Featured Article

Surgery for endocarditis in patients with bicuspid aortic valves

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Background: The objective of this study is to investigate clinical outcomes in patients with bicuspid aortic valves (BAV) after surgical treatment for endocarditis.

Methods: This was a population-based, observational cohort study, conducted on all patients who received aortic valve surgery for native or prosthetic valve endocarditis at Karolinska University Hospital between 2002–2020. Baseline characteristics and postoperative complications were collected from the institutional surgical database and patient medical charts. The primary endpoint was all-cause mortality. We used unadjusted and adjusted Cox regression to determine the association between valve morphology and long-term mortality.

Results: Of the 338 patients, 122 (36%) had a BAV and 216 (64%) had a tricuspid aortic valve (TAV). The mean follow-up was 5.8 years (maximum 18.4 years). Survival rates at one, five, ten and 14 years were 88%, 81%, 78% and 76% versus 85%, 69%, 58% and 43%, in BAV and TAV patients, respectively [adjusted hazard ratio (HR) 0.64; 95% confidence interval (CI): 0.39–1.05]. In patients with native valve endocarditis, those with BAV had lower all-cause mortality compared to those with TAV (adjusted HR 0.44; 95% CI: 0.22–0.89), despite having a higher prevalence of perivalvular abscess (40% versus 22%, respectively, in BAV and TAV patients). In patients with prosthetic valve endocarditis, original valve morphology did not affect all-cause mortality (adjusted HR 1.94; 95% CI: 0.64–5.87).

Conclusions: In patients with native valve endocarditis, a BAV was associated with improved survival after surgical treatment. In patients with prosthetic valve endocarditis, survival was not affected by the original valve morphology of the patient.

Keywords: Endocarditis; epidemiology; heart valves; surgery, complications; outcomes

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Introduction

Bicuspid aortic valve (BAV) has an incidence of 0.5–2.0% in the general population (1-4). It has been found to be present in up to 25% of patients with infective endocarditis (IE) (5). Persons with BAV face a risk of contracting native valve IE up to 23 times higher compared to persons with tricuspid aortic valves (TAV) (6), indicating that valve morphology is an important contributor to the risk of IE. Overall, approximately 50% of the BAV population needs an aortic valve replacement during their lifetime, the vast majority for non-infective pathologies. Consequently, these patients also carry an increased risk of prosthetic valve endocarditis (7,8).

While surgery is required in approximately half of all native valve IE cases (9,10), this figure in patients with BAV is nearly 75%, suggesting a higher prevalence of invasive disease (3,11-14). Previous studies on endocarditis in BAV populations have seldom analyzed long-term outcomes for surgically treated patients independently and have focused exclusively on native valve IE patients (6,11,15-17). Thus, analysis is warranted to confirm that presentation and outcomes of prosthetic valve IE in BAV patients is the same as that of prosthetic valve IE in TAV patients.

This background justifies further studies of native as well as prosthetic valve IE in patients born with BAV. Therefore, we performed an observational cohort study including all patients with native or prosthetic aortic valve IE requiring surgery, investigating all-cause mortality and reoperation after aortic valve surgery for endocarditis in patients with BAV compared to patients with TAV.

Methods

Study design

We performed an observational, population-based cohort study approved by the Swedish Ethical Review Authority (Dnr: 2020-03294). The requirement for informed consent was waived. The study was reported according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) recommendations (18).

Setting

We included all patients who received surgery for active IE of the aortic valve between 2002–2020 at Karolinska University Hospital, Sweden. Our department is the only referral center for cardiac surgery in Stockholm County and serves approximately 25% of the Swedish population. Follow-up ended on August 17, 2020.

Data sources

The study cohort was identified from the institutional surgical database and the local Cardiac Surgery Registry, a subset of the Swedish Web-System for Enhancement and Development of Evidence-based care in Heart disease Evaluated According to Recommended Therapies (SWEDEHEART) registry. SWEDEHEART is a comprehensive registry that tracks patient information for a variety of heart conditions, including cardiac surgery (19,20).

Patients

All consecutive patients with BAV or TAV, with and without previous aortic valve surgery, who had been allocated the International Classification of Diseases-10 code for IE (I33, I38 or I39) or who had undergone first-time surgery for active endocarditis, were identified. Patients were excluded if they did not meet the modified Duke criteria for definite IE (21), had no proof of endocardial involvement, did not have aortic valve involvement or had had previous surgery for IE. Information on baseline characteristics and valve morphology were sourced through patient medical records and the local SWEDEHEART registry. Patients with unknown valve morphology were excluded (n=17). A flowchart of the study population is provided in Figure S1. Infectious causes were obtained by reviewing patient medical records. Pathogens were confirmed through preoperative blood cultures or 16S rRNA gene variability analysis of valvular tissue.

Surgical technique

Surgeons in Sweden follow international endocarditis guidelines to evaluate indications for and timing of endocarditis surgery (22). Patients in this study received a median sternotomy, cold blood cardioplegia and cardiopulmonary bypass. The aim of surgery was to achieve radical debridement of infected tissue and valve repair or reconstruction via implantation of a heart valve prosthesis. Homografts, xenografts, mechanical composite grafts and mechanical valve prostheses were used at the discretion of the surgeon, taking into account patient and surgical factors.

Exposure and endpoints

In this study, we included both native and prosthetic valve IE patients. Valve morphology refers to the native valve morphology of the patient. Exposure was first-time surgery for aortic valve endocarditis. The primary endpoint was all-cause mortality. The secondary endpoint was rate of reoperation, obtained by review of patient medical records. Reoperation was defined as valve or ascending aorta reoperation for any reason during follow-up, and indications for reoperation, including prosthetic valve IE, were recorded. Information on survival status and death date were obtained from the national Total Population Register, which is updated daily (23).

