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Original Research

Propensity-Matched Outcomes Comparing TAVR in Bicuspid vs Surgery in Tricuspid Aortic Valve Stenosis

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ABSTRACT

Objective: To compare 1-year outcomes in patients at low surgical risk with bicuspid aortic valve stenosis (AS) following transcatheter aortic valve replacement (TAVR) and low-risk patients with tricuspid AS following surgical aortic valve replacement (SAVR).

Background: The pivotal randomized, prospective, multicenter TAVR trials compared TAVR vs SAVR in patients with tricuspid AS. No such trials exist for bicuspid AS.

Methods: The Low Risk Bicuspid Study is a prospective, single-arm, TAVR trial that enrolled 150 patients from 25 sites in the United States. A screening committee confirmed bicuspid anatomy and valve classification based on computed tomography using the Sievers classification. Annular measurements guided valve sizing. These patients were propensity-matched to the SAVR patients in the randomized Evolut Low Risk Trial using 1:1 5-to-1-digit Greedy method, resulting in 144 matched pairs. For both trials, an independent clinical events committee adjudicated all serious adverse events, and the same independent core laboratory assessed all echocardiograms.

Results: The 1-year composite of death, disabling stroke, or aortic valve–related rehospitalization for bicuspid TAVR vs tricuspid SAVR was 6 (4.2%) vs 6 (4.2%) ($P = .99$). The effective orifice area (2.2 ± 0.7 cm^2 vs 2.0 ± 0.6 cm^2) was larger and the valve gradient was lower (8.7 ± 3.9 mm Hg vs 11.2 ± 4.7 mm Hg) in the TAVR group at 1 year (both $P < .001$). Moderate/severe aortic regurgitation was present in 1 TAVR and 2 SAVR patients (0.8% vs 1.6%; $P > .99$).

Conclusions: In this select group of low-risk bicuspid patients, in the short-term follow-up, TAVR appears to have similar outcomes to those seen in comparable low-risk tricuspid patients undergoing SAVR.

Introduction

Transcatheter aortic valve replacement (TAVR) has become an alternative to surgery in patients with a tricuspid aortic valve and severe acquired calcific stenosis regardless of the surgical risk.[1-6] Patients with a congenital bicuspid aortic valve were excluded in the principal randomized trials. The incidence of bicuspid aortic valve is uncommon (1%-2% of the population), yet the abnormal variants in anatomical structure can lead to earlier valve deterioration than that seen in atherosclerotic tricuspid aortic valve stenosis.[7]

The advent of TAVR led to the concept of a multidisciplinary heart team to assess patients with advanced aortic valve stenosis to determine risk of early surgical mortality and morbidity and develop a lifetime management treatment plan, which could include both

Abbreviations: AR, aortic valve regurgitation; AS, aortic valve stenosis; CT, computed tomographic; EOA, effective orifice area; KCCQ, Kansas City Cardiomyopathy Questionnaire; NYHA, New York Heart Association; SAVR, surgical aortic valve replacement; TAVR, transcatheter aortic valve replacement.

Keywords: aortic stenosis; bicuspid aortic valve; supra-annular; transcatheter aortic valve replacement.

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transcatheter and surgical options.[8,9] These multidisciplinary heart teams are now often faced with assessing patients with bicuspid aortic valve stenosis (AS). Recent single-arm observational and retrospective studies have evaluated TAVR in bicuspid AS and have shown promising early results.[10-14] No randomized trials have been performed in patients with congenital bicuspid aortic valve stenosis that compare transcatheter with surgical aortic valve replacement (SAVR).

In the absence of randomized trials, we accessed data from existing low-risk trials and compared outcomes in patients with bicuspid AS who underwent TAVR in the Low Risk Bicuspid Study[11] to propensity-matched patients with tricuspid AS from the surgical arm of the Evolut Low Risk trial.[4] Our goal is to glean additional information to aid in lifetime management planning for patients with severe bicuspid AS.

Methods

Study design

The Low Risk Bicuspid Study (NCT03635424) is a multicenter, prospective, single-arm study that enrolled patients from December 2018 to October 2019 at 25 sites in the United States. These sites also participated in the multicenter, prospective, randomized Evolut Low Risk Trial (NCT02701283), which enrolled patients from March 2016 to November 2018 and compared TAVR to SAVR in low-surgical-risk patients with tricuspid valve AS. Details of both studies have been published.[4,11] For each study, the institutional review boards approved the study protocols and each patient provided written, informed consent. The trials were conducted in accordance with the International Conference on Harmonization, Good Clinical Practice Guidelines, and the Declaration of Helsinki. Follow-up is planned through 10 years. In-person clinical assessment, review of adverse events, and transthoracic echo are planned for 2, 3, 4, 5, 7, and 10 years. Telephone visits to review adverse events are planned for 6, 8, and 9 years. The decision to submit the manuscript was that of the first author (G.M.D.).

Study procedures

Patient eligibility into the Low Risk Bicuspid Study and the Evolut Low Risk Trial was reviewed by the same national screening committee comprising interventional cardiologists and cardiovascular surgeons. Computed tomography (CT) studies were reviewed to confirm appropriate access anatomy, valve sizing, and native aortic valve type. The bicuspid patients were categorized using the Sievers classification, and no Sievers classification or subtype of a classification was excluded from the trial.[15] The same independent clinical events committee adjudicated all deaths and end point–related adverse events for both studies. All echocardiograms were assessed by the same independent core laboratory (Mayo Clinic, Rochester, Minnesota). Patients were evaluated at baseline, discharge, 30 days, and 1 year and will be followed annually for 10 years.

