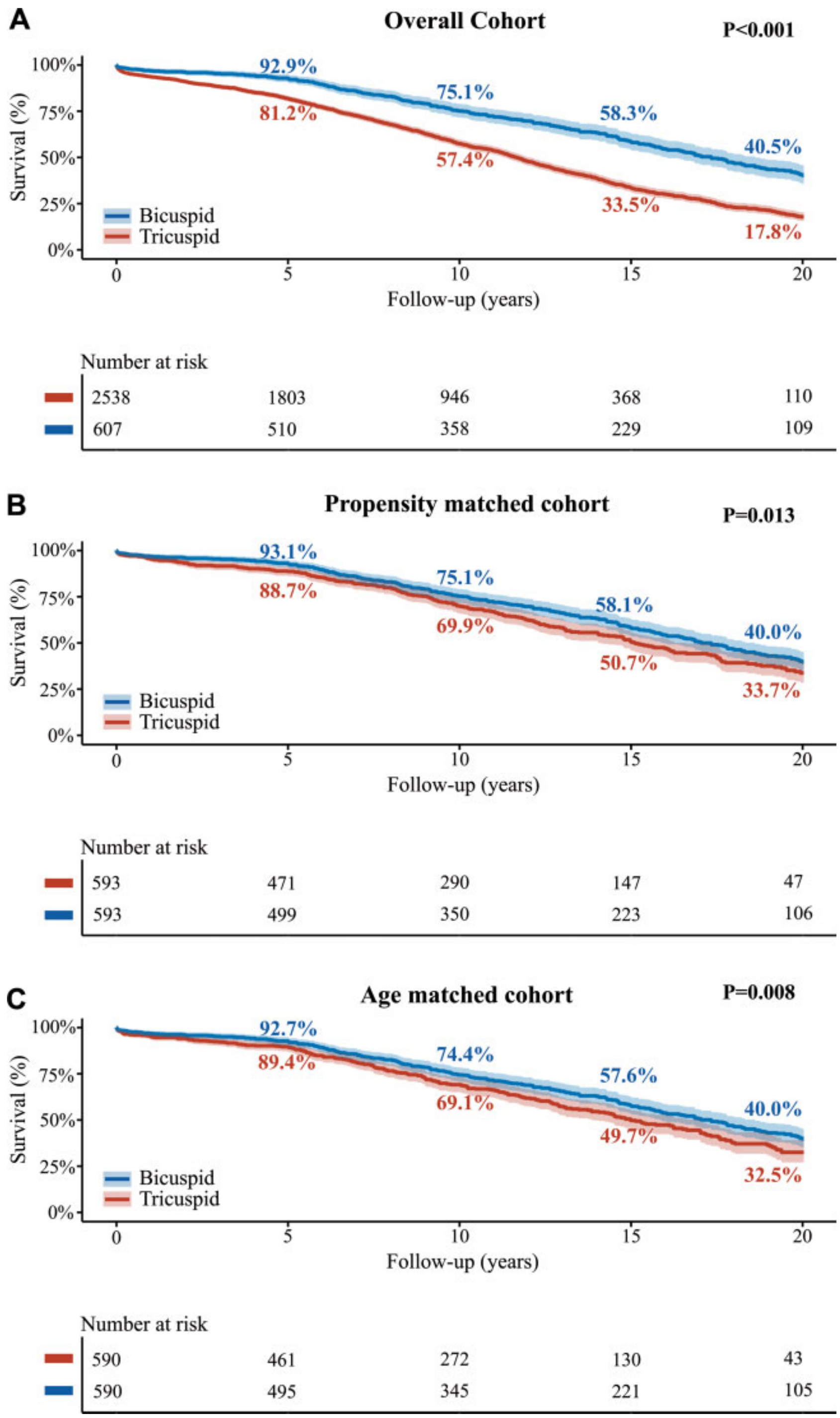


Figure 2: Long-term survival after surgical aortic valve replacement ± coronary artery bypass grafting. (**A**) Survival in overall cohort. (**B**) Survival in propensity-matched cohort. (**C**) Survival in age-matched cohort. Blue lines represent patients with bicuspid aortic valve and red lines represent patients with tricuspid aortic valve.