Statistical methods

Categorical variables are presented as numbers and percentages and continuous variables as means and standard deviations. Patients contributed person-times from the date of surgery until the date of death, of reoperation or until the

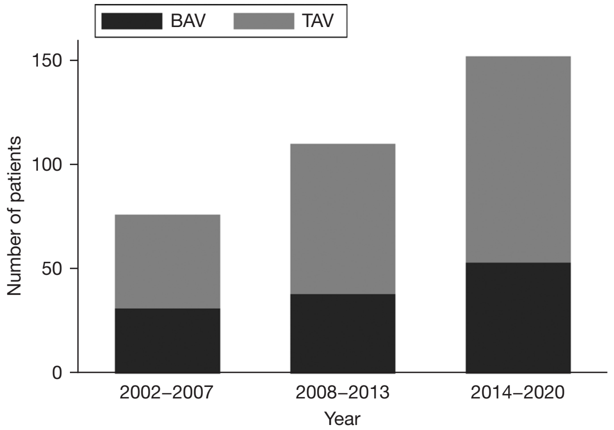

Figure 1 Number of patients who underwent aortic valve surgery for endocarditis at Karolinska University Hospital between 2002 and 2020 according to aortic valve morphology. BAV, bicuspid aortic valve; TAV, tricuspid aortic valves.

end of follow-up (August 17, 2020), whichever came first. Crude incidence rates and 95% confidence intervals (CI) were calculated. Survival curves were constructed using the Kaplan-Meier method. The χ^2-test was used to analyze the association between valve type and early mortality, which was defined as death within 30 days following surgery. Univariable and multivariable Cox proportional hazard regression was used to calculate hazard ratios (HR) and 95% CI. To avoid overfitting the model, only age and sex were included in the multivariable model. All analyses were stratified by year of surgery. To account for the competing risk of death, flexible parametric models (24) were used to graphically illustrate and to calculate the cumulative incidence of reoperation. Data management and statistical analyses were performed using Stata version 16.1 (Stata Corp. LP., College Station, TX, USA).

Results

Study population

Between January 1, 2002 and August 17, 2020, 359 patients received surgery for endocarditis of the aortic valve at our institution. Of these patients, 338 met the inclusion criteria (*Figure 1*). One hundred and twenty-two (36%) patients had BAV, of which 80 (66%) had native valve IE and 42 (34%) had prosthetic valve IE. Two hundred and sixteen (64%) patients had TAV, of which 181 (84%) had native valve IE and 35 (16%) had prosthetic valve IE. Overall, patients were predominantly male (80%) and BAV patients were younger than TAV patients (mean ages 53 versus 63 years, respectively). More BAV patients had concomitant surgery of the ascending aorta compared to TAV patients (31% versus 16%, respectively). Among patients with native valve IE, BAV patients had fewer comorbidities such as hypertension, atrial fibrillation and diabetes mellitus compared to those with TAV, and more BAV patients had perivalvular abscess formation compared to TAV patients (40% versus 22%, respectively). There were also fewer intravenous drug users among BAV patients compared to TAV patients (8% versus 13%, respectively). In patients with prosthetic valve IE, BAV and TAV patients were more similar in terms of comorbidities. Baseline characteristics according to valve morphology and prosthetic valve status are presented in *Table 1* and according to valve morphology only in Table S1.

Microbiological etiology

In native valve IE patients, viridans streptococci were responsible for 53% and 34% of infections in BAV and TAV patients, respectively. In prosthetic valve IE patients, *Staphylococcus aureus* was the most common pathogen in BAV patients (29%), whereas viridans streptococci were most common in TAV patients (20%) (*Table 2*).

Mortality

During a mean and maximum follow-up of 5.8 and 18.4 years (total of 1,959 person-years), 25 (21%) and 78 (36%) patients died in the BAV and TAV groups, respectively. Of these, 12 (9.8%) and 12 (5.6%) patients died within 30 days of surgery in the BAV and TAV groups (P=0.14), respectively. No patients were lost to follow-up. In patients with native valve IE, survival at 1, 5, 10 and 14 years was 95%, 88%, 83% and 80%, respectively, among BAV patients compared to 84%, 69%, 59% and 49%, respectively, among TAV patients. Both in the univariable and age- and sex-adjusted analysis, all-cause mortality was lower for BAV patients compared to TAV patients (unadjusted HR 0.36; 95% CI: 0.19–0.68; P=0.002, and adjusted HR 0.44; 95% CI: 0.22–0.89; P=0.021).

In patients with prosthetic valve IE, survival at one, five, and ten years was 74%, 68% and 68%, respectively, among BAV patients and 88%, 71% and 56%, respectively, among TAV patients. In the univariable and age- and sex-adjusted analysis, there was no significant difference in all-cause mortality among BAV patients compared to TAV patients

Table 1 Baseline characteristics according to aortic valve morphology in 338 patients who underwent valve surgery for aortic valve endocarditis at Karolinska University Hospital, Sweden, between 2002–2020

