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Transcatheter Aortic Valve Replacement in Bicuspid Versus Tricuspid Aortic Valves From the STS/ACC TVT Registry

John K. Forrest, MD,[a] Ryan K. Kaple, MD,[a] Basel Ramlawi, MD,[b] Thomas G. Gleason, MD,[c] Christopher U. Meduri, MD, MPH,[d] Steven J. Yakubov, MD,[e] Hasan Jilaihawi, MD,[f] Fang Liu, MD, MS,[g] Michael J. Reardon, MD[h]

ABSTRACT

OBJECTIVES This study sought to compare outcomes in patients with bicuspid versus tricuspid anatomy undergoing transcatheter aortic valve replacement (TAVR).

BACKGROUND TAVR has shown excellent safety and efficacy in patients with tricuspid aortic valve stenosis, but limited data are available on the use of self-expanding valves in patients with bicuspid valves.

METHODS The Society of Thoracic Surgeons/American College of Cardiology TVT Registry was used to analyze patients who underwent TAVR with the Evolut R or Evolut PRO valves. Clinical and echocardiographic outcomes were analyzed through 1-year follow-up.

RESULTS Between July 2015 and September 2018 a total of 932 patients with bicuspid aortic valve stenosis underwent elective TAVR with the self-expanding Evolut R or Evolut PRO valve. These patients were compared with a group of 26,154 patients with tricuspid aortic stenosis who underwent TAVR during that same time period. At baseline, patients with bicuspid valves were younger, had fewer cardiac comorbidities, and had lower Society of Thoracic Surgeons Predicted Risk of Mortality scores (5.3 $\pm$ 4.2% vs. 6.9 $\pm$ 4.8%; $p < 0.001$). To account for these differences, propensity matching was performed, which resulted in 929 matched pairs. Within these match groups, the rates of all-cause mortality at 30 days (2.6% vs. 1.7%; $p = 0.18$) and 1 year (10.4% vs. 12.1%; $p = 0.63$), as well the rate of stroke at 30 days (3.4% vs. 2.7%; $p = 0.41$) and 1 year (3.9% vs. 4.4%; $p = 0.93$), were comparable.

CONCLUSIONS All-cause mortality, stroke, and valve hemodynamics did not differ at 30 days or 1 year between patient groups. In patients at increased surgical risk, TAVR for bicuspid aortic valve stenosis indicates acceptable safety outcomes with low complications rates. (J Am Coll Cardiol Intv 2020;13:1749–59) © 2020 by the American College of Cardiology Foundation.

From the [a]Section of Cardiovascular Medicine, Yale School of Medicine, New Haven, Connecticut; [b]Department of Cardiothoracic Surgery, Valley Health System, Winchester, Virginia; [c]Department of Cardiothoracic Surgery, University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania; [d]Department of Interventional Cardiology, Piedmont Heart Institute, Atlanta, Georgia; [e]Department of Interventional Cardiology, Riverside Methodist-Ohio Health, Columbus, Ohio; [f]Heart Valve Center, New York University Langone Health, New York, New York; [g]Department of Statistics, Medtronic, Minneapolis, Minnesota; and the [h]Department of Cardiothoracic Surgery, Houston Methodist DeBakey Heart and Vascular Center, Houston, Texas. This work received funding from Medtronic. This research was supported by the American College of Cardiology's National Cardiovascular Data Registry. The views expressed in this manuscript represent those of the author(s) and do not necessarily represent the official views of the National Cardiovascular Data Registry or its associated professional societies. Dr. Forrest has received grant support or research contracts and consultant, honoraria, or Speakers Bureau fees from Edwards Lifesciences and Medtronic. Dr. Kaple has served as a speaker for Abbott; and received honoraria from Edwards Lifesciences. Dr. Ramlawi has received grant support, personal fees, and nonfinancial support from Medtronic, LivaNova,