< 0.001), previous myocardial infarction (*P* = 0.05) and concomitant CABG (*P* < 0.001) were predictors of mortality in the age-matched BAV population (Table 3). In the age-matched TAV population, increasing age (*P* < 0.001), diabetes (*P* = 0.003), chronic obstructive pulmonary disease (*P* = 0.01) and concomitant CABG (*P* = 0.01) were independent predictors of mortality (Table 3). Sensitivity analysis for patients with isolated SAVR is shown in Supplementary Material, Table S3.

DISCUSSION

This study describes the association of aortic valve morphology, patient characteristics at the time of SAVR and the subsequent long-term survival. We found that (i) younger patients had a higher prevalence of BAV at the time of the index procedure; (ii) patients with BAV had fewer cardiovascular risk factors; (iii) this difference in cardiovascular risk factors remained after adjusting for age; (iv) long-term survival is comparable in patients with

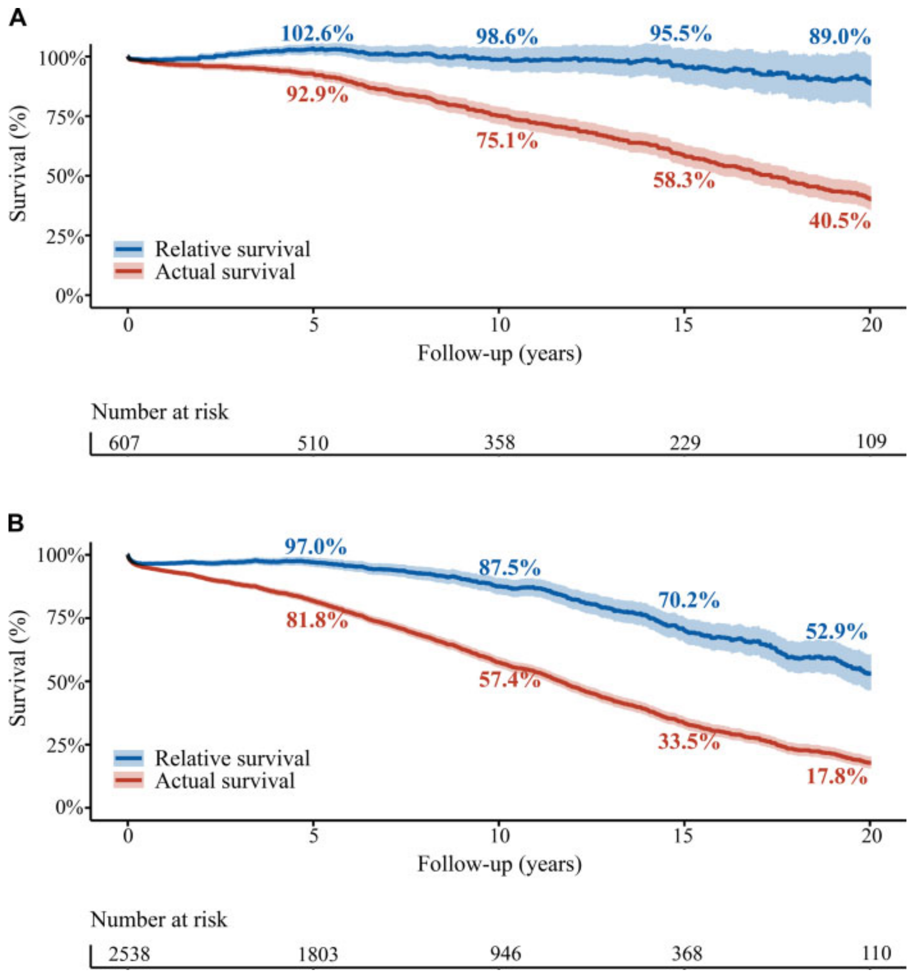


Figure 3: Long-term survival in overall cohort. (**A**) Actual survival (red line) in the bicuspid aortic valve cohort and relative survival compared to the age-, gender- and year-matched population (blue line). Note the excellent relative survival after surgical aortic valve replacement in patients with bicuspid aortic valve compared to the matched general population at 20 years. (**B**) Actual survival (red line) in the tricuspid aortic valve cohort and relative survival compared to the age-, gender- and year-matched population (blue line). Note the satisfactory relative survival after surgical aortic valve replacement in patients with tricuspid aortic valve compared to the matched general population at 20 years.

BAV and TAV after adjusting for baseline characteristics; and (v) the long-term survival after SAVR is exceptionally high in patients with BAV compared to the age, sex and calendar-matched Dutch population.

In an era where TAVI indications are expanding and becoming an alternative treatment for younger patients with low surgical risk, the knowledge regarding the prevalence of bicuspid valvular morphology in the current SAVR population is of utmost importance. The prevalence of bicuspid morphology in patients undergoing SAVR is higher than that of the general