ORIGINAL ARTICLE

SURGICAL AORTIC VALVE REPLACEMENT FOR BICUSPID AND TRICUSPID VALVE DISEASE: 7-YEAR OUTCOMES IN >1100 PATIENTS

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Abstract

Introduction: *Bicuspid aortic valve affects 0.5-2% of the population in developed countries. Given uncertainties about the best aortic valve replacement (AVR) option in this often younger, low-risk, population, it is important to understand how newer bioprostheses perform in these patients. The primary objective of this analysis was to compare 7-year outcomes of surgical AVR (SAVR) with the Avalus bioprosthesis between patients with a congenital bicuspid or tricuspid valve.*

Methods: *This prospective, non-randomized study included 1132 patients with aortic valve stenosis or chronic severe aortic regurgitation who underwent successful SAVR with the Avalus bioprosthesis. Patients were categorized into bicuspid (n=339) and tricuspid (n=775) groups; 18 patients had unknown etiology. Kaplan-Meier analyses estimated valve-related adverse events over 7 years. Multivariable Cox proportional hazard models with propensity score adjustments evaluated the association of valve etiology with clinical outcomes, and a multivariable analysis identified risk factors for all-cause mortality.*

Results: *Patients with a tricuspid valve were older with more advanced heart failure symptoms and a higher mean Society of Thoracic Surgeons risk score (P<0.01). At 7 years postimplant, mortality was lower [8.9% (95% CI: 5.9%-13.4%) versus 21.3% (95% CI: 18.1%-24.9%), P<0.01] and non-structural valve dysfunction was higher in the bicuspid cohort [2.9% (95% CI: 1.5%-5.5%) versus 0.6% (95% CI: 0.2%-1.6%), P<0.01]. Other safety parameters were not significantly different. In the bicuspid and tricuspid cohorts, the respective mean effective orifice area was 2.0±0.5 and 2.0±0.5 at 7 years, and the respective mean aortic gradient was 13.6±6.4 and 14.1±5.7. Reintervention rates were low [6.8% (95% CI: 4.1%-10.9%) versus 5.4% (95% CI: 3.7%-7.8%), P=0.54] in both cohorts.*

Conclusions: *SAVR with the Avalus bioprosthesis yielded excellent 7-year outcomes for patients with either a congenital bicuspid or tricuspid valve. Hemodynamic performance and reintervention rates were similar between cohorts with low rates of other valve-related adverse events.*

Keywords*: Surgical aortic valve replacement, congenital bicuspid aortic valve, tricuspid aortic valve, aortic valve surgery, aortic stenosis, aortic regurgitation.*

INTRODUCTION

A bicuspid aortic valve (BAV) is a common congenital heart condition, affecting 0.5% to 2% of the population in developed countries.[1] An analysis of the Society of Thoracic Surgeons (STS) database found 50% of adults undergoing surgical aortic valve replacement (SAVR) for severe aortic stenosis who were <65 years of age had a bicuspid valve.[2] These patients present unique challenges for AVR because of associated aortopathies and their often younger age, which places them at higher risk for early bioprosthetic valve failure and necessitates longer-term management.[3-5] Transcatheter

aortic valve implantation (TAVI) has emerged as an alternative to SAVR after several registries reported positive outcomes in BAV patients unsuitable for surgery[6] and after the STS/American College of Cardiology (ACC) transcatheter registry showed that newer generation TAVI bioprostheses perform similarly to surgical valves in terms of paravalvular leak (PVL) rates and 30-day and 1-year mortality.[6] Although TAVI is an alternative to SAVR, its use in patients with a BAV lacks strong evidence due to their exclusion from low-risk TAVI trials.[6]

Recent studies indicate SAVR may still offer better outcomes for certain bicuspid patients and support careful consideration of the best treatment option.[7,8] A subanalysis of the NOTION-2 trial found lower stroke and mortality rates at 1 year for SAVR compared to TAVI in low-risk patients ≤75-years-old,[7] and an analysis of data from the US Medicare and Medicaid claims database, found lower stroke and composite stroke, valve reintervention, or death in BAV patients treated with SAVR as compared with TAVI.[8] Current guidelines from the ACC and American Heart Association (AHA) on the treatment of valvular heart disease provide a class 2b recommendation (usefulness is uncertain) for alternative use of TAVI over SAVR in BAV patients with symptomatic and severe aortic stenosis when performed at a Comprehensive Valve Center.[9] The European Society of Cardiology and European Association for Cardio-Thoracic Surgery (ESC/EACTS) guidelines on valvular heart disease, state that SAVR is more appropriate in BAV patients with aortic stenosis, especially in those with associated disease requiring a surgical approach.[6]

Given the uncertainties in treating patients with a BAV, it is important to understand how newer bioprostheses perform in this subset of patients. The primary objective of this study was to provide 7-year outcomes of SAVR using the Avalus bioprosthesis, which received CE mark and FDA approval in 2017, in patients with a congenital bicuspid or tricuspid valve. The secondary objective is to identify baseline clinical predictors of 7-year mortality.