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ABBREVIATIONS AND ACRONYMS

AR = aortic regurgitation

ASD = absolute standardized difference

IQR = interquartile range

TAVR = transcatheter aortic valve replacement

Over the past decade, there has been a paradigm shift in the management of severe symptomatic aortic stenosis with the development and maturation of transcatheter aortic valve replacement (TAVR) therapies. Numerous large-scale and randomized clinical trials have demonstrated the safety and effectiveness of TAVR as compared with surgical aortic valve replacement (1–6). Based on these data, TAVR has now been approved as a therapy for patients with severe symptomatic aortic stenosis, regardless of their surgical risk profile (7). However, in all these trials, patients with bicuspid disease were excluded, and as such, data for patients with bicuspid aortic valve disease undergoing TAVR is limited. Bicuspid aortic valve disease affects 1% to 2% of the U.S. population (8,9), and up to 20% of these patients will require aortic valve intervention in adulthood (10). Further understanding of TAVR performance in bicuspid aortic valve disease is needed.

SEE PAGE 1760

A recent analysis from the Society of Thoracic Surgeons/American College of Cardiology Transcatheter Valve Therapy (TVT) Registry of patients with bicuspid aortic valve disease who underwent TAVR with the balloon-expandable SAPIEN 3 transcatheter aortic valve (Edwards Lifesciences, Irvine, California) showed no significant differences in 30-day or 1-year mortality as compared with a propensity-matched group of patients with tricuspid aortic valve stenosis (11). To date, there are limited data evaluating the self-expanding Evolut valve (Medtronic, Minneapolis, Minnesota) in treating patients with bicuspid aortic stenosis. The purpose of this study was to assess the clinical and hemodynamic data from the TVT Registry in patients with bicuspid aortic valve stenosis undergoing TAVR with the self-expanding Evolut R valve or Evolut PRO valve (Medtronic).

METHODS

STUDY POPULATION. The study cohort for this retrospective analysis comprised patients implanted with the Evolut R or Evolut PRO transcatheter valves from July 2015 to September 2018, which includes follow-up through December 2018. During this time, a total of 37,903 patients underwent TAVR with Evolut R or Evolut PRO valves. Patients with a previous transcatheter or surgical aortic valve who were undergoing a valve-in-valve procedure, those who underwent an emergency or salvage TAVR, or those with an aortic valve characterized as having "other morphology" (not specified as bicuspid and not tricuspid) were excluded. This left a total of 27,086 patients, with 932 identified by the site as having bicuspid aortic stenosis (**Figure 1**) and who underwent TAVR with the Evolut R or Evolut PRO valve in the TVT Registry.

The TVT Registry serves as the national database for medical device tracking of all commercially available transcatheter aortic valves implanted in the United States. Entry of patient data into the TVT Registry is mandated as a condition of TAVR coverage by the Centers for Medicare and Medicaid Services and is performed by each individual site. A random audit of 10% of data elements is performed on site, remotely, or both. The American College of Cardiology Foundation submitted a protocol to its Institutional Review Board of record for the activities carried out by the American College of Cardiology Foundation and the Society of Thoracic Surgeons as operators of the TVT Registry. The Institutional Review Board reviewed and approved the protocol and in accordance with 45 CFR 46.116(d) of the federal regulations. Chesapeake's Institutional Review Board waived the requirement for obtaining consent for the TVT Registry. The TVT Registry publication committee has reviewed the final version of this paper.

VALVE DESIGN. Valve design details of the Evolut R and Evolut PRO have been previously reported (12,13). The Evolut R valve is available in 23-mm,

Boston Scientific, and AtriCure. Dr. Gleason has received institutional grant support from Boston Scientific and Medtronic, but no personal income; and has served on a medical advisory board for Abbott and Cytosorbents Corporation. Dr. Meduri has served on the advisory board for 4Tech, Admedus, Boston Scientific, and Cardiovalve; and has received consulting fees from Medtronic and Boston Scientific. Dr. Yakubov has received institutional research grants from and served on the advisory board for Boston Scientific and Medtronic. Dr. Jilaihawi has served a consultant for Edwards Lifesciences, Boston Scientific, Medtronic, and Venus Medtech; and has received grant or research support from Medtronic and Abbott Vascular. Dr. Liu is an employee and shareholder of Medtronic. Dr. Reardon has received consulting fees paid to his institution from Medtronic.
The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the *JACC: Cardiovascular Interventions* author instructions page.