population [3, 15]. An echocardiographic evaluation of a Chinese population showed a negative correlation of age and prevalence of BAVs; increasing prevalence with decreasing age (1.16% in patients aged 0–20; 0.18% in patients aged 60–83) [15]. A similar trend was noted in a Western cohort undergoing SAVR and reporting a prevalence of 76% for quinquagenarians, 60% for sexagenarians and 42% for septuagenarians [3], which was notably higher than in our cohort. The included patients underwent isolated SAVR and only had aortic valvular problems, whereas our cohort also included a proportion of patients with concomitant CABG. Of note, the currently observed prevalence of BAV in a surgical cohort is higher than the current incidence in the TAVI population, even after reviewing an age-matched TAVI population [16], reflecting the current relative contraindications for patients with BAV to undergo transcatheter aortic valve replacement.

Patients with BAV more often have (pure) AS and fewer cardiovascular risk factors compared to patients with TAV. To account for the difference in age and the association of age with cardiovascular risk factors [17], we additionally analysed an age-matched group. Yet, the difference in systemic cardiovascular risk factors remained in the age-matched cohort, which reflects the congenital component in aberrant morphology in those with BAV [18, 19]. This difference in AS is also partly explained by an accelerated calcification process compared to patients with TAV [20], whereas the calcification mechanism is the same [21]. Cardiovascular risk factors such as diabetes, hypertension and hypercholesterolaemia occur less frequently in patients with BAV compared to TAV, highlighting the difference in the disease process [22]. The aortic prosthesis was larger in patients with BAV (24.4 vs 23.4; $P < 0.001$). This difference persisted in the age-adjusted population (24.4 vs 23.7; $P < 0.001$). Bicuspid morphology is associated with increased prevalence of aortic root dilatation and ascending aortic aneurysms [19], even in patients without valvular dysfunction, such as or AR, due to BAV

Table 2: Between-group differences in survival among patients in the overall, propensity score-matched and age-matched cohorts divided by age at index procedure