METHODS

Study Design and Patients

This study is a post hoc analysis of the PERIcardial SurGical AOrtic Valve ReplacemeNt (PERIGON) Pivotal Trial of the Avalus valve, a prospective, nonrandomized multicenter trial conducted at 39 sites in Europe, Canada, and the United States. The trial enrolled consecutive adults, receiving the Avalus bioprosthesis (Medtronic, Minneapolis, MN, USA), a stented bovine pericardial aortic valve. The study design, including eligibility criteria, sample size, surgical procedure, event definitions, institutional review board and ethics committee (IRB/EC) approval dates and follow-up assessments, were previously described.[10]

Initially planned for 5 years, the trial was extended to 12 years with 19 sites and 576 patients agreeing to participate in the Long-Term Follow-Up (LTFU) study.

For this analysis, patients were stratified according to the presence of a congenital bicuspid or tricuspid aortic valve. The bicuspid group (n=339) included patients with "congenital bicuspid" etiology as assessed on the implant case report form. The tricuspid group (n=775) included patients without "congenital bicuspid" selected as the etiology of aortic disease. Those marked as "other, specify" were reviewed and classified as either bicuspid, tricuspid or unknown; cases of unknown etiology were not included in the BAV or tricuspid aortic valve (TAV) cohorts.

In-person follow-up was performed at 3 to 6 months, 1 year, and then annually through 5 years. Details on information collected at each visit for the pivotal trial were previously described.[11] 6-year follow-up was in-person or by telephone, and in-person at 7-years. NYHA classification, medication use (ie, aspirin, other antiplatelet, anticoagulant, and indication), vital status, and safety endpoints were collected at 6 and 7 years. Transthoracic echocardiography and 12-lead electrocardiography were conducted at the 7-year visit. The visit cutoff date for this analysis was 15 December 2023.

The trial was designed and conducted in accordance with the Declaration of Helsinki and good clinical practice guidelines. The study protocols for the pivotal trial and the LTFU study were approved by the institutional review board or ethics committee of each participating center, and all patients provided written informed consent before enrollment in the pivotal trial and before continuing in the LTFU study. This trial is registered at www.clinicaltrials.gov, NCT02088554.

Study oversight was conducted through the Baim Institute for Clinical Research (Boston, MA, USA), with an independent data and safety monitoring board and an independent clinical events committee adjudicating deaths and serious adverse events. Explanted bioprostheses were examined at the CVPath Institute (Gaithersburg, MD, USA), and an independent core laboratory (Mayo Clinic, Rochester, MN, USA) assessed echocardiograms obtained at the 3- to 6-month, 1-year, 5-year, and 7-year visits.

Objectives and Endpoints

The primary objective is a comparison of safety and effectiveness between BAV and TAV cohorts. Clinically relevant effectiveness outcomes, including hemodynamics, and functional status through 7 years of follow-up are evaluated. For hemodynamic performance, aortic gradients and effective orifice area (EOA) are presented for each cohort, as is the proportion with residual regurgitation. Functional status was assessed based on the percentage of subjects in each specific New York Heart Association (NYHA) class.

Safety outcomes include mortality; valve-related thromboembolism; valve thrombosis; endocarditis; non-structural valve dysfunction (NSVD); aortic regurgitation; explant and reintervention, including reintervention for structural valve dysfunction and severe hemodynamic dysfunction (SVD/SHD). As previously reported, the endpoint of SVD/SHD requiring reintervention is presented as a composite endpoint to address the limitations of the protocol definition of SVD.[10]

The secondary objective was to identify baseline predictors of 7-year all-cause mortality in the BAV and TAV cohorts.