Characteristics	All patients, N=338	Tricuspid aortic valve, N=181 (54%)	Bicuspid aortic valve, N=80 (24%)	PVE, originally tricuspid, N=35 (10%)	PVE, originally bicuspid, N=42 (12%)
Age, years, mean (SD)	59 (17.5)	63 (11.8)	48 (14.9)	64 (14.9)	62 (11.7)
Female	69 (20.4)	41 (22.7)	8 (10.0)	7 (20.0)	13 (31.0)
Body mass index (kg/m^2), mean (SD)	25.9 (4.7)	26.2 (4.7)	24.9 (4.5)	25.4 (4.5)	26.6 (4.9)
Hypertension	101 (29.9)	58 (32.0)	11 (13.8)	15 (42.9)	17 (40.5)
Diabetes mellitus	43 (12.7)	28 (15.5)	5 (6.3)	3 (8.6)	7 (16.7)
Intravenous drug user	31 (9.2)	23 (12.7)	6 (7.5)	1 (2.9)	1 (2.4)
Prior percutaneous coronary intervention	11 (3.4)	8 (4.4)	0 (0.0)	1 (2.9)	2 (4.8)
Prior stroke	73 (21.6)	29 (16.0)	15 (18.8)	13 (37.1)	16 (38.1)
Atrial fibrillation	45 (13.3)	24 (13.3)	6 (7.5)	7 (20.0)	8 (19.0)
Chronic obstructive pulmonary disease	25 (7.4)	18 (9.9)	4 (5.0)	3 (8.6)	0 (0.0)
Peripheral artery disease	9 (2.7)	5 (2.8)	2 (2.5)	1 (2.9)	1 (2.4)
Critical preoperative state	50 (14.8)	31 (17.1)	16 (20.0)	1 (2.9)	2 (4.8)
EuroSCORE I, mean (SD)	10.0 (3.6)	9.4 (3.2)	8.4 (3.5)	12.9 (2.6)	13.2 (3.3)
Left ventricular ejection fraction					
>50	139 (41.1)	79 (43.6)	30 (37.5)	14 (40.0)	16 (38.1)
31–50	74 (21.9)	35 (19.3)	18 (22.5)	7 (20.0)	14 (33.3)
21–30	5 (1.5)	4 (2.2)	1 (1.3)	0 (0.0)	0 (0.0)
<20	2 (0.6)	1 (0.5)	1 (1.3)	0 (0.0)	0 (0.0)
eGFR (mL/min/1.73 m^2)					
>60	230 (68.0)	116 (64.0)	64 (80.0)	23 (65.7)	27 (64.3)
30–60	74 (21.9)	42 (23.2)	12 (15.0)	9 (25.7)	11 (26.2)
0–29	17 (5.0)	11 (6.1)	2 (2.5)	1 (2.9)	3 (7.1)
Preoperative dialysis	13 (3.8)	9 (5.0)	1 (1.3)	2 (5.7)	1 (2.4)
Prior cardiac surgery	88 (26.0)	6 (3.3)	5 (6.3)	35 (100)	42 (100)
Prior endocarditis	14 (4.1)	5 (2.8)	2 (2.5)	2 (5.7)	5 (11.9)
Cardiovascular implantable electronic device	17 (5.0)	6 (3.3)	2 (2.5)	2 (5.7)	7 (16.7)
Preoperative complications					
Central nervous system embolic event	53 (15.7)	18 (9.9)	10 (12.5)	13 (37.1)	12 (28.6)
Peripheral embolic event	33 (9.8)	16 (8.8)	10 (12.5)	5 (14.3)	2 (4.8)
Valvular abscess	111 (32.8)	39 (21.5)	32 (40.0)	19 (54.3)	21 (50.0)
Vegetations	245 (72.5)	135 (74.6)	61 (76.2)	28 (80.0)	21 (50.0)

Table 1 (*continued*)

Table 1 (*continued*)

Characteristics	All patients, N=338	Tricuspid aortic valve, N=181 (54%)	Bicuspid aortic valve, N=80 (24%)	PVE, originally tricuspid, N=35 (10%)	PVE, originally bicuspid, N=42 (12%)
Concomitant surgery					
CABG	18 (5.3)	15 (8.3)	1 (1.2)	1 (2.9)	1 (2.4)
Ascending aorta	72 (21.3)	17 (9.4)	16 (20.0)	17 (48.6)	22 (52.4)
Biological aortic valve replacement	209 (61.8)	122 (69.3)	29 (38.7)	28 (84.8)	30 (73.2)
Acute kidney injury[c]	172 (50.9)	91 (52.0)	30 (39.0)	23 (65.7)	28 (66.7)
Year of surgery					
2002–2007	76 (22.5)	38 (21.0)	25 (31.2)	7 (20.0)	6 (14.3)
2008–2013	110 (32.5)	60 (33.1)	24 (30.0)	12 (34.3)	14 (33.3)
2014–2019	152 (45.0)	83 (45.9)	31 (38.8)	16 (45.7)	22 (52.4)

Data are presented as n (%) unless otherwise noted. [c], defined as >0.3 mg/dL (>26 µmol/L) increase in postoperative creatinine concentrations, or postoperative creatinine >1.5*baseline, or new postoperative dialysis. PVE, prosthetic valve endocarditis; eGFR, estimated glomerular filtration rate; SD, standard deviation; CABG, coronary artery bypass graft.

Table 2 Microbiological data according to aortic valve morphology and prosthetic valve status in 338 patients, who underwent valve surgery for aortic valve endocarditis at Karolinska University Hospital, Sweden, between 2002–2020

Pathogens	All patients, N=338	Tricuspid aortic valve, N=181	Bicuspid aortic valve, N=80	PVE, originally tricuspid, N=35	PVE, originally bicuspid, N=42
Staphylococcus aureus	72 (21.3)	39 (21.5)	15 (18.8)	6 (17.1)	12 (28.6)
Viridans group streptococci[a]	117 (34.6)	62 (34.3)	42 (52.5)	7 (20.0)	6 (14.3)
Coagulase-negative staphylococci	21 (6.2)	13 (7.2)	4 (5.0)	3 (8.6)	1 (2.4)
Enterococcus species	39 (11.5)	27 (14.9)	7 (8.8)	2 (5.7)	3 (7.1)
HACEK	9 (2.7)	2 (1.1)	3 (3.8)	1 (2.9)	3 (7.1)
Other streptococci	22 (6.5)	14 (7.7)	2 (2.5)	6 (17.1)	0 (0.0)
Other bacteria	34 (10.0)	12 (6.6)	2 (2.5)	9 (25.7)	10 (23.6)
Polymicrobial infection	5 (1.5)	5 (2.8)	0 (0.0)	0 (0.0)	0 (0.0)
Unknown	20 (5.9)	7 (3.9)	5 (6.2)	1 (2.9)	7 (16.7)

Data are presented as n (%). [a], Viridans group streptococci includes *Streptococcus mutans*, *Streptococcus salivarius*, *Streptococcus anginosus*, *Streptococcus mitis*, and *Streptococcus sanguinis*. HACEK, *Haemophilus* species, *Aggregatibacter* species, *Cardiobacterium hominis*, *Eikenella corrodens*, and *Kingella* species; PVE, prosthetic valve endocarditis.