Patients

The Low-Risk Bicuspid Study and the Evolut Low Risk Trial had the same patient inclusion and exclusion criteria (Supplemental Table S1), except for criteria specifically related to aortic valve morphology, as noted in the table. Specifically, the Low Risk Bicuspid Study also allowed patients as young as 60 years of age, required an ascending aortic diameter of $\leq$4.5 cm, and included all bicuspid valve morphologies.[11,16] Because the volume of calcium on the bicuspid valve leaflets was not an exclusion criterion, no patient was excluded from the trial for calcium volume or position of calcium on the bicuspid aortic valve. Supplemental Table S2 defines all anatomic bicuspid valve types and quantifies the number of patients with each valve type. Details of the screening process and anatomical reasons patients were excluded from the bicuspid study have been published.[11]

Eligible patients for both studies had either symptomatic severe AS or met American Heart Association/American College of Cardiology class IIa criteria for asymptomatic severe AS.[17] A predicted risk of 30-day surgical mortality less than 3.0% was required based on local multidisciplinary heart team assessment. Patients with bicuspid AS who underwent TAVR were propensity matched to patients with tricuspid AS who underwent SAVR in the Evolut Low Risk Trial.[4] Because there are no randomized trials comparing TAVR vs SAVR in patients with bicuspid AS, our goal was to compare outcomes following TAVR in low-risk patients with bicuspid AS to low-risk patients with tricuspid AS who underwent SAVR under conditions that eliminated as many variables and selection biases between the 2 groups as possible.

Valve selection and implant technique

All patients in the Low Risk Bicuspid Study underwent TAVR with a self-expanding supra-annular Evolut R or Evolut PRO valve (Medtronic). The type of surgical bioprosthetic valve for patients with tricuspid AS in the SAVR group was determined at the discretion of the operating surgeon. All surgical valves were sized at the time of implantation using the surgical sizer provided by the manufacturer for the selected valve type. Surgical access site, bioprosthetic valve types, and sizes for the tricuspid SAVR group are listed in Supplemental Table S3.

End points

The primary outcome for this post hoc analysis is the composite of death, disabling stroke, or aortic valve–related hospitalization. Secondary outcomes include the composite of death or disabling stroke, death, stroke (disabling and nondisabling), repeat hospitalization for aortic valve disease, major bleeding, pacemaker implantation, prosthetic valve endocarditis, clinical valve thrombosis, and valve–related dysfunction requiring repeat procedure at 1 year. Valve hemodynamics to 1 year are also reported. Quality of life up to 1 year is reported as New York Heart Association functional class and the Kansas City Cardiomyopathy Questionnaire score. Prosthesis-patient mismatch was based on the Valve Academic Research Consortium-3 definition[18]; an indexed mean effective orifice area (EOA) of $>$0.65 and $\leq$0.85 cm^2/m^2 for patients with a body mass index (BMI) of $<$30 kg/m^2 or $>$0.55 and $\leq$0.70 cm^2/m^2 for patients with a BMI of $\geq$30 kg/m^2 as moderate and severe prosthesis-patient mismatch as an indexed EOA of $\leq$0.65 cm^2/m^2 for a BMI of $<$30 kg/m^2 and $\leq$0.55 cm^2/m^2 for patients with a BMI of $\geq$30 kg/m^2.

All patients underwent CT imaging before the procedure, which was centrally assessed (Medtronic). Comprehensive quantitative calcium analyses were derived from the semiautomated calcium scoring tool in 3mensio software system (Research Version 8.1, Pie Medical). The segmentation threshold was set to the mode of Houndsfield units in contrast-enhanced blood in the aortic root plus 200 Houndsfield units for each patient. Total calcium volume was the sum of the aortic root at the valve basal plane to the top of the leaflets and the basal plane to 10 mm into the left ventricular outflow tract.

Statistical methods

The primary analysis cohort comprised patients who underwent an attempted TAVR or SAVR. Echocardiographic outcomes are reported for patients with an implanted transcatheter or surgical valve. Continuous variables are reported as mean $\pm$ SD and were compared using the *t* test. Categorical variables are presented as frequencies and percentages.

Ordinal data were compared using the Cochran-Mantel-Haenszel test, and categorical data were compared using the Fisher exact test or χ^2 test. Propensity score matching (1:1) was performed using a 5-to-1-digit Greedy match to patients with tricuspid AS who underwent SAVR in the Evolut Low Risk Trial. Matching was based on age (≤70 vs >70 years), sex, body surface area (≤1.9 m^2 vs >1.9 m^2), Society of Thoracic Surgeons (STS) score (≤1.3% vs >1.3%), diabetes mellitus, cerebrovascular disease, atrial fibrillation or flutter, prior myocardial infarction, aortic annular perimeter (≤80 mm vs >80 mm) and total calcium volume (≤735 mm^3 vs >735 mm^3). The categorical cutoffs were based on the median values in the bicuspid patient cohort. Absolute standardized differences were calculated for the baseline characteristics to evaluate the balance before and after matching, with values of <0.10 used to indicate balance. Adverse events at 1 year are reported as Kaplan-Meier estimates and compared using the log-rank test. No adjustments were made for multiple comparisons. All statistical analyses were performed using SAS software, version 9.4 (SAS Institute).

Results

Patients

A total of 150 patients underwent attempted TAVR using the Evolut or Evolut PRO valve in the Low Risk Bicuspid Study and 684 patients underwent SAVR with a bioprosthetic surgical aortic valve in the Evolut Low Risk Trial. Propensity matching resulted in 144 matched pairs (Figure 1).

There were significant differences in baseline characteristics in the unmatched bicuspid TAVR and tricuspid SAVR groups (Table 1). Compared with the tricuspid AS SAVR group, the bicuspid AS TAVR patients were younger (70.3 ± 5.5 vs 73.7 ± 5.9 years; $P < .001$), more often female (48.0% vs 34.1%; $P = .001$), had a lower STS risk score (1.4% ± 0.6% vs 1.9% ± 0.7%; $P < .001$), and had less atrial fibrillation or flutter (7.3% vs 14.4%; $P = .02$). After matching, the mean STS score was significantly lower in the bicuspid AS group (1.4% ± 0.6% vs 1.6% ± 0.7%; $P = .002$).