Table 1 **Baseline characteristics**

Characteristic	Bicuspid N=339	Tricuspid N=775	p value
Age (years)			
Mean±SD	64.3±9.3	72.8±7.2	<0.01
Reported range	21.1, 84.6	43.0, 90.9	
Male sex	78.8%	73.9%	0.09
Body surface area, m^2	2.03±0.23	1.97±0.22	<0.01
NYHA III/IV	122 (36.0%)	344 (44.4%)	<0.01
STS risk of mortality, %	1.3±0.8	2.2±1.4	<0.01
Aortic aneurysm	59 (17.4%)	38 (4.9%)	<0.01
Atrial enlargement	35 (10.3%)	68 (8.8%)	0.41
Atrial fibrillation	23/338 (6.8%)	94/769 (12.2%)	<0.01
Cancer	40 (11.8%)	117 (15.1%)	0.15
COPD	25 (7.4%)	105 (13.5%)	<0.01
Coagulopathy	0 (0%)	5 (0.6%)	0.33
Congestive heart failure	55 (16.2%)	162 (20.9%)	0.07
Coronary artery disease	101 (29.8%)	389 (50.2%)	<0.01
Diabetes – insulin	12 (3.5%)	16 (2.1%)	0.15
Dyslipidemia	193 (56.9%)	496 (64.0%)	0.03
Endocarditis	2 (0.6%)	2 (0.3%)	0.60
Hypertension	222 (65.5%)	627 (80.9%)	<0.01
Left ventricular hypertrophy	125 (36.9%)	329 (42.5%)	0.08
Myocardial infarction	24 (7.1%)	74 (9.5%)	0.18
Renal dysfunction/insufficiency not requiring dialysis or with a GFR>30mL/min/1.73 m^2	19 (5.6%)	99 (12.8%)	<0.01
Rheumatic heart disease	1 (0.3%)	10 (1.3%)	0.19
Prior coronary artery bypass	4 (1.2%)	18 (2.3%)	0.25
Primary indication for valve re-placement			0.59
Aortic stenosis	283 (83.5%)	664 (85.7%)	0.34
Aortic regurgitation	21 (6.2%)	38 (4.9%)	0.38
Mixed	35 (10.3%)	71 (9.2%)	0.54
Failed prosthesis	0 (0.0%)	2 (0.3%)	>0.9999
Surgical approach			<0.01
Median sternotomy	259 (76.4%)	628 (81.0%)	
Hemisternotomy	41 (12.1%)	103 (13.3%)	
Right thoracotomy	34 (10.0%)	35 (4.5%)	
Other	5 (1.5%)	9 (1.2%)	
Concomitant CABG	61 (18.0%)	304 (39.2%)	<0.01
Concomitant ascending aortic aneurysm repair not requiring circulatory arrest	55(16.2%)	32(4.1%)	<0.01
Concomitant dissection repair not requiring circulatory arrest	1(0.3%)	0(0.0%)	0.30
Implanted valve size			<0.01
17 mm	0 (0.0%)	1 (0.1%)	
19 mm	5 (1.5%)	37 (4.8%)	
21 mm	48 (14.2%)	160 (20.6%)	
23 mm	97 (28.6%)	298 (38.5%)	
25 mm	115 (33.9%)	230 (29.7%)	
27 mm	57 (16.8%)	43 (5.5%)	
29 mm	17 (5.0%)	6 (0.8%)	

Abbreviations: NYHA: New York Heart Association, SVD: Structural valve deterioration, COPD: Chronic obstructive pulmonary disease, CABG: coronary artery bypass graft.

Table 2 **Kaplan-Meier rates of death and valve-related safety events at 30 days and 1, 5 and 7 years follow-up[a]**

	Bicuspid N=339				Tricuspid N=775				
	Event rate	Kaplan-Meier event rate (95% CI)[b]			Event rate	Kaplan-Meier event rate (95% CI)[b]			
Endpoint	30-days % (N)	1 Year	5 Years	7 Years	30-days % (N)	1 Year	5 Years	7 Years	P value[c]
All-cause death	0.9 (3)	1.8 (0.8-3.9)	5.0 (3.1-8.0)	8.9 (5.9-13.4)	0.9 (7)	3.5 (2.4-5.1)	14.6 (12.2-17.4)	21.3 (18.1-24.9)	<0.01
Valve related death	0.0 (0)	0.0 (0.0-0.0)	0.3 (0.0-2.4)	1.0 (0.2-4.1)	0.0 (0)	0.4 (0.1-1.2)	2.1 (1.3-3.5)	3.5 (2.2-5.5)	0.02
Thromboembolism	1.2 (3)	1.5 (0.6-3.6)	4.5 (2.7-7.5)	5.1 (3.1-8.5)	1.5 (12)	3.0 (2.0-4.5)	5.8 (4.3-7.8)	6.6 (4.9-8.8)	0.28
Valve thrombosis	0.0 (0)	0.0 (0.0-0.0)	0.3 (0.0-2.2)	0.3 (0.0-2.2)	0.0 (0)	0.0 (0.0-0.0)	0.4 (0.1-1.4)	0.4 (0.1-1.4)	0.78
Endocarditis	0.3 (1)	1.2 (0.5-3.2)	4.5 (2.7-7.4)	6.1 (3.8-9.8)	0.1 (1)	1.2 (0.6-2.3)	4.5 (3.2-6.3)	6.6 (4.8-9.1)	0.81
Non-structural valve dysfunction	0.3 (1)	1.5 (0.6-3.6)	2.9 (1.5-5.5)	2.9 (1.5-5.5)	0.1 (1)	0.1 (0.0-0.9)	0.6 (0.2-1.6)	0.6 (0.2-1.6)	<0.01
SVD/SHD[d]	0.0 (0)	0.0 (NA)	0.0 (NA)	1.3 (0.3-5.2)	0.0 (0)	0.0 (NA)	0.3 (0.1-1.2)	1.1 (0.5-2.8)	0.79
SVD requiring reintervention[e]	0.0 (0)	0.0 (NA)	0.0 (NA)	0.0 (NA)	0.0 (0)	0.0 (NA)	0.0 (NA)	0.0 (NA)	NA
SHD requiring reintervention	0.0 (0)	0.0 (NA)	0.0 (NA)	1.3 (0.3-5.2)	0.0 (0)	0.0 (NA)	0.3 (0.1-1.2)	1.1 (0.5-2.8)	0.79
Reintervention	0.6 (2)	1.2 (0.5-3.2)	3.8 (2.2-6.6)	6.8 (4.1-10.9)	0.3 (2)	0.8 (0.4-1.8)	3.2 (2.1-4.8)	5.4 (3.7-7.8)	0.54
Explant	0.6 (2)	1.2 (0.5-3.2)	3.5 (1.9-6.2)	5.2 (3.0-8.7)	0.3 (2)	0.8 (0.4-1.8)	2.7 (1.7-4.3)	4.0 (2.7-6.1)	0.50