Overall cohort Restricted mean survival time at 10 years (95% CI)	Years	95% CI	*P*-value
Difference (years)	0.242	0.116 to 0.369	<0.001
Difference (years) (50–59 years)	0.168	-0.036 to 0.373	0.11
Difference (years) (60–69 years)	0.141	0.019 to 0.262	0.023
Difference (years) (70–79 years)	0.210	0.082 to 0.339	0.001
Restricted mean survival time at 20 years (95% CI)		95% CI	*P*-value
Difference (years)	0.592	0.305 to 0.880	<0.001
Difference (years) (50–59 years)	0.440	-0.020 to 0.901	0.06
Difference (years) (60–69 years)	0.343	0.060 to 0.627	0.018
Difference (years) (70–79 years)	0.506	0.214 to 0.798	0.001
Propensity score-matched cohort			
Restricted mean survival time at 10 years (95% CI)		95% CI	*P*-value
Difference (years)	0.062	-0.100 to 0.223	0.45
Difference (years) (50–59 years)	0.067	-0.163 to 0.298	0.57
Difference (years) (60–69 years)	0.033	-0.111 to 0.178	0.65
Difference (years) (70–79 years)	0.070	-0.096 to 0.236	0.41
Restricted mean survival time at 20 years (95% CI)		95% CI	*P*-value
Difference (years)	0.212	-0.156 to 0.579	0.26
Difference (years) (50–59 years)	0.224	-0.297 to 0.744	0.40
Difference (years) (60–69 years)	0.141	-0.199 to 0.480	0.42
Difference (years) (70–79 years)	0.221	-0.156 to 0.598	0.25
Age-matched cohort			
Restricted mean survival time at 10 years (95% CI)		95% CI	*P*-value
Difference (years)	0.127	-0.045 to 0.298	0.15
Difference (years) (50–59 years)	0.191	-0.081 to 0.464	0.17
Difference (years) (60–69 years)	0.188	0.011 to 0.365	0.037
Difference (years) (70–79 years)	0.129	-0.045 to 0.303	0.15
Restricted mean survival time at 20 years (95% CI)		95% CI	*P*-value
Difference (years)	0.291	-0.096 to 0.678	0.14
Difference (years) (50–59 years)	0.451	-0.155 to 1.057	0.14
Difference (years) (60–69 years)	0.399	-0.001 to 0.800	0.051
Difference (years) (70–79 years)	0.281	-0.111 to 0.673	0.16

CI: confidence interval.

[23]. However, even after excluding patients with concomitant procedures due to dilating annulopathy or ascending aorta, we might notice beginning dilating annulopathy.

In our population, patients with BAV had better survival even after propensity score matching; this difference did not disappear after adjusting for age only. This finding could be explained by the lower prevalence of the cardiovascular risk profile of those patients, again reflecting the systemic component of the disease, which could be related to factors not captured in our cohort, such as higher body mass index in patients with TAV [18], which might affect survival [24], especially because small prosthesis implants were more prevalent in those undergoing SAVR with TAV. Crude survival alone does not adjust for death due to other, non-intervention related causes. Relative survival is a comparison of the investigated population to the survival of the general population, proving an estimate of the disease-related risk [25]. In patients with BAV, the relative survival in the age-, sex- and calendar year-matched Dutch population was historically high after 20 years of follow-up (89.0%), which is close to that in the general population.

Future outlook

Bicuspid valvular aortic disease has systematically been excluded from the pivotal TAVI trials [26, 27]. Initial experience with early generation transcatheter aortic valve replacement devices in bicuspid anatomy lead to high incidences of paravalvular leakage and high permanent pacemaker implantation [28], which is decreasing with newer generation devices. Patients with BAV who have TAVI have a higher risk of short-term mortality and morbidity compared to patients with tricuspid AS [29]. Until long-term data from well-conducted randomized trials with new-generation TAVI devices in patients with BAVs are available, surgery remains a feasible and well-accepted strategy for those with BAVs.

Limitations

Our study has multiple limitations. First, because our study is retrospective and single-centre, it has the inherent shortcomings related to data capture, changes in definitions of comorbidities and patients being lost to follow-up, especially with a 30-year follow-up. Second, we did not base the final decision of aortic valve morphology on echocardiographic or computed tomography findings but on surgical reports, wherein the prevalence of BAV differs from that in population studies. Third, our study evaluated the patient characteristics and long-term mortality as outcomes. Other aspects of clinical outcome and specific valve-related outcomes, including symptom improvement, quality of life and structural valve dysfunction at long-term follow-up, were not assessed and should be studied in further trials.