Clinical outcomes at 30 days

Clinical outcomes at 30 days for the adjusted cohort are shown in Table 2. There were no significant differences in any serious adverse event rates between the bicuspid TAVR group and tricuspid SAVR group. The primary composite end point of all-cause mortality, disabling stroke, or aortic valve–related rehospitalization for the bicuspid TAVR vs tricuspid SAVR groups was 2.8% vs 3.5% ($P = .74$). At 30 days, 1 patient in the bicuspid TAVR group died, and no patients in the tricuspid SAVR group died (0.7% vs 0.0%; $P = .32$). The disabling stroke rate was 0.7% vs 1.4% ($P = .56$), and repeat aortic valve–related hospitalization occurred in 3 patients (2.1%) in each group. More patients in the TAVR group received a pacemaker (15.7% vs 6.4%; $P = .01$), and more patients in the SAVR group had acute kidney injury (8.3% vs 2.1%; $P = .02$).

Clinical outcomes at 1 year

From 30 days to 1 year, there were no additional deaths in either group; there was 1 additional stroke in the tricuspid SAVR group, and there were 2 additional rehospitalizations in the bicuspid TAVR group and no additional rehospitalizations in the tricuspid SAVR group (Table 2). The composite of death, disabling stroke, or aortic valve–related hospitalization was 4.2% in each group. New permanent pacemaker implantation at 1 year was 17.9% in the TAVR group and 7.2% in the SAVR group ($P = .006$).

Valve performance

The EOA and aortic valve gradient are shown in Figure 2. The EOA was significantly larger for patients in the bicuspid TAVR group compared with that for the tricuspid SAVR group at 30 days (2.3 ± 0.7 vs 2.0 ± 0.6 cm^2; $P < .001$) and 1 year (2.2 ± 0.7 vs 2.0 ± 0.6 cm^2; $P < .001$). Significant differences in the mean gradient between the TAVR and SAVR groups were also seen at 30 days (7.7 ± 3.7 vs 10.4 ± 4.2 mm Hg; $P < .001$) and 1 year (8.7 ± 3.9 vs 11.2 ± 4.7 mm Hg; $P < .005$). There were 2 patients in the TAVR group (1.6%) and 7 patients (5.4%) in the SAVR group with a mean gradient of >20 mm Hg at 1 year ($P = .17$).

As shown in Figure 3A, the overall severity of aortic regurgitation (AR) was significantly worse in the bicuspid TAVR group than in the tricuspid SAVR group at 30 days ($P < .001$) and 1 year ($P = .01$), driven by the amount of mild AR. There were no patients in either group with more than mild AR at 30 days. At 1 year, there was 1 patient (0.8%) in the TAVR group and 2 patients (1.6%) in the SAVR group ($P > .99$) with more than mild AR. There were significant differences in the proportion of patients who had changes in the severity of AR from 30 days to 1 year

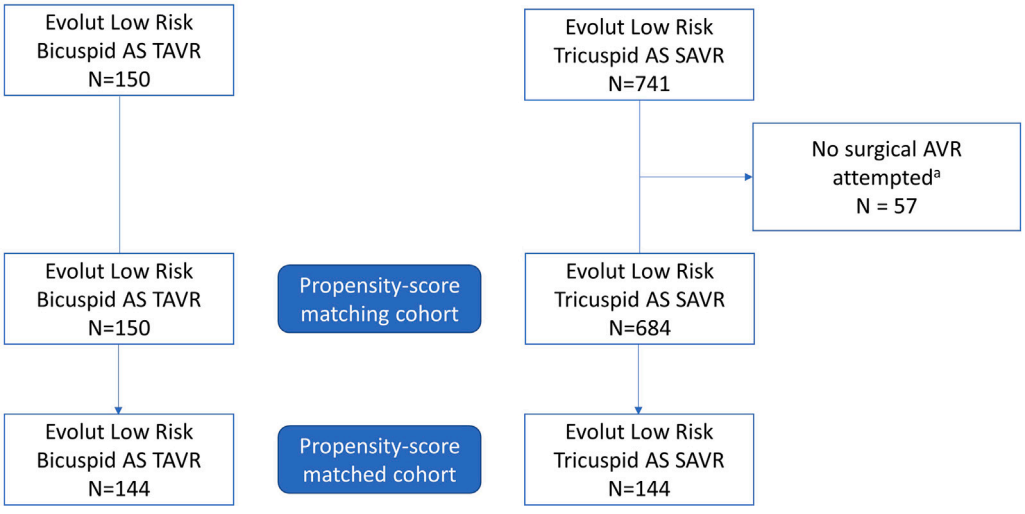


Figure 1.
Patient flow. All 150 patients from the Low Risk Bicuspid Study were propensity matched with patients in the surgical aortic valve replacement (SAVR) arm of the Evolut Low Risk Trial. [a]After randomization to SAVR, 54 patients did not undergo AVR, and 3 patients underwent transcatheter aortic valve replacement (TAVR). AS, aortic stenosis.