[a] Analysis cohort is all implanted patients with known valve etiology (N=1114).
[b] Patients may have had >1 event.
[c] Log-rank test. P value is for the comparison between the 2 cohorts at the 7-year endpoint.
[d] SVD/SHD = composite endpoint of structural valve deterioration requiring reintervention or severe hemodynamic dysfunction requiring reintervention.
[e] There were no adjudicated cases of SVD requiring or not requiring reintervention.
Abbreviations: SVD: structural valve deterioration, SHD: structural hemodynamic dysfunction

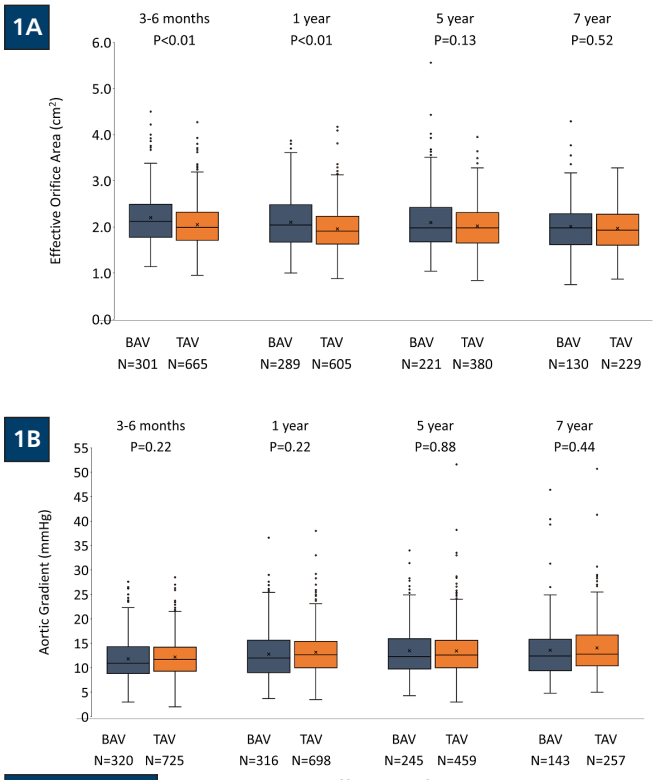


Figure 1 *Hemodynamics: A, Effective orifice area in bicuspid versus tricuspid patients. B, Aortic gradients in bicuspid versus tricuspid patients.*
Abbreviations: BAV: bicuspid aortic valve, TAV: tricuspid aortic valve.

Statistical Analysis

Categorical variables are reported as counts and frequencies and compared using the χ^2 or Fisher exact test where appropriate. Continuous variables are reported as mean and standard deviation (SD) and compared using the t test. For ordinal data, the Cochran-Mantel-Haenszel test was used. Clinical events are reported as Kaplan-Meier estimates and compared using the log-rank test.

Univariable Cox proportional hazard models were used to assess the impact of etiology on clinical outcomes. Because of the inherent differences between patients with a congenital bicuspid or tricuspid aortic valve, multivariable Cox proportional hazard models with propensity score adjustments were also performed. The following baseline and procedural characteristics were selected, based on clinical relevance and statistical consideration, to calculate the propensity score used in the models: age, sex, NYHA class, STS risk of mortality, aortic aneurysm, atrial fibrillation, chronic obstructive lung disease, congestive heart failure, coronary artery disease, diabetes, dyslipidemia, hypertension, peripheral vascular disease, renal dysfunction/ insufficiency not requiring dialysis or with a GFR>30mL/min/1.73 m^2, percutaneous coronary intervention, left ventricular hypertrophy, concomitant coronary artery bypass graft (CABG), stroke/cerebrovascular accident, current smoker, implanted cardiac device and valve size.