(unadjusted HR 1.94; 95% CI: 0.65–5.77; P=0.24, and adjusted HR 1.94; 95% CI: 0.64–5.87; P=0.24).

Among all patients, survival rates at 1, 5, 10 and 14 years were 88%, 81%, 78% and 76%, respectively, among BAV patients, and 85%, 69%, 58% and 43% among TAV patients. In the univariable analysis, TAV patients had a higher risk of death compared to BAV patients (unadjusted HR 0.53; 95% CI: 0.33–0.85; P=0.008), while in the age- and sex-adjusted analysis, this difference did not reach statistical significance (adjusted HR 0.64, 95% CI: 0.39–1.05, P=0.076). Event rates and relative risks according to valve morphology and prosthetic valve status are presented

Table 3 Event rates and relative risks according to aortic valve morphology for all-cause mortality and reoperation in 338 patients who underwent aortic valve surgery for endocarditis at Karolinska University Hospital, Sweden, between 2002–2020

Outcomes	Tricuspid aortic valve, N=181			Bicuspid aortic valve, N=80			PVE, originally tricuspid, N=35			PVE, originally bicuspid, N=42		
	Events/ PY	Crude rate (95% CI) per 100 PY	HR (95% CI)	Events/ PY	Crude rate (95% CI) per 100 PY	HR (95% CI)	Events/ PY	Crude rate (95% CI) per 100 PY	HR (95% CI)	Events/ PY	Crude rate (95% CI) per 100 PY	HR (95% CI)
All-cause mortality												
Unadjusted	64/939	6.82 (5.33–8.71)	1.00	12/619	1.94 (1.10–3.41)	0.36 (0.19–0.68)	14/199	7.02 (4.16–11.9)	1.00	13/201	6.46 (3.75–11.12)	1.94 (0.65–5.77)
Adjusted for age and sex			1.00			0.44 (0.22–0.89)			1.00			1.94 (0.64–5.87)
Valve reoperation												
Unadjusted	20/863	2.32 (1.50–3.59)	1.00	12/525	2.28 (1.30–4.02)	1.11 (0.52–2.36)	7/168	4.16 (1.98–8.73)	1.00	6/188	3.19 (1.43–7.10)	1.14 (0.28–4.59)
Adjusted for age and sex			1.00			0.58 (0.23–1.45)			1.00			1.11 (0.27–4.60)

PVE, prosthetic valve endocarditis; CI, confidence interval; HR, hazard ratio; PY, person-years.

in *Table 3*. Kaplan Meier estimated survival curves and percentages according to valve morphology and prosthetic valve status are shown in *Figure 2* and Table S2.

Cause of death and postoperative complications

The causes of death are shown in Table S3; postoperative complications according to valve morphology are listed in *Table 4*.

Valve reoperation

During a mean and maximum follow-up of 5.2 and 18.4 years (total of 1,744 person-years), 18 (15%) patients in the BAV group and 27 (13%) patients in the TAV group underwent reoperation. Among native valve IE patients, the cumulative incidence of reoperation at one, five and ten years were 6.0%, 11% and 17%, respectively, among BAV patients, and 5.3%, 9.2% and 14% among TAV patients (*Figure 3* and Table S4). In the univariable and age- and sex-adjusted analysis, there was no significant difference in reoperation rates among BAV compared to TAV patients with native valve IE (unadjusted HR 1.11; 95% CI: 0.52–2.36; P=0.781, and adjusted HR 0.58; 95% CI: 0.23–1.45; P=0.245).

Among prosthetic valve IE patients, there was likewise no difference in reoperation between the groups and the same held true for the overall study population. Event rates and relative risks according to valve morphology and prosthetic valve status are presented in *Table 3*.

Indications for all reoperations are shown in Table S5. During follow-up, four (4.9%) and 13 (7.2%) BAV and TAV patients, respectively, underwent reoperation for reinfection among native valve IE patients. Among prosthetic valve IE patients, three (7.0%) BAV patients and two (5.6%) TAV patients underwent reoperation for reinfection.

In patients with BAV, we also looked at reinfection with or without surgery during follow-up: four patients (5.0%) with native valve IE and four patients (9.5%) with prosthetic valve IE were reinfected, corresponding to a yearly incidence of 0.7% in BAV patients with native valve IE, and 2.1% in BAV patients with prosthetic valve IE. Cumulative incidence of reinfection for BAV-patients is presented in Figure S2. Of all patients with BAV who were reinfected, all except for one were treated surgically.

Missing data

Data was missing for the following baseline characteristics: body mass index (2.7%), EuroSCORE I (3.8%), left ventricular ejection fraction (35%) and glomerular filtration rate (1.2%). For all other data and for our primary outcome, data was complete.

Discussion

This study found that, in patients with native valve IE, BAV patients had higher survival than TAV patients. In patients