Table 1. Baseline characteristics of the unadjusted and adjusted patient cohorts

Characteristic	Unadjusted				Adjusted			
	Bicuspid TAVR n = 150	Tricuspid SAVR n = 684	*P*	ASD	Bicuspid TAVR n = 144	Tricuspid SAVR n = 144	*P*	ASD
Age, y	70.3 ± 5.5	73.7 ± 5.9	<.001	.58	70.5 ± 5.5	70.8 ± 6.5	.65	.05
Body surface area, m^2	1.9 ± 0.2	2.0 ± 0.2	.01	.23	2.0 ± 0.2	2.0 ± 0.2	.66	.05
Female	72 (48.0)	233 (34.1)	.001	.29	66 (45.8)	68 (47.2)	.81	.03
STS score, %	1.4 ± 0.6	1.9 ± 0.7	<.001	.83	1.4 ± 0.6	1.6 ± 0.7	.002	.38
New York Heart Association class			.31				.20	
I	3 (2.0)	63 (9.2)	–	–	3 (2.1)	17 (11.8)	–	–
II	106 (70.7)	428 (62.6)	–	–	102 (70.8)	88 (61.1)	–	–
III	40 (26.7)	190 (27.8)	–	–	38 (26.4)	39 (27.1)	–	–
IV	1 (0.7)	3 (0.4)	–	–	1 (0.7)	0 (0.0)	–	–
Diabetes mellitus	37 (24.7)	209 (30.6)	.15	.13	35 (24.3)	32 (22.2)	.68	.05
Hypertension	112 (74.7)	563 (82.4)	.03	.19	108 (75.0)	112 (78.3)	.51	.08
Chronic lung disease/COPD	26 (17.7)	118 (18.0)	.93	.009	25 (17.7)	23 (16.5)	.79	.03
Peripheral arterial disease	14 (9.3)	56 (8.2)	.65	.04	14 (9.7)	10 (6.9)	.39	.10
Cerebrovascular disease	10 (6.7)	82 (12.0)	.06	.18	10 (6.9)	12 (8.3)	.66	.052
SYNTAX I score[a]	1.1 ± 2.9	2.1 ± 3.9	<.001	.30	1.1 ± 2.9	1.4 ± 3.0	.43	.09
Previous CABG	2 (1.3)	14 (2.0)	.75	.06	2 (1.4)	1 (0.7)	>.99	.07
Previous PCI	11 (7.3)	88 (12.9)	.06	.18	11 (7.6)	13 (9.0)	.67	.05
Previous myocardial infarction	6 (4.0)	33 (4.8)	.67	.04	6 (4.2)	6 (4.2)	>.99	.00
Atrial fibrillation or flutter	11 (7.3)	98 (14.4)	.02	.23	11 (7.6)	7 (4.9)	.33	.12
Pre-existing pacemaker or implanted defibrillator	4 (2.7)	26 (3.8)	.63	.07	4 (2.8)	4 (2.8)	>.99	.00
LV ejection fraction[b,c], %	63.5 ± 8.3	61.9 ± 7.7	.03	.19	63.3 ± 8.4	61.8 ± 6.7	.10	.20
Mean AV area[c], cm^2	0.8 ± 0.2	0.8 ± 0.2	.02	.22	0.8 ± 0.2	0.8 ± 0.2	.48	.08
Mean AV gradient[c], mm Hg	49.9 ± 15.5	46.5 ± 12.2	.01	.24	49.3 ± 15.1	48.1 ± 12.3	.44	.09
Aortic annulus diameter[d], mm	25.2 ± 2.5	25.1 ± 2.3	.52	.06	25.3 ± 2.5	25.0 ± 2.4	.41	.10
Total calcium volume, mm^3	855.3 ± 580.2	772.8 ± 528.5	.09	.15	849.2 ± 584.6	833.9 ± 594.0	.83	.03

Data are presented as means ± SD or number (percentage).
ASD, absolute standardized difference; AV, aortic valve; CABG, coronary artery bypass grafting; COPD, chronic obstructive pulmonary disease; LV, left ventricular; PCI, percutaneous coronary intervention; SAVR, surgical aortic valve replacement; STS, Society of Thoracic Surgeons, TAVR, transcatheter aortic valve replacement.
[a] Synergy Between PCI With Taxus and Cardiac Surgery (SYNTAX) score is a measure of the severity and extent of coronary artery disease. [b] By visual estimate. [c] Site reported. [d] Perimeter-derived.

between the groups (Figure 3B). From 30 days to 1 year, 43 bicuspid TAVR patients (34.1%) compared with 7 tricuspid SAVR patients (6.5%) saw improvement in the severity of AR, whereas 7 bicuspid TAVR (5.6%) and 24 tricuspid SAVR (19.4%) patients experienced worsening in the severity of AR.

Quality of life

The Kansas City Cardiomyopathy Questionnaire overall summary score is shown in Figure 4. The change from baseline was significantly better in the TAVR than SAVR group at 30 days ($P < .001$) but showed no difference at 1 year ($P = .49$). The New York Heart Association class showed similar improvement from baseline by increasing at least 1 class in 84.3% of patients in the bicuspid TAVR group and 80.9% of patients in the tricuspid SAVR group at 1 year.

Discussion

The results of this study show that TAVR in patients with congenital bicuspid severe AS had similar clinical outcomes and superior forward flow hemodynamics at 1 year compared with SAVR in the more prevalent calcific acquired tricuspid AS (Central Illustration).

Similar to all the previous prospective randomized controlled trials comparing TAVR with SAVR, the mild AR rate was higher in the TAVR group than in the SAVR group. We do not believe this difference was associated with bicuspid valve morphology because the previously published paper comparing 1-year outcomes between bicuspid and tricuspid valves receiving TAVR showed no significant difference in AR based on valve morphology.[16] Rather than an anatomical effect, we feel the difference in mild AR is most likely a treatment effect, similarly seen in other reports of randomized trials of TAVR vs SAVR. With respect to the need for new permanent pacemaker implantation, this study once again shows the disparity between a self-expanding TAVR and a surgical valve and emphasizes the need for employing the cusp overlap technique in contemporary practice.[19]

Given the controversy in commercial TAVR practice concerning best measurement for bicuspid TAVR sizing (annular perimeter size, commissure to commissure dimension, or perimeter/area somewhere superior to the annulus), the bicuspid trial standardized that all TAVR sizing was determined using annular perimeter. This sizing was verified by the screening committee for all patients in the study, thereby eliminating a variable from the study that could have a significant impact for diminishing the effect of the valve morphology as the main factor studied. Having the annulus perimeter as the site for TAVR sizing in the Low Risk Bicuspid study also allowed for better propensity matching between the 2 study groups because the Evolut Low Risk trial also used annular perimeter for sizing of the TAVR. A nonrandomized registry study comparing in-hospital outcomes of bicuspid AS patients receiving TAVR vs SAVR reported similar in-hospital mortality rates between groups.[20] However, this study was neither prospective nor controlled, whereas our study allowed the benefit of using 2 prospective trials, including one randomized controlled trial.