In addition, to identify baseline clinical predictors of 7-year all-cause mortality, univariable and multivariable analyses were performed using Cox proportional hazard models. The final multivariable model was obtained using

Table 3 **Predictors of 7-year all-cause mortality in the implanted cohort (N=1132).**

	Univariate Model		Multivariate Model	
	Hazard Ratio (95% CI)	P Value	Hazard Ratio (95% CI)	P Value
STS risk of mortality (%)	1.4 (1.3-1.5)	<0.01	1.1 (1.0-1.3)	0.05
Age (years)	1.1 (1.1-1.1)	<0.01	1.0 (1.0-1.1)	<0.01
Atrial fibrillation	3.0 (2.1-4.4)	<0.01	2.2 (1.5-3.3)	<0.01
Renal dysfunction/ insufficiency not requiring dialysis or with a GFR>30mL/min/1.73 m^2	2.5 (1.7-3.7)	<0.01	1.7 (1.1-2.6)	0.01
Congenital bicuspid vs. tricuspid	0.4 (0.2-0.6)	<0.01	0.6 (0.4-1.0)	0.06
Congestive heart failure	1.8 (1.3-2.6)	<0.01	1.5 (1.1-2.1)	0.02
Cancer	1.8 (1.2-2.6)	<0.01	NA	NA
Coagulopathy	5.2 (1.7-16.4)	<0.01	NA	NA
Prior coronary artery bypass	2.2 (1.0-4.7)	0.04	NA	NA
NYHA III/IV	1.4 (1.0-1.8)	0.06	NA	NA
Arrhythmia surgery	2.2 (1.0-4.9)	0.06	NA	NA
Hypertension	1.5 (1.0-2.2)	0.06	NA	NA
Concomitant CABG	1.3 (1.0-1.9)	0.07	NA	NA
Aortic aneurysm	0.5 (0.3-1.1)	0.07	NA	NA
Coronary artery disease	1.3 (1.0-1.8)	0.08	NA	NA
COPD	1.5 (1.0-2.2)	0.08	NA	NA

Stepwise selection was used with criteria for model entry set at P = 0.15 and remaining in model set at P = 0.1.
Abbreviations: STS: Society of Thoracic Surgery; NYHA: New York Heart Association; CABG: coronary artery bypass graft; COPD: Chronic obstructive pulmonary disorder.

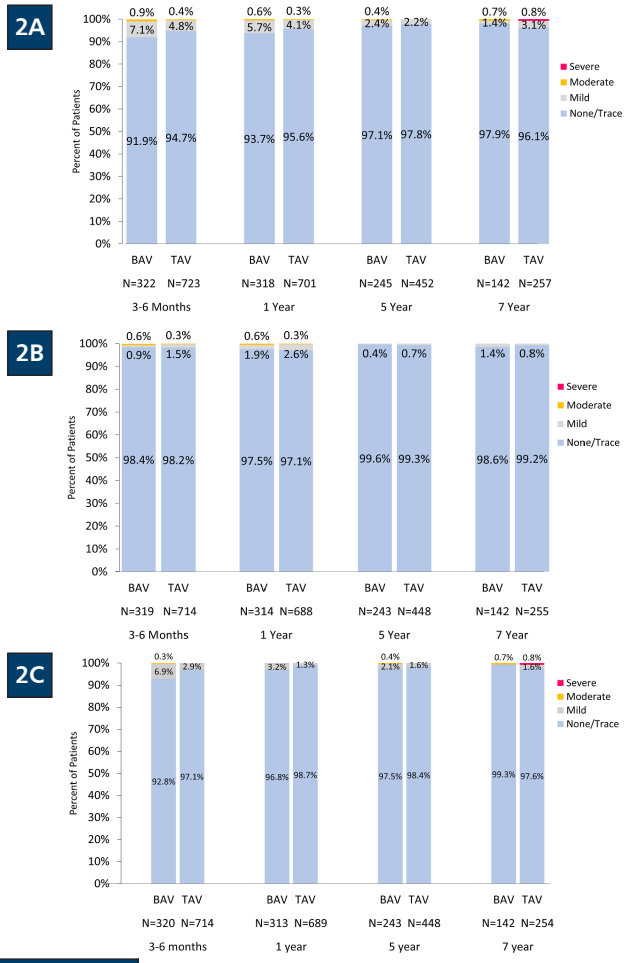


Figure 2 *Regurgitation post-operatively at 3-6 months, 1-year, 5-years, and 7-years: A, total; B, paravalvular; and C, transvalvular. Abbreviations: BAV: bicuspid aortic valve, TAV: tricuspid aortic valve.*

backward elimination with a stay criterion of P = 0.10. No adjustments were made for multiple comparisons.

Results were considered statistically significant at P<0.05, and all P values were 2-sided. All statistical analyses were performed using SAS software, version 9.4 (SAS Institute, Cary, NC, USA).