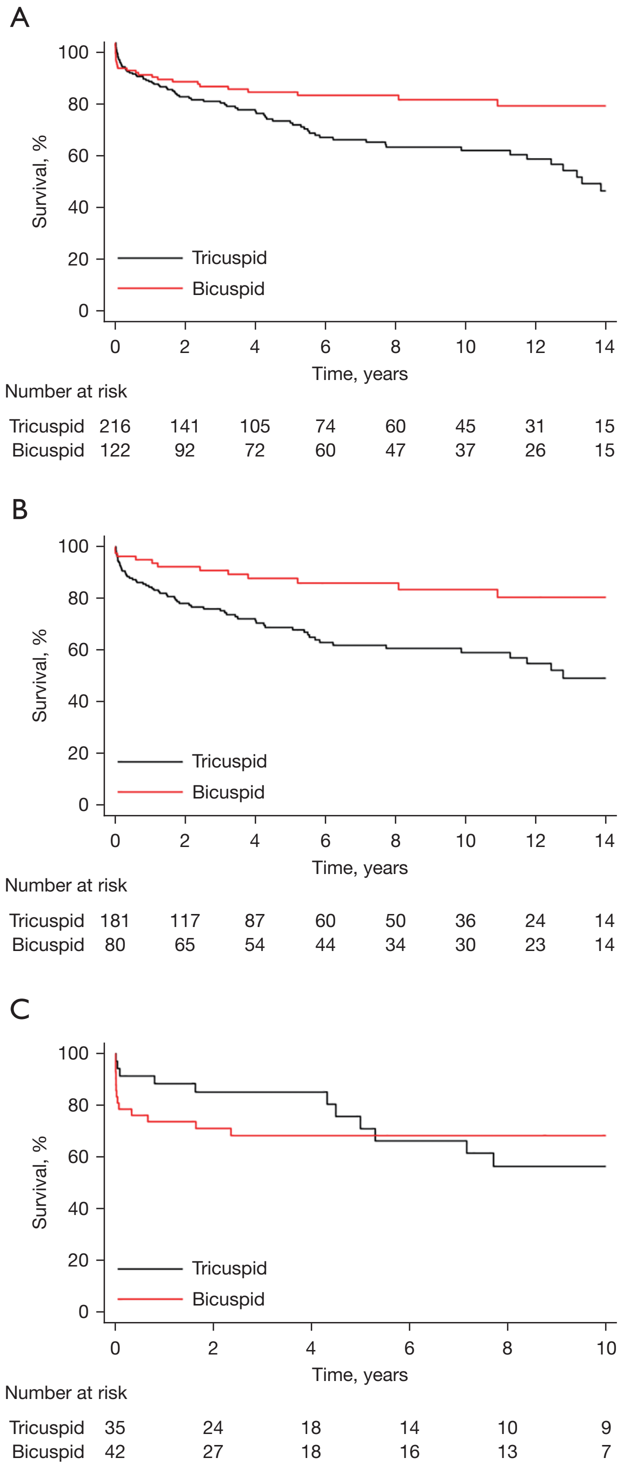

Figure 2 Kaplan-Meier estimated survival according to valve morphology and prosthetic valve status after aortic valve endocarditis surgery at Karolinska University Hospital, Sweden, between 2002 and 2020 in (A) all patients, (B) native valve endocarditis patients and (C) prosthetic valve endocarditis patients.

with prosthetic valve IE, there was no difference in survival between BAV and TAV patients. The risk of reoperation was similar for BAV and TAV patients, regardless of native or prosthetic valve IE. Rate of reoperation for reinfection was low in both BAV and TAV patients. Moreover, this study confirms that BAV patients who receive surgery for native valve IE have a high degree of perivalvular complications.

Both BAV and endocarditis are relatively rare occurrences, which make them particularly challenging to study together. Previous research on survival among BAV patients with endocarditis have included both conservatively and surgically managed patients and focused exclusively on native valve IE. The current study provides new insights into long-term prognosis after aortic valve surgery for endocarditis in patients with BAV and includes data on native as well as prosthetic valve endocarditis.

In a prior study performed at two centers in France between 1991 and 2007, Tribouilloy *et al.* analyzed survival of patients with native valve IE in patients with BAV compared to patients with TAV (11). The study included both conservatively and surgically managed patients. Of 310 patients, 50 patients (16%) had BAV. There was a higher proportion of surgical treatment among BAV compared to TAV patients (72% *vs.* 61%, respectively), and like in our study, BAV patients were younger and healthier than TAV patients. Tribouilloy *et al.* found no significant difference in five-year survival between the groups (adjusted HR 0.75; 95% CI: 0.40–1.41; P=0.37). They did not present survival for the surgically managed patients separately.

Becerra-Muñoz *et al.* performed an observational cohort study analyzing one-year survival for 118 patients with native aortic valve IE, of which 18 patients had BAV (16). Like Tribouilloy *et al.*, Becerra-Muñoz *et al.* included conservatively and surgically managed patients. BAV patients were found to be younger and healthier than TAV patients and a higher proportion of BAV patients received surgery (83% versus 44%). They found higher one-year survival in BAV patients than in TAV patients (94% versus 69%; P=0.048).

While Tribouilloy *et al.* (11) and Becerra-Muñoz *et al.* (16) analyzed survival for conservatively and surgically treated BAV patients, our study adds the angle of the surgically treated population specifically, as well as information about reoperation and reinfection in patients with BAV. While the study by Tribouilloy *et al.*, and Becerra-Muñoz *et al.* followed their cohorts for five- and one-year, respectively, our study confirms that long-term survival after surgery is high in the BAV population up to

Table 4 Postoperative complications according to valve morphology in 338 patients who underwent aortic valve surgery for endocarditis at Karolinska University Hospital, Sweden, between 2002–2020

Complications	Tricuspid aortic valve, N=181	Bicuspid aortic valve, N=81	PVE, originally tricuspid, N=35	PVE, originally bicuspid, N=42
Mechanical circulatory support	3 (1.7%)	2 (2.5%)	1 (2.8%)	7 (16%)
Reoperation for sternal insufficiency	0 (0.0%)	1 (1.2%)	0 (0.0%)	1 (2.4%)
Reoperation for bleeding within 24 hours	13 (7.2%)	4 (5.0%)	2 (5.7%)	3 (7.1%)
Stroke	6 (5.9%)	2 (4.0%)	1 (5.6%)	4 (18%)
New dialysis	38 (22%)	11 (14%)	5 (14%)	14 (33%)
Atrial fibrillation	36 (30%)	8 (16%)	5 (20%)	4 (12%)
New cardiovascular implantable electronic device	9 (5.0%)	8 (10%)	3 (8.6%)	6 (14%)

PVE, prosthetic valve endocarditis.

14 years of follow-up. This is reassuring considering the severity of the perivalvular complications and the high percentage that require surgery in this patient population. It is also reassuring that we found no difference in the rate of reoperations between the groups, and that the rate of reinfection was low in patients with BAV. It is likely that the favorable prognosis is due to the younger age of the BAV patients and their healthier leadoff.