Short- and mid-term clinical outcomes following bioprosthetic SAVR in patients with bicuspid vs tricuspid AS are similar up to 5 years, after which mortality increases significantly in the patients with tricuspid AS, and the reoperation rate increases significantly in the patients with bicuspid AS.[21-23] The patients with bicuspid AS are younger, have less associated cardiovascular risk factors, and often outlive their bioprosthetic devices.[21-23] There is no reason to assume that patients with bicuspid AS receiving bioprosthetic transcatheter valves will not outlive

Table 2. Clinical outcomes at 30 days and 1 year for the matched patient cohort.

	30 d			1 y		
	Bicuspid TAVR N = 144	Tricuspid SAVR N = 144	*P*	Bicuspid TAVR N = 144	Tricuspid SAVR N = 144	*P*
All-cause mortality, disabling stroke, or aortic valve–related rehospitalization	4 (2.8)	5 (3.5)	.74	6 (4.2)	6 (4.2)	.99
All-cause mortality or disabling stroke	2 (1.4)	2 (1.4)	>.99	2 (1.4)	3 (2.1)	.65
All-cause mortality	1 (0.7)	0 (0.0)	.32	1 (0.7)	0 (0.0)	.32
Cardiovascular mortality	1 (0.7)	0 (0.0)	.32	1 (0.7)	0 (0.0)	.32
Any stroke	6 (4.2)	2 (1.4)	.15	6 (4.2)	3 (2.1)	.31
Disabling stroke	1 (0.7)	2 (1.4)	.56	1 (0.7)	3 (2.1)	.31
Nondisabling stroke	5 (3.5)	0 (0.0)	.02	5 (3.5)	0 (0.0)	.02
Myocardial infarction	1 (0.7)	0 (0.0)	.32	2 (1.4)	0 (0.0)	.16
Major bleeding	2 (1.4)	5 (3.5)	.25	3 (2.1)	6 (4.2)	.31
Acute kidney injury[a]	3 (2.1)	12 (8.3)	.02	3 (2.1)	12 (8.3)	.02
Clinical valve thrombosis	1 (0.7)	0 (0.0)	.32	2 (1.4)	0 (0.0)	.16
Valve endocarditis	0 (0.0)	0 (0.0)	NA	1 (0.7)	0 (0.0)	.32
Valve-related dysfunction requiring repeat procedure	0 (0.0)	1 (0.7)	.32	1 (0.7)	1 (0.7)	>.99
Permanent pacemaker implantation[b]	22 (15.3)	9 (6.2)	.01	25 (17.4)	10 (7.0)	.007
Permanent pacemaker implantation[c]	22 (15.7)	9 (6.4)	.01	25 (17.9)	10 (7.2)	.006
Aortic valve–related rehospitalization	3 (2.1)	3 (2.1)	.99	5 (3.5)	3 (2.1)	.48
Coronary artery obstruction	1 (0.7)	0 (0.0)	.32	1 (0.7)	0 (0.0)	.32
Conversion to open surgery	1 (0.7)	0 (0.0)	.32	1 (0.7)	0 (0.0)	.32
Mean AV gradient >20 mm Hg[d]	2 (1.4)	6 (4.4)	.17	2 (1.6)	7 (5.4)	.17
Prosthesis patient mismatch[d,e]	–	–	.45	–	–	.09
None	111 (86.7)	99 (83.2)	–	99 (90.0)	94 (82.5)	–
Moderate	13 (10.2)	16 (13.4)	–	9 (8.2)	13 (11.4)	–
Severe	4 (3.1)	4 (3.4)	–	2 (1.8)	7 (6.1)	–

Data are presented as number of patients with events (Kaplan-Meier estimate) except for the valve gradient and prosthesis-patient mismatch data, which are presented as number of patients (percentage).
AV, aortic valve; NA, not applicable; SAVR, surgical aortic valve replacement; TAVR, transcatheter aortic valve replacement.
[a] Acute kidney injury is only reported up to 7 days postprocedure. [b] Including patients with a pacemaker at baseline. [c] Excluding patients with a pacemaker at baseline. [d] Echocardiographic data provided for patients with a successful implant. [e] Per Valve Academic Research Consortium-3.[18]

their device similar to that observed in the surgical patient population. The decision about type of index procedure for bicuspid AS revolves around the differences or similarities in durability between the transcatheter and surgical bioprosthetic valves and the ability to perform TAV-in-TAV as a second procedure. The likelihood of a second procedure and exposure to the associated risks is more likely in patients with bicuspid AS. In addition, patients with bicuspid AS without evidence of clinically significant aortopathy undergoing surgical AVR can