RESULTS

A total of 1132 patients were implanted with an Avalus bioprosthesis. Eighteen patients had an "other" etiology of aortic disease and were not included in the BAV or TAV cohorts. Among the remaining 1114 patients, 339 had a congenital bicuspid valve and 775 a tricuspid valve. Figure S1 shows the follow-up of patients in this analysis through 7 years. Of the bicuspid and tricuspid patients included in this analysis, 432 out of 449 patients (96.2%) with an expected 7-year visit had completed the visit.

Patient characteristics and procedural data

Table 1 lists baseline patient characteristics and procedural data for the bicuspid and tricuspid groups. Patients with a bicuspid valve were younger than those with a tricuspid valve [64.3±9.3 years (range: 21-85 years) vs 72.8±7.2 years (range: 43-91 years), respectively; P<0.01], had a significantly lower STS risk of mortality (1.3±0.8% vs 2.2±1.4%, P<0.01), had fewer comorbidities and better functional status, and less frequently underwent concomitant CABG (61/339 [18.0%] vs 304/775 [39.2%]; P<0.01). Patients in the bicuspid group were significantly more likely to have an aortic aneurysm (59/339 [17.4%] vs 38/775 [4.9%], P<0.01), a larger body surface

area (2.03±0.23 vs. 1.97±0.22, P<0.01), to undergo surgery through a right thoracotomy (34/339 [10.0%] vs 35/775 [4.5%], P<0.01 for the difference in all surgical approaches), and to have a larger valve implanted (189/339 [55.8%] vs 279/775 [36.0%] for 25- to 29-mm valves, P<0.01 for the difference in all valve sizes) than those in the tricuspid group (Table 1).

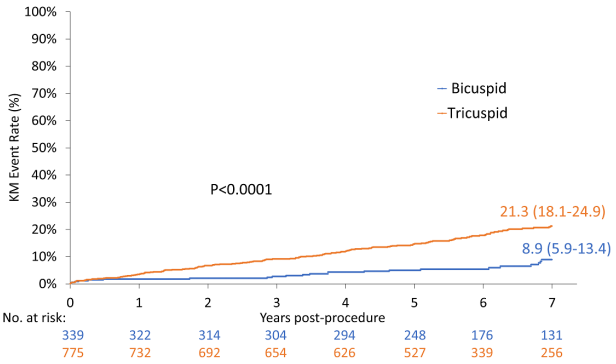
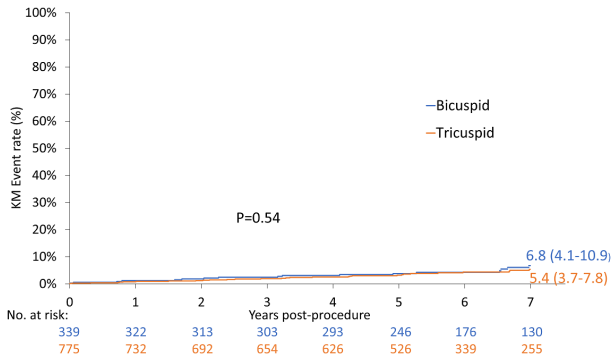


Figure 3 *Kaplan-Meier event rate for all-cause mortality. Abbreviations: KM: Kaplan Meier, No.: Number.*

4A



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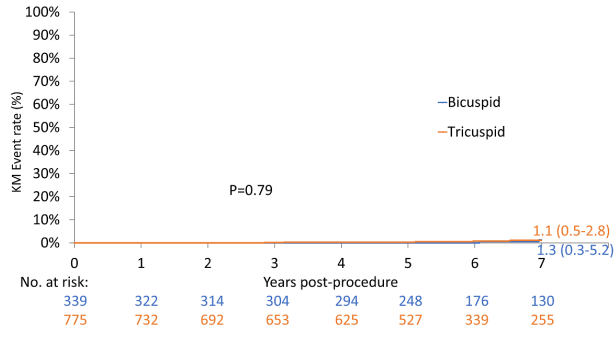

Figure 4 *Kaplan-Meier reintervention rates: A, all reinterventions; B, composite SVD/SHD requiring reintervention endpoint.*

Abbreviations: KM: Kaplan Meier, No.: Number.

Efficacy Outcomes

At 3 to 6 months, EOA was 2.2±0.6 cm^2 and 2.1±0.5cm^2 in the bicuspid and tricuspid groups, respectively. Mean aortic gradient was 11.8±4.5 mmHg and 12.2±4.0 mmHg in the bicuspid and tricuspid groups, respectively. These values remained stable with minimal differences through 7 years of follow-up (Fig. 1).

At 7 years post-operatively, total regurgitation was none/trace in 98% and 96% in the bicuspid and tricuspid groups, respectively. At 7 years post-operatively, <1% of patients in each cohort had moderate or severe transvalvular regurgitation, and there were no cases of greater than mild paravalvular regurgitation in either cohort (Fig. 2).