Prior studies found a higher degree of perivalvular abscess formation in BAV compared to TAV patients (11,15,16). This is in line with our findings, where perivalvular abscess was present in 40% of BAV patients with native valve IE and in 22% of TAV patients. In prosthetic valve IE patients, we found a high prevalence of perivalvular abscess formation among all patients, but no difference dependent on valve morphology (50% and 54% for BAV and TAV patients, respectively). Non-infectious complications of the aortic root and ascending aorta are well-known phenomena in BAV patients (25) Yet, the pathophysiological explanation for these complications remains unknown. It has been hypothesized that the increased risk of aortopathy in BAV patients is due to turbulent blood flow, resulting from the bicuspid valve, and/or genetic modifications of the aortic wall intima that are connected to a bicuspid valve morphology (1,2,13). It is possible that these theories may, in part, also explain why the BAV aortic root is more vulnerable to bacteria spreading and abscess formation. In patients with prosthetic valve IE, however, our data suggests that original valve morphology has no bearing on abscess formation.

The findings of this study confirm the important risk of IE in BAV patients, their risk of invasive disease and expand our understanding of long-term outcomes after aortic valve surgery for IE in BAV patients. Our data reaffirms that surgical treatment, when indicated, has excellent outcomes in BAV patients with native valve IE. Another interesting finding is the high prevalence of patients with BAV among patients who undergo surgery for IE combined with a high percentage of viridans streptococci infections. This finding may support the need for antibiotic prophylaxis in patients with BAV. The data on prosthetic valve IE likewise provides important information, suggesting that long-term outcomes are similar for BAV and TAV patients.

Strengths and limitations

It is often a challenge to account for differences in age and other baseline characteristics. Even though we adjusted for age and sex in the analysis, it is possible that the large difference in age between the groups was not fully adjusted for. Also, due to the limited study population, we could not adjust for differences in comorbidities between the groups. We acknowledge that pre-operative factors and the presence of comorbidities may be of great importance to our endpoints. Furthermore, there are factors that we did not have information about, such as BAV subtype, persistent preoperative sepsis and antibiotic regimen. At our center, endocarditis patients are accepted for surgery through multidisciplinary conferences with the major hospitals in the Stockholm area, which all follow international guidelines on antibiotic treatment for endocarditis. Thus, we can assume that all patients will have received adequate antibiotic regimens for the relevant bacteria at the time of surgery. Specific strengths of our study are the relatively large study

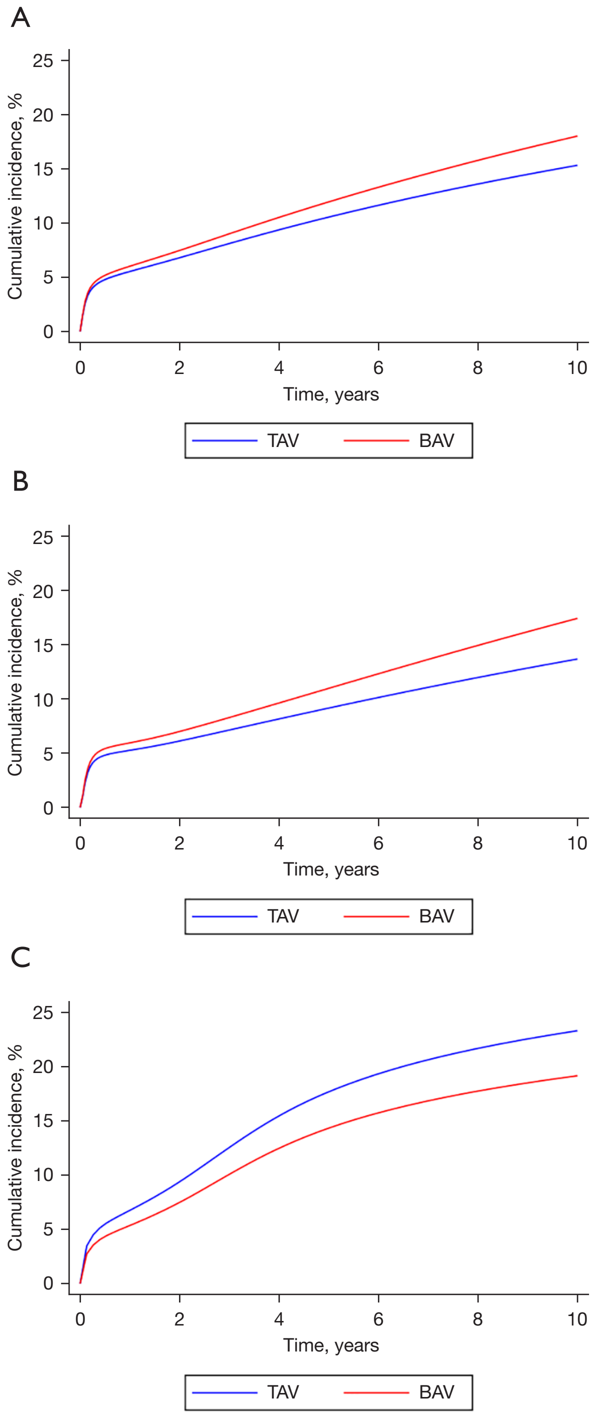

Figure 3 Cumulative incidence of reoperation according to valve morphology and prosthetic valve status after aortic valve endocarditis surgery at Karolinska University Hospital, Sweden, between 2002 and 2020 in (A) all patients, (B) native valve endocarditis patients and (C) prosthetic valve endocarditis patients. TAV, tricuspid aortic valves; BAV, bicuspid aortic valve.

cohort and long follow-up. Furthermore, we included all patients who underwent surgery for IE at our center during the study period, which increases generalizability. Because we have access to both registry data and medical records, we have few missing data points, particularly regarding BAV status, and follow-up for our primary outcome was complete.

Conclusions

In patients with native valve endocarditis, BAV patients had higher survival than TAV patients, whereas in patients with prosthetic valve endocarditis, no difference was found between the groups. There was no difference in reoperation rates between BAV and TAV patients and rates of reoperation for reinfection were low. Our findings shed new light on the prognosis in BAV patients after aortic valve surgery for endocarditis and are reassuring for these patients. Still, it is notable that such a high portion of native valve IE patients requiring surgery have BAV; it suggests it may be time to consider antibiotic prophylaxis for this patient population. We call on further research with larger study cohorts to confirm our findings.