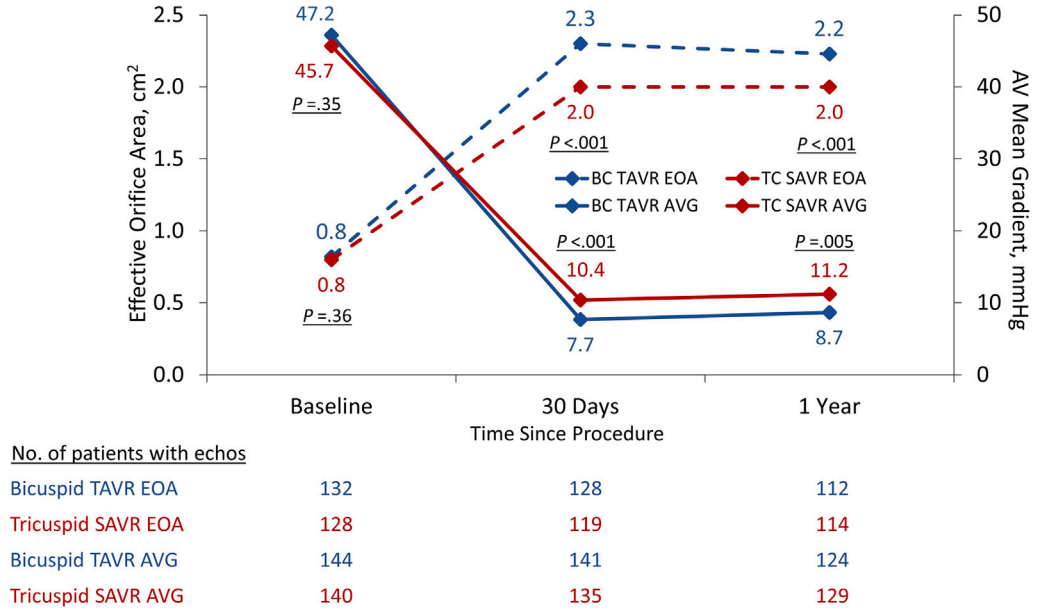


Figure 2.
Valve hemodynamics. Mean effective valve orifice (EOA) and mean aortic valve gradient (AVG) at 30 days and 1 year for the matched patients in the bicuspid (BC) transcatheter aortic valve replacement (TAVR) and tricuspid (TC) surgical aortic valve replacement (SAVR) groups. All echocardiographic results are based on independent core laboratory assessment. *P* value based on the Fisher exact or χ^2 test.

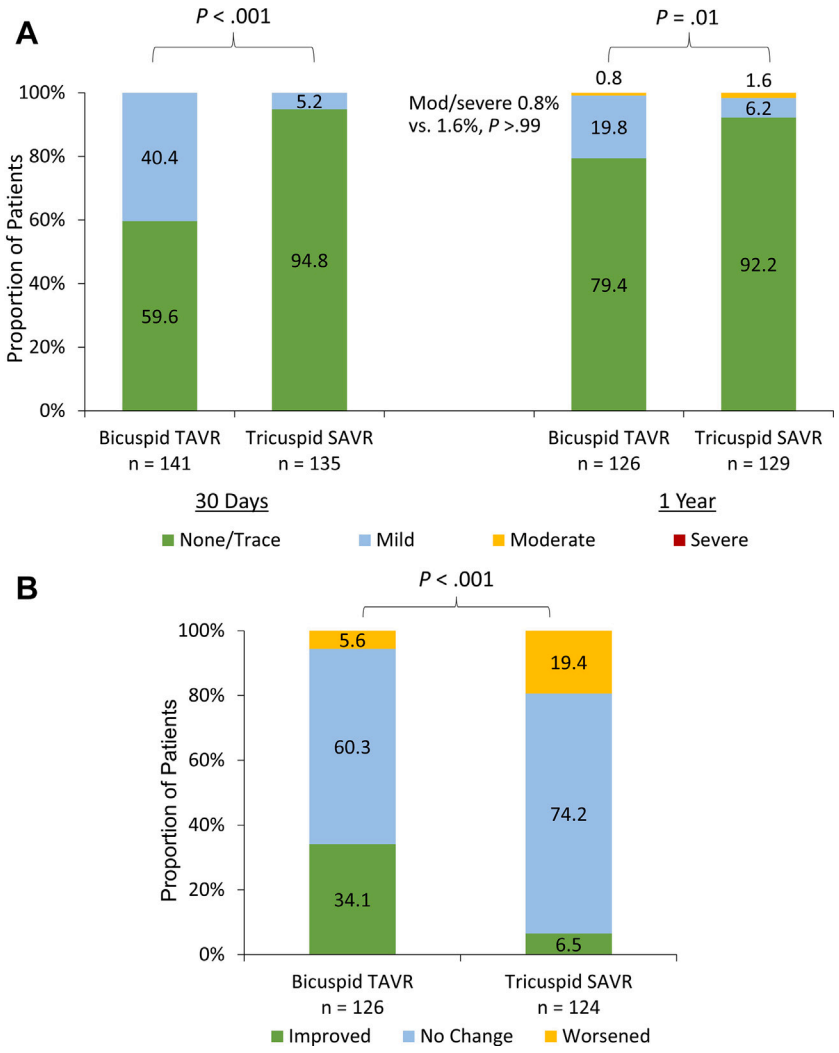


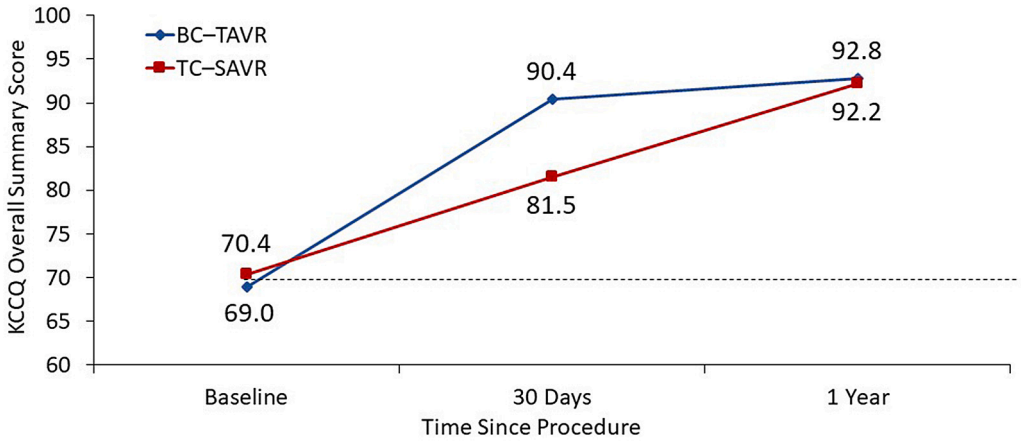
Figure 3.
Total aortic regurgitation. (**A**) Aortic regurgitation (AR) at 30 days and 1 year for the matched patients in the bicuspid transcatheter aortic valve replacement (TAVR) and tricuspid surgical aortic valve replacement (SAVR) groups; (**B**) changes in AR from 1 month to 1 year. All echocardiographic results are based on independent core laboratory assessment. Mild or more AR was compared using the Fisher exact or χ^2 test. Ordinal data were compared using the Cochran-Mantel-Haenszel test.