At baseline, most patients in both groups were in NYHA class II or III. Functional status improved after SAVR with the majority of patients in both groups in NYHA class I or II through 7 years of follow-up (Fig. S2). A higher percentage of patients in the bicuspid cohort were in class I compared to the tricuspid cohort, which had a higher percent in class II.

Clinical outcomes

All-cause as well as valve-related mortality rates were higher in the tricuspid group (Fig 3). By 7 years, there were no statistically significant differences between groups for thromboembolism, valve thrombosis, endocarditis, explants, and reinterventions (including SVD/SHD requiring reinterventions). NSVD was higher in the bicuspid group (Table 2). Regarding the composite endpoint of reinterventions due to SVD/SHD, all 7 cases were adjudicated as SHD requiring reintervention, and none were adjudicated as SVD requiring, or not requiring, reintervention (Table 2 and Fig. 4).

Multivariable analysis demonstrated a higher risk of all-cause mortality in older patients, in those with a higher STS risk of mortality score, and in those with atrial fibrillation, renal dysfunction or insufficiency not requiring dialysis or with a GFR>30mL/min/1.73 m^2, and congestive heart failure at baseline (Table 3).

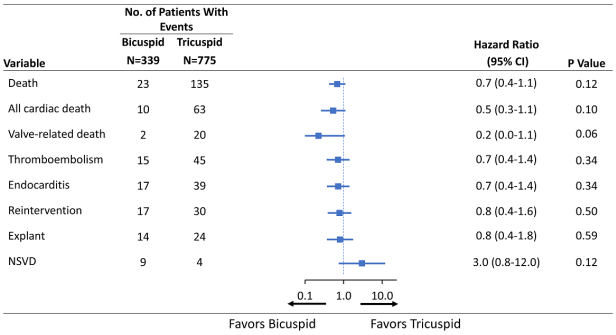

Figure 5 *Impact of valve type (bicuspid or tricuspid) on clinical outcomes through 7 years of follow-up. A multivariable Cox proportional hazard regression analysis performed after propensity score adjustment demonstrated no significant differences in clinical events or mortality between groups through 7 years.*

Abbreviations: NSVD: non-structural valve deterioration.

After adjusting for baseline differences between the groups using propensity score, the hazard ratios for mortality, thromboembolism, endocarditis, reintervention, explant, and NSVD were not significantly different between groups (Fig.5), Although NSVD trended worse for bicuspid patients because of a higher rate of minor (ie, not resulting in reintervention) PVL. Of the 13 patients with NSVD, 3 patients (2 bicuspid and 1 tricuspid) had NSVD not related to PVL. Of the remaining 10 patients with PVL, 8 had minor PVL (5 bicuspid and 3 tricuspid): two of these cases resolved spontaneously, and 6 were ongoing at the time of study exit. For the 3 patients with NSVD not related to PVL, the cause for 2 patients was entrapment by pannus, tissue, or suture, and for 1 patient, possible prosthesis-patient mismatch (PPM) was noted.

DISCUSSION

This analysis compared outcomes of SAVR with the Avalus bioprosthesis in patients with congenital bicuspid and tricuspid aortic valves. Clinical and hemodynamic outcomes through 7 years were excellent overall. The mortality rate was higher among patients with a tricuspid native valve due to the older age and greater comorbidity burden of this cohort. The Kaplan-Meier (KM) rate of NSVD at 7 years was low in both cohorts but higher among patients with a congenital bicuspid valve. However, a multivariable model with propensity score adjustment demonstrated no association between valve type and NSVD at 7 years. Hemodynamic performance was stable in both groups through 7 years with average EOAs and aortic gradients trending slightly better in the BAV cohort - an expected finding given understood anatomical differences predisposing BAV patients to larger valves[12] (Table S1 and S2). Reinterventions, including reinterventions for the composite endpoint of SVD/SHD, were low in both cohorts at 7-years.

Grades of valvular regurgitation, both paravalvular and transvalvular, as determined by the Echocardiography Core Lab, were similar between groups and stable over the 7 years, with very few patients having moderate or greater PVL at any time point (Fig. 2). In contrast, the KM estimates of PVL, that drove higher KM rates of NSVD in bicuspid patients (Table 2) were site reported. This discrepancy in PVL outcomes is due, in part, to the difference between cumulative and non-cumulative data. But the difference may also be due to inconsistent reporting of PVL among sites, especially reporting of minor PVL, which was defined in the protocol as PVL not requiring surgical or percutaneous intervention. Therefore, the clinical relevance of the higher KM rate of NSVD for the bicuspid cohort is unclear.

The multivariable analysis demonstrated that several baseline characteristics were associated with all-cause mortality at 7 years, including age, STS risk of mortality score, atrial fibrillation, renal dysfunction or insufficiency, and congestive heart failure, suggesting the higher mortality rate observed in tricuspid patients is due to the older age and greater comorbidity burden of this cohort. Otherwise, there were no significant differences in the safety and effectiveness between patients with a congenital bicuspid or tricuspid valve.