CONCLUSION

Patients with BAV compared to those with TAV have fewer cardiovascular risk factors and exhibit excellent survival rates after SAVR. Additional studies are needed to examine the exact effect of differing cardiovascular risk profiles on other end points such as quality of life and risk of structural valvular dysfunction and the relation to the expected burden of transcatheter aortic valve replacement.

SUPPLEMENTARY MATERIAL

Supplementary material is available at *EJCTS* online.

Conflict of interest: none declared.

Author contributions

Mevlüt Çelik: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Validation; Visualization; Writing–original draft; Writing–review & editing. **Milan Milojevic:** Conceptualization; Methodology; Supervision; Validation; Writing–original draft; Writing–review & editing. **Andras P. Durko:** Conceptualization; Methodology; Supervision; Validation; Writing–original draft; Writing–review & editing. **Frans B.S. Oei:** Conceptualization; Methodology; Supervision; Validation; Writing–original draft; Writing–review & editing. **Ad. J.J.C. Bogers:** Conceptualization; Methodology; Supervision; Validation; Writing–original draft; Writing–review & editing. **Edris A.F. Mahtab:** Conceptualization; Methodology; Supervision; Validation; Visualization; Writing–original draft; Writing–review & editing.

Table 3: Predictors of survival after surgical aortic valve replacement in overall age-matched cohort with bicuspid aortic valve and tricuspid aortic valve

Characteristics	Age-matched BAV population		Age-matched TAV population	
	Univariable HR (95% CI); *P*-value	Multivariable HR (95% CI); *P*-value	Univariable HR (95% CI); *P*-value	Multivariable HR (95% CI); *P*-value
Age	1.07 (1.06–1.09); $P < 0.001$	1.07 (1.05–1.09); $P < 0.001$	1.07 (1.05–1.08); $P < 0.001$	1.05 (1.03–1.07); $P < 0.001$
Sex (female)	1.0 (0.7–1.2); $P = 0.76$		1.0 (0.8–1.3); $P = 0.97$	
AS	2.3 (1.3–4.2); $P = 0.007$	1.0 (0.5–1.9); $P = 0.97$	1.5 (1.1–2.2); $P = 0.014$	1.1 (0.8–1.6); $P = 0.62$
Hypertension	1.2 (0.9–1.6); $P = 0.16$	1.1 (0.9–1.5); $P = 0.35$	1.3 (1.0–1.6); $P = 0.08$	1.0 (0.8–1.3); $P = 0.97$
Hypercholesterolaemia	1.0 (0.8–1.1); $P = 0.29$		0.9 (0.6–1.3); $P = 0.54$	
Diabetes mellitus	1.4 (0.9–2.1); $P = 0.14$	0.9 (0.6–1.5); $P = 0.77$	2.1 (1.5–3.0); $P < 0.001$	1.7 (1.2–2.3); $P = 0.003$
Arterial disease	1.4 (0.6–3.1); $P = 0.44$		2.3 (1.3–4.1); $P = 0.003$	1.6 (0.9–2.8); $P = 0.13$
Renal failure	1.3 (0.6–3.0); $P = 0.49$		3.4 (1.8–6.4); $P < 0.001$	3.6 (1.8–7.1); $P < 0.001$
Previous MI	1.6 (1.1–2.4); $P = 0.013$	1.5 (1.0–2.2); $P = 0.05$	1.8 (1.3–2.5); $P = 0.001$	1.2 (0.8–1.7); $P = 0.34$
Previous PCI	1.1 (0.6–2.1); $P = 0.74$		1.2 (0.8–2.0); $P = 0.41$	
Decompensated heart failure	1.8 (1.3–2.5); $P < 0.001$	1.5 (1.1–2.0); $P = 0.023$	1.6 (1.2–2.1); $P = 0.003$	1.3 (1.0–1.8); $P = 0.08$
LVEF <50%	0.9 (0.5–1.8); $P = 0.86$		0.9 (0.5–1.5); $P = 0.56$	
Atrial fibrillation	2.1 (1.5–3.0); $P < 0.001$	2.0 (1.4–2.8); $P < 0.001$	1.9 (1.3–2.6); $P < 0.001$	1.4 (1.0–2.0); $P = 0.06$
Previous stroke or TIA	1.2 (0.7–2.0); $P = 0.47$		1.3 (0.9–1.9); $P = 0.24$	
COPD	1.9 (1.3–2.8); $P = 0.002$	1.9 (1.3–2.9); $P = 0.002$	1.7 (1.1–2.5); $P = 0.01$	1.7 (1.1–2.5); $P = 0.01$
Concomitant CABG	1.6 (1.3–2.1); $P < 0.001$	1.4 (1.1–1.8); $P = 0.008$	2.2 (1.7–2.8); $P < 0.001$	1.5 (1.1–2.0); $P = 0.01$
Emergency SAVR vs non-emergency	1.3 (0.4–4.0); $P = 0.67$		1.1 (0.3–4.5); $P = 0.87$	
Mechanical prosthesis	0.5 (0.4–0.6); $P < 0.001$	0.9 (0.7–1.3); $P = 0.67$	1.7 (1.1–2.5); $P = 0.01$	0.9 (0.6–1.2); $P = 0.40$