still develop an aortic aneurysm over time requiring reoperation, which adds to the challenges facing multidisciplinary heart teams when deciding lifetime management of these patients.

The gold standard of randomized, prospective, multicenter trials was used to compare TAVR in patients with severe acquired calcific AS to the standard of care of medical therapy in extreme-risk patients[24] and to SAVR in patients at other risk levels based on the STS score and other factors.[1-6] The short- and mid-term outcomes for all these trials demonstrated that TAVR was noninferior or superior to medical therapy or SAVR.[1-6] Data are still being collected in many of these trials and will provide 10-year outcomes upon completion. These long-term trials will provide solid scientific information to allow physicians to make evidence-based decisions when trying to develop a specific lifetime management plan for each patient with tricuspid AS. These trials demonstrated an excellent scientific approach to answer the question concerning TAVR viability as a therapeutic approach to treat severe symptomatic AS in the TAV patient population.

The trials that evaluated the efficacy of TAVR in patients with severe congenital bicuspid AS did not include a randomization scheme, such as comparing TAVR to the accepted gold standard of SAVR treatment in this patient population. Instead, the use of TAVR in bicuspid patients has been based on small prospective studies or retrospective propensity-matched comparisons of TAVR in patients with bicuspid vs tricuspid severe AS.[11-14,25,26] While it is encouraging that TAVR in bicuspid AS shows similar performance as TAVR in tricuspid AS with respect to short-term outcomes, there are important etiological, morphologic, and anatomical differences between tricuspid and bicuspid valves that could impact the mid-term and long-term outcomes between TAVR in the 2 groups. Have we performed the best studies to justify the use of TAVR as the initial procedure in young low-risk bicuspid AS patients?

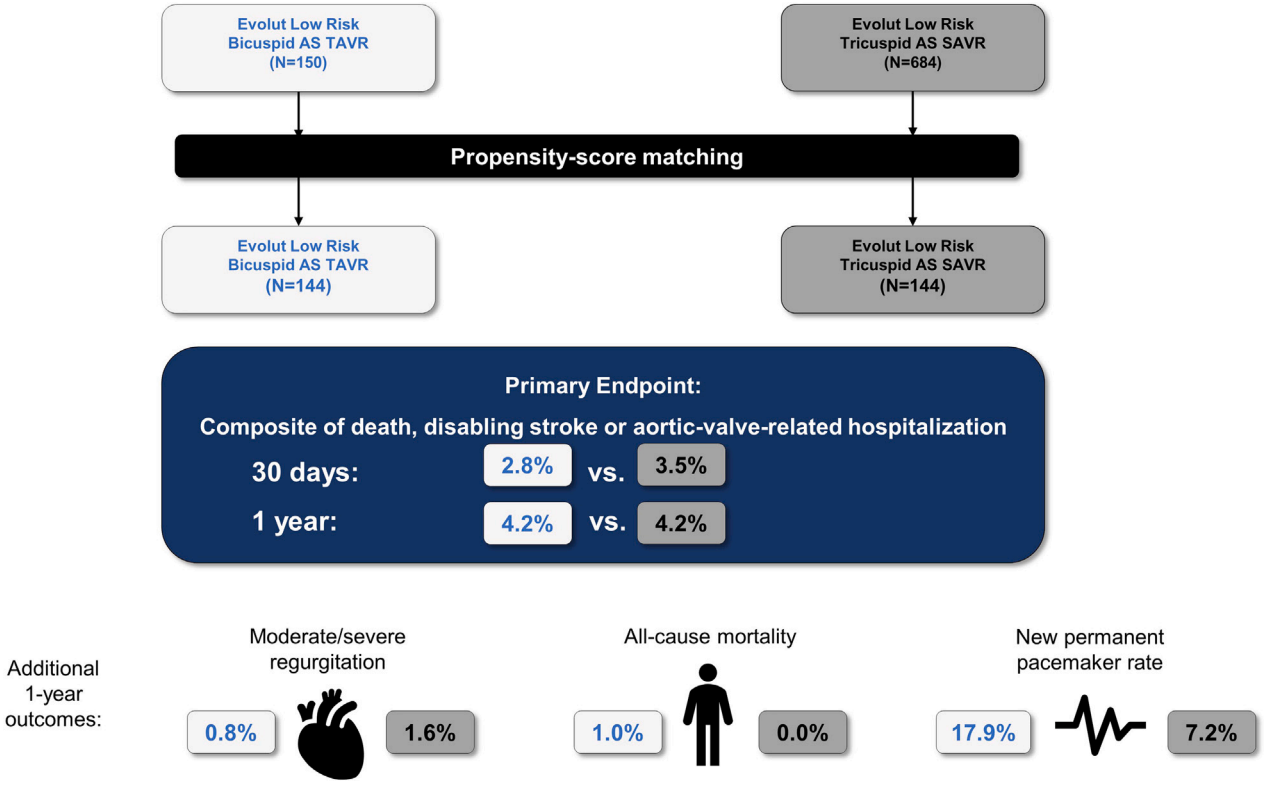
Bicuspid aortic valve pathology occurs at a younger age, more often in men, and can have multiple anatomical variants, as described by Sievers and Schmidtke.[15] There are also associated physiological and anatomical conditions that vary between patients with congenital bicuspid AS and acquired tricuspid AS. In patients with bicuspid AS, there is a spectrum that ranges from hypoplastic left heart syndrome to isolated aortic stenosis to aortic stenosis associated with aortopathy. Aortopathy can occur in the root, ascending aorta, aortic arch including arch vessels (bovine arch), or in a combination of any of the above locations and in association with coarctation of the aorta. Bicuspid aortic valve pathology is also associated with Turner syndrome.[27,28] Acquired tricuspid AS is more commonly associated with its own cadre of pathologies at a much higher incidence than in bicuspid aortic valve disease, such as coronary artery disease, peripheral vascular disease, renal