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Footnote

Conflicts of Interest: The authors declare no conflicts of interest.

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Supplementary

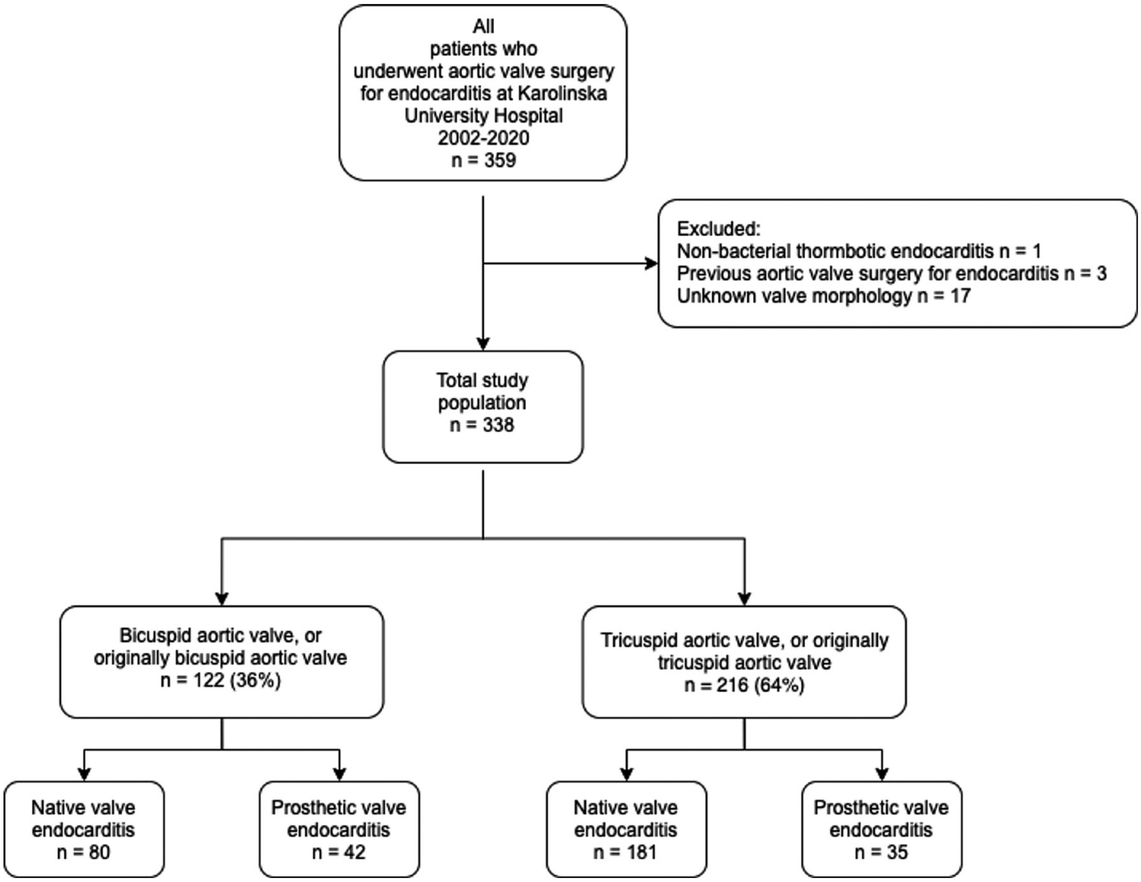

Figure S1 Flow chart of the study sample.

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Table S1 Baseline characteristics according to aortic valve morphology in 338 patients who underwent valve surgery for native aortic valve endocarditis or prosthetic aortic valve endocarditis at Karolinska University Hospital, Sweden, 2002–2020

	All patients, N=338	Tricuspid aortic valve, N=216 (64%)	Bicuspid aortic valve, N=122 (36%)
Age, years, mean (SD)	59 (17.5)	63 (12.3)	53 (15.3)
Female	69 (20.4)	48 (22.2)	21 (17.2)
Body mass index (kg/m^2), mean (SD)	25.9 (4.7)	26.0 (4.7)	25.6 (4.8)
Hypertension	101 (29.9)	73 (33.8)	28 (22.3)
Diabetes mellitus	43 (12.7)	31 (14.4)	12 (9.8)
Intravenous drug user	31 (9.2)	24 (11.1)	7 (5.7)
Prior percutaneous coronary intervention	11 (3.4)	9 (4.2)	2 (1.6)
Prior stroke	73 (21.6)	42 (19.4)	31 (25.4)
Atrial fibrillation	45 (13.3)	30 (13.9)	14 (11.5)
Chronic obstructive pulmonary disease	25 (7.4)	21 (9.7)	4 (3.3)
Peripheral arterial disease	9 (2.7)	6 (2.8)	3 (2.5)
Critical preoperative state	50 (14.8)	32 (14.8)	18 (14.8)
EuroSCORE I, mean (SD)	10.0 (3.6)	10.0 (3.4)	10.1 (3.5)
Left ventricular ejection fraction			
>50	139 (41.1)	93 (43.1)	46 (37.7)
31–50	74 21.9)	42 (30.0)	32 (26.2)
21–30	5 (1.5)	4 (2.9)	1 (0.8)
<20	2 (0.6)	1 (0.7)	1 (0.8)
eGFR (mL/min/1.73 m^2)			
>60	230 (68.0)	139 (64.3)	91 (74.6)
30–60	74 (21.9)	51 (23.6)	23 (18.9)
0–29	17 (5.0)	12 (5.6)	5 (4.1)
Preoperative dialysis	13 (3.8%)	11 (5.1)	2 (1.6)
Prior cardiac surgery	88 (26.0)	41 (19.0)	47 (38.5)
Prior endocarditis	14 (4.1)	7 (3.2)	7 (5.7)
Cardiovascular implantable electronic device	17 (5.0)	8 (6.6)	9 (7.4)
Preoperative complications			
Central nervous system embolic event	53 (15.7)	31 (14.4)	22 (18.0)
Peripheral embolic event	33 (9.8)	21 (9.7)	12 (9.8)
Valvular abscess	111 (32.8)	58 (26.9)	53 (43.4)
Vegetations	245 (72.5)	163 (75.5)	82 (67.2)
Concomitant surgery			
CABG	18 (5.3)	16 (7.4)	2 (1.4)
Aorta ascendens	72 (21.3)	34 (15.7)	38 (31.4)