AS: aortic stenosis; CABG: coronary artery bypass grafting; CI: confidence interval; COPD: chronic obstructive pulmonary disease; HR: hazard ratio; LVEF: left ventricular ejection fraction; MI: myocardial infarction; PCI: percutaneous coronary intervention; SAVR: surgical aortic valve replacement; TIA: transient ischaemic attack.

Reviewer information

European Journal of Cardio-Thoracic Surgery thanks Dimitrios Vasileios Avgerinos, Luca Koechlin and the other, anonymous reviewer(s) for their contribution to the peer review process of this article.

REFERENCES

[1] Nistri S, Basso C, Marzari C, Mormino P, Thiene G. Frequency of bicuspid aortic valve in young male conscripts by echocardiogram. Am J Cardiol 2005;96:718–21.
[2] Braverman AC, Guven H, Beardslee MA, Makan M, Kates AM, Moon MR. The bicuspid aortic valve. Curr Probl Cardiol 2005;30:470–522.
[3] Roberts WC, Ko JM. Frequency by decades of unicuspid, bicuspid, and tricuspid aortic valves in adults having isolated aortic valve replacement for aortic stenosis, with or without associated aortic regurgitation. Circulation 2005;111:920–5.
[4] Mordi I, Tzemos N. Bicuspid aortic valve disease: a comprehensive review. Cardiol Res Pract 2012;2012:196037.
[5] Cozijnsen L, van der Zaag-Loonen HJ, Cozijnsen MA, Braam RL, Heijmen RH, Bouma BJ *et al.* Differences at surgery between patients with bicuspid and tricuspid aortic valves. Neth Heart J 2019;27:93–9.
[6] Gahl B, Celik M, Head SJ, Vanoverschelde JL, Pibarot P, Reardon MJ *et al.* Natural history of asymptomatic severe aortic stenosis and the association of early intervention with outcomes: a systematic review and meta-analysis. JAMA Cardiol 2020;5:1102.
[7] Baumgartner H, Falk V, Bax JJ, De Bonis M, Hamm C, Holm PJ *et al.*; ESC Scientific Document Group. 2017 ESC/EACTS Guidelines for the management of valvular heart disease. Eur Heart J 2017;38:2739–91.
[8] Nishimura RA, Otto CM, Bonow RO, Carabello BA, Erwin JP 3rd, Fleisher LA *et al.* 2017 AHA/ACC focused update of the 2014 AHA/ACC Guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol 2017;70:252–89.
[9] Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L *et al.* Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. Eur Heart J Cardiovasc Imaging 2015;16:233–70.
[10] Silber JH, Rosenbaum PR, Trudeau ME, Even-Shoshan O, Chen W, Zhang X *et al.* Multivariate matching and bias reduction in the surgical outcomes study. Med Care 2001;39:1048–64.
[11] Perme MP, Pavlic K. Nonparametric relative survival analysis with the R package relsurv. J Stat Softw 2018;87:27.
[12] The Human Mortality Database, 2019. https://www.mortality.org/ (1 August, date last accessed).
[13] Pohar M, Stare J. Relative survival analysis in R. Comput Methods Programs Biomed 2006;81:272–8.