	Change from Baseline	
Bicuspid TAVR	21.4 ± 17.4	23.7 ± 20.0
Tricuspid SAVR	11.0 ± 23.6	22.0 ± 20.2
P Value	< .001	.49

Figure 4.
Quality of life. Kansas City Cardiomyopathy Questionnaire (KCCQ) overall summary scores at baseline, 30 days, and 1 year. The dashed line represents the baseline values for contrast. BC, bicuspid; SAVR, surgical aortic valve replacement; TAVR, transcatheter aortic valve replacement; TC, tricuspid.

disease, cerebrovascular disease, myocardial infarction, hypertension, diabetes, and previous interventions for coronary or peripheral artery disease. The assumption that bicuspid and tricuspid AS, which are so anatomically and pathologically dissimilar, will have equivalent outcomes with TAVR and SAVR therapy is without merit because there are no scientific data prospectively comparing TAVR in patients with



Central Illustration.
Clinical outcomes in bicuspid transcatheter aortic valve replacement (TAVR) vs tricuspid surgical aortic valve replacement (SAVR) patients. All 150 patients from the Low Risk Bicuspid Study were propensity matched with patients in the SAVR arm of the Evolut Low Risk Trial. Primary composite end point of death, disabling stroke, or aortic valve–related hospitalization was similar at 30 days and 1 year. AS, aortic stenosis.

bicuspid vs tricuspid AS or TAVR vs SAVR in patients with bicuspid AS to make an evidence-based conclusion.[28]

All patients with severe AS should ideally be assessed at their initial presentation for a projected cumulative survival based on their age and overall medical condition to allow for a lifetime management strategy that will provide the least number of procedures, with the lowest amount of cumulative risk for mortality and morbidity and the minimal amount of trauma in their lifetime. To be able to effectively do this for patients with bicuspid aortic valve disease, we need more data and information acquired through benchmark randomized, prospective, multicenter controlled trials.

To our knowledge, our study is the first to examine 2 prospective studies to gain perspective of bicuspid TAVR vs surgery and contributes to the foundation of data and helps identify gaps for multidisciplinary heart team decisions concerning lifetime management for patients with bicuspid AS. The study does show similar rates at 1 year of the composite of death, disabling stroke, or rehospitalization in patients with bicuspid AS undergoing TAVR (4.2%) and in patients with tricuspid AS undergoing SAVR (4.2%). However, we know from the prior surgical data referenced above that these populations will most likely diverge soon because the difference in outcome is due to the disease process and not the valve type used. What this study emphasizes is the lack of rigorous trial data available to make an evidence-based decision for lifetime management in patients with bicuspid AS and the need for a randomized, prospective, multicenter controlled trial comparing TAVR vs bioprosthetic SAVR in the bicuspid AS population.

Limitations

There are many limitations to this study: there were only 150 patients enrolled in the Low Risk Bicuspid Study, and our analysis compares 2 patient populations with vastly different valve anatomy, associated cardiovascular components, and other clinical characteristics. However, propensity matching eliminated many of these factors, allowing a similar subsegment of both populations for short-term comparison. The study also compared a multisite, prospective, controlled registry TAVR trial in patients with bicuspid AS with the SAVR arm of a multisite, randomized, prospective, controlled TAVR vs SAVR trial in patients with tricuspid AS. However, based on the stringent inclusion and exclusion criteria of the Low Risk Bicuspid study, it includes a subsegment of patients with bicuspid AS with similar medical characteristics as patients with tricuspid AS because the same inclusion and exclusion criteria were used for both low-risk trials (Supplemental Table S1). Another limitation is that the trials did not occur simultaneously, yet for comparison, both are prospective trials performed at the same TAVR centers that utilized the same screening committee, the same independent core echo laboratory, and the same CT scan measurement laboratory, and the same independent clinical events committee that adjudicated all deaths and end point–related adverse events for both studies. Given these facts, this is currently the closest possible way to compare TAVR in low-risk bicuspid patients to a similar SAVR cohort of patients using data from prospective trials.

Conclusions

There currently are no strong scientific data to allow physicians to determine the best evidence-based lifetime management strategy for patients with bicuspid AS at the time of their initial presentation. The data in this study are the best available data to try and fill our evidence-based knowledge gap for patients with bicuspid AS. In this specifically enrolled anatomical subset, TAVR for bicuspid disease was clinically equivalent and hemodynamically better than SAVR for tricuspid AS in propensity-matched cohorts at 1 year.

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Declaration of competing interest

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Ethics statement and patient consent

For the Low Risk Bicuspid Study and the Evolut Low Risk Trial, the institutional review boards approved the study protocols and each patient provided written, informed consent. The trials were conducted in accordance with the International Conference on Harmonization, Good Clinical Practice Guidelines, and the Declaration of Helsinki.

Supplementary material

To access the supplementary material accompanying this article, visit the online version of the *Journal of the Society for Cardiovascular Angiography & Interventions* at https://doi.org/10.1016/j.jscai.2022.100525.

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