Use of TAVI to manage bicuspid aortic stenosis has been increasing, with many investigators achieving good outcomes with newer generation TAVI devices.[13-18] However, TAVI is limited to certain bicuspid patients; those with aortopathy and primary aortic regurgitation may not be suitable, and highly calcified cases were excluded from recent evaluations.[17] Lifetime management is crucial in patients with a bicuspid valve, especially given the challenges in explanting TAVI devices.[19-21] Consideration of SAVR therapy is important, as recent outcomes from the NOTION-2 trial in low-risk, ≤75-year-old patients had lower stroke and mortality rates at 1 year following SAVR as compared to TAVI.[7] In addition, a subanalysis of data from the US Medicare and Medicaid claims database found lower rates of stroke and a composite endpoint of stroke, valve reintervention, or death in BAV patients treated with SAVR as compared with TAVI.[8] These findings emphasize the need for long-term, randomized studies of the use of TAVI versus SAVR in bicuspid patients.

Surgical valve replacement has historically been the treatment of choice for bicuspid aortic stenosis and remains the first-line therapy for many patients with this condition. This study included bicuspid patients with ages ranging between 21to 85 years and was inclusive of those with aortic stenosis, aortic regurgitation, and mixed valve disease. Although use of bioprosthetic valves in younger patients is associated with an increased risk of SVD and calcification, the KM rate of SVD/SHD requiring reintervention at 7 years achieved with the Avalus valve was low and similar between the bicuspid and tricuspid cohorts (1.3 [0.3-5.2%] vs 1.1 [0.5-2.8%]; P=0.79). Differences in all-cause mortality, valve-related mortality, and NSVD were observed between cohorts, but KM rates of other valve-related safety events were similar through 7 years. Furthermore, regurgitation rates, and functional status were excellent and stable in both cohorts throughout follow-up.

Several studies have reported long-term survival after SAVR in bicuspid patients compared to tricuspid patients, but few have reported hemodynamic outcomes. Bavaria et al.[22] looked at SAVR outcomes in bicuspid (N=214) patients after implantation with the PERIMOUNT Magna EASE valve with Resilia tissue leaflets 5 years post-operatively and found similar rates of survival (95.9% vs 95%), freedom from reintervention (98.5% vs 96.2%), freedom from explant (98.5% vs 96.5%), paravalvular leak ≥mild (0.7% vs 0.4%), and transvalvular regurgitation ≥mild (2.9% vs 2.5%) as found in this study, respectively. Hemodynamic performance at 5 years was similar and stable in the bicuspid cohorts of both the COMMENCE and PERIGON studies, with mean aortic gradients of 11.5±6.4 vs. 13.5±5.3 and EOAs of 1.66±0.56 vs. 2.1±0.64, respectively. The excellent and stable hemodynamics and low reintervention rates in BAV patients may be due, in part, to anatomical differences predisposing BAV patients to larger valve sizes (Table S1 and S2),12 which can result in improved hemodynamic performance and low reintervention rates.[23]

These results are encouraging for use of the Avalus bioprosthesis in congenital bicuspid patients. Although bicuspid patients were younger, valve performance and clinical events were similar after propensity score adjustment to the tricuspid cohort.

Limitations

The echocardiogram follow-up in this analysis is not annual and does not include baseline data, so comparisons at baseline were not possible. But echocardiograms taken at the 3- to 6-month, 1-, 5-, and 7-year visits still provide valuable insights into ongoing hemodynamic performance. Echocardiographic data for KM estimates of death and valve-related safety events (Table 2), including PVL, are reported by the site and adjudicated by the clinical events committee. In contrast, the degree of regurgitation at each time point depicted in Figure 2 is assessed by the Echocardiography Core Lab. This discrepancy in reporting accounts, in part, for the similar and low PVL rates between cohorts in Figure 2 and the higher KM estimates of NSVD in the BAV cohort in Table 2. Subanalyses of congenital bicuspid valve patients would have further added to our clinical understanding of SAVR use in these patients; however, this could not be done because Sievers subtype and details on calcification burden were not collected at baseline, and only a small number of bicuspid patients had aortic regurgitation. While the SVD endpoint is based on the traditional surgical definition, which poses challenges given the increased use of valve-in-valve procedures, it remains a valid comparison point alongside studies using longitudinal hemodynamic data criteria.

CONCLUSIONS

Although patients with a congenital bicuspid valve are younger and at higher risk of bioprosthetic valve SVD and calcification, SAVR with the Avalus bioprosthesis yielded excellent 7-year outcomes for patients with either a congenital bicuspid or tricuspid valve. Hemodynamic performance and reintervention rates were similar between cohorts with low rates of other valve-related adverse events. These results demonstrate that the Avalus valve is appropriate for either valve etiology and highlight the durability of the Avalus valve in younger patients with a bicuspid valve.

Conflict of interest

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