[14] Pohar M, Stare J. Making relative survival analysis relatively easy. Comput Biol Med 2007;37:1741–9.
[15] Li Y, Wei X, Zhao Z, Liao Y, He J, Xiong T *et al.* Prevalence and complications of bicuspid aortic valve in chinese according to echocardiographic database. Am J Cardiol 2017;120:287–91.
[16] Zhao ZG, Jilaihawi H, Feng Y, Chen M. Transcatheter aortic valve implantation in bicuspid anatomy. Nat Rev Cardiol 2015;12:123–8.
[17] Dhingra R, Vasan RS. Age as a risk factor. Med Clin North Am 2012;96:87–91.
[18] Huntley GD, Thaden JJ, Alsidawi S, Michelena HI, Maleszewski JJ, Edwards WD *et al.* Comparative study of bicuspid vs. tricuspid aortic valve stenosis. Eur Heart J Cardiovasc Imaging 2018;19:3–8.
[19] Tadros TM, Klein MD, Shapira OM. Ascending aortic dilatation associated with bicuspid aortic valve: pathophysiology, molecular biology, and clinical implications. Circulation 2009;119:880–90.
[20] Wallby L, Janerot-Sjoberg B, Steffensen T, Broqvist M. T lymphocyte infiltration in non-rheumatic aortic stenosis: a comparative descriptive study between tricuspid and bicuspid aortic valves. Heart 2002;88:348–51.
[21] Lewin MB, Otto CM. The bicuspid aortic valve: adverse outcomes from infancy to old age. Circulation 2005;111:832–4.
[22] Yan AT, Koh M, Chan KK, Guo H, Alter DA, Austin PC *et al.* Association between cardiovascular risk factors and aortic stenosis: the CANHEART Aortic Stenosis Study. J Am Coll Cardiol 2017;69:1523–32.
[23] Nkomo VT, Enriquez-Sarano M, Ammash NM, Melton LJ 3rd, Bailey KR, Desjardins V *et al.* Bicuspid aortic valve associated with aortic dilatation: a community-based study. Arterioscler Thromb Vasc Biol 2003;23:351–6.

[24] Wang B, Yang H, Wu S, Cao G, Yang H. Obesity and the risk of late mortality after aortic valve replacement with small prosthesis. J Cardiothorac Surg 2013;8:174.
[25] Sarfati D, Blakely T, Pearce N. Measuring cancer survival in populations: relative survival vs cancer-specific survival. Int J Epidemiol 2010;39:598–610.
[26] Mack MJ, Leon MB, Thourani VH, Makkar R, Kodali SK, Russo M *et al.* Transcatheter aortic-valve replacement with a balloon-expandable valve in low-risk patients. N Engl J Med 2019;380:1695–705.
[27] Popma JJ, Deeb GM, Yakubov SJ, Mumtaz M, Gada H, O'Hair D *et al.* Transcatheter aortic-valve replacement with a self-expanding valve in low-risk patients. N Engl J Med 2019;380:1706–15.
[28] Yoon SH, Lefevre T, Ahn JM, Perlman GY, Dvir D, Latib A *et al.* Transcatheter aortic valve replacement with early- and new-generation devices in bicuspid aortic valve stenosis. J Am Coll Cardiol 2016;68: 1195–205.
[29] Makkar RR, Yoon SH, Leon MB, Chakravarty T, Rinaldi M, Shah PB *et al.* Association between transcatheter aortic valve replacement for bicuspid vs tricuspid aortic stenosis and mortality or stroke. JAMA 2019;321: 2193–202.