Table S1 (*continued*)

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Table S1 (*continued*)

	All patients, N=338	Tricuspid aortic valve, N=216 (64%)	Bicuspid aortic valve, N=122 (36%)
Biological aortic valve replacement	209 (61.8)	150 (69.4)	59 (48.4)
Acute kidney injury[c]	172 (50.9)	114 (52.8)	58 (47.5)
Year of surgery			
2002–2007	76 (22.5)	45 (20.8)	31 (25.4)
2008–2013	110 (32.5)	72 (33.3)	38 (31.1)
2014–2019	152 (45.0)	99 (45.8)	53 (43.4)

Data are presented as n (%) unless otherwise noted. [c], Defined as >0.3 mg/dL (>26 μmol/L) increase in postoperative creatinine concentrations, or postoperative creatinine >1.5*baseline, or new postoperative dialysis. PVE, prosthetic valve endocarditis; Egfr, estimated glomerular filtration rate; SD, standard deviation

Table S2 Survival according to valve morphology and prosthetic valve status in 338 patients who underwent aortic valve surgery due to endocarditis at Karolinska University Hospital, Sweden, 2002–2020

	Tricuspid aortic valve, n=181 (53%)	Bicuspid aortic valve, n=80 (24%)	Prosthetic valve endocarditis, originally tricuspid, n=35 (11%)	Prosthetic valve endocarditis, originally bicuspid, n=42 (13%)
Early mortality, number (%)	10 (5.5%)	3 (3.8%)	2 (5.7%)	9 (21%)
All-cause mortality, number (%)	64 (35%)	12 (15%)	14 (39%)	13 (30%)
1 year	84%	95%	89%	74%
5 years	69%	88%	71%	68%
10 years	59%	83%	56%	68%
14 years	49%	80%	17%	68%

Table S3 Causes of death for 103 patients who underwent aortic valve surgery due to endocarditis at Karolinska University Hospital, Sweden, 2002–2020

	Tricuspid aortic valve, n=78	Bicuspid aortic valve, n=25
Death within 30 days of surgery	12	12
Prosthetic valve endocarditis	10	2
Heart failure	6	3
Cancer	6	2
Covid-19	2	1
Mediastinal abscess	0	1
Acute coronary syndrome	4	0
Other/multiorgan failure	8	0
Cardiac arrest	2	0
Intracerebral lesions	6	0
Sepsis or pneumonia	7	0
Choking	1	0
Unknown	14	4

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Table S4 Cumulative incidence of reoperation according to valve morphology and prosthetic valve endocarditis in 338 patients who underwent aortic valve surgery due to endocarditis at Karolinska University Hospital, Sweden, 2002–2020

	Number of patients	Cumulative incidence (95% CI)		
		1 year	5 years	10 years
Tricuspid aortic valve	181 (54%)	5.3% (3.1–9.1%)	9.2% (5.9–14.4%)	13.7% (9.1–20.7%)
Bicuspid aortic valve	80 (24%)	6.0% (3.0–11.8%)	11.0% (6.2–19.6%)	17.5% (10.4–29.2%)
Prosthetic valve endocarditis, originally tricuspid	35 (10%)	6.8% (2.6–17.8%)	17.7% (8.7–35.8%)	23.3% (12.2–44.8%)
Prosthetic valve endocarditis, originally bicuspid	42 (12%)	5.4% (1.9–15.1%)	14.4% (6.6–31.1%)	19.2% (9.3–39.5%)

CI, confidence interval.

Table S5 Indications for valve reoperations according to valve morphology

	Tricuspid aortic valve, n=181	Bicuspid aortic valve, n=81	Prosthetic valve endocarditis, originally tricuspid, n=36	Prosthetic valve endocarditis, originally bicuspid, n=43
Prosthetic valve endocarditis	13 (7.2%)	4 (4.9%)	2 (5.6%)	3 (7.0%)
Aortic valve insufficiency (including paravalvular leakage)	3 (1.7%)	4 (4.9%)	2 (5.6%)	1 (2.3%)
Structural valve deterioration	2 (1.1%)	3 (3.7%)	1 (2.8%)	0 (0.0%)
Pseudoaneurysm	0 (0.0%)	1 (1.2%)	0 (0.0%)	1 (2.3%)
Type A dissection	1 (0.6%)	0 (0.0%)	1 (2.8%)	0 (0.0%)
Other	1 (0.6%)	0 (0.0%)	1 (2.8%)	1 (2.3%)

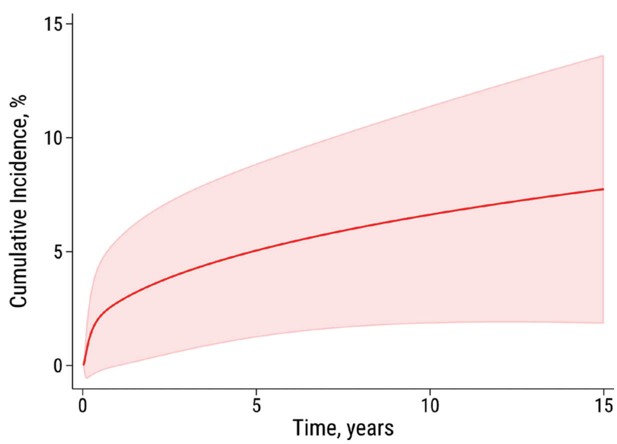

Figure S2 Cumulative incidence of reinfection in patients with bicuspid aortic valves after endocarditis surgery at Karolinska University Hospital, Sweden, 2002–2020.

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