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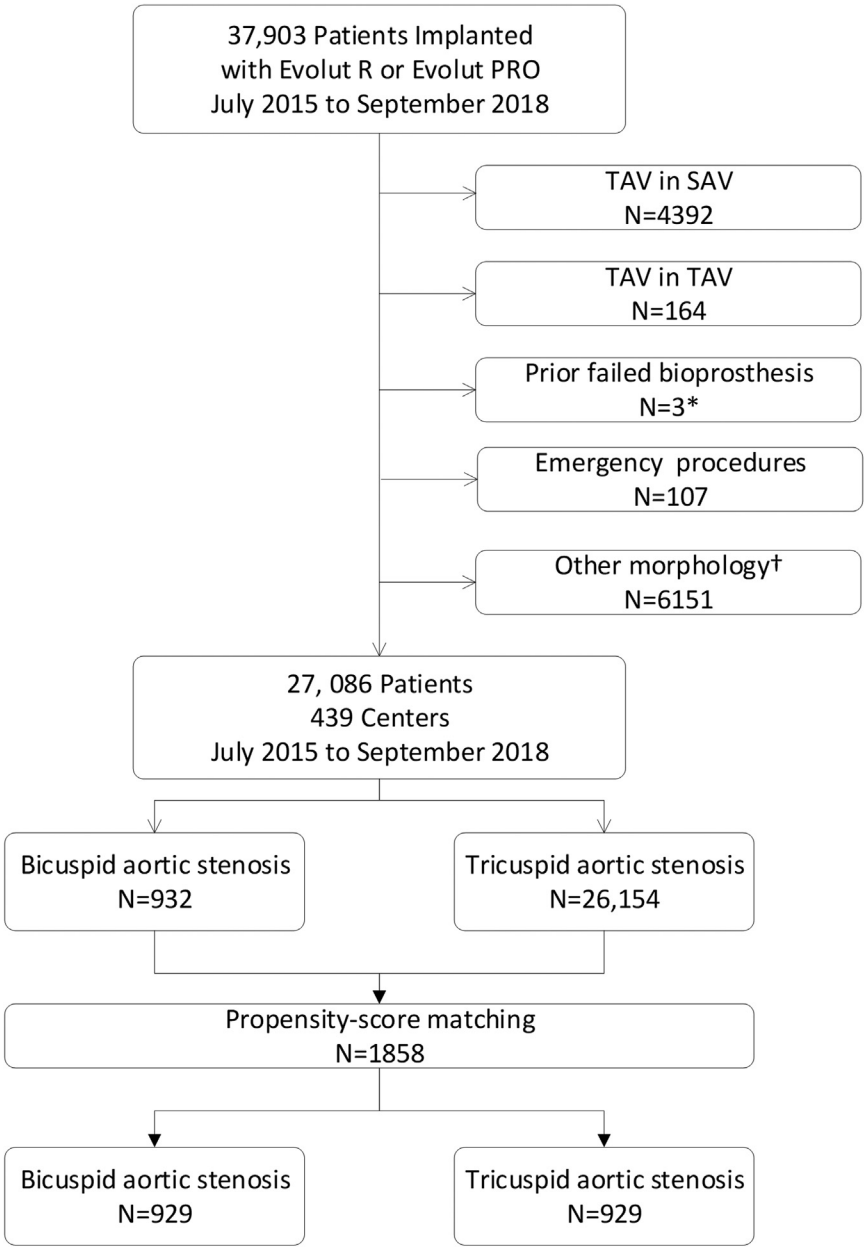
FIGURE 1 Study Flow



Patient cohorts from the Transcatheter Valve Therapy (TVT) Registry dataset. *Excluding patients with a previously implanted transcatheter aortic valve (TAV). †Patients with valve morphology other than bicuspid or tricuspid. SAV = surgical aortic valve.

26-mm, 29-mm, and 34-mm sizes and is implanted via a 14-F InLine Sheath (Medtronic) (for all sizes except the 34 mm, which requires a 16-F InLine Sheath). For this study, the Evolut PRO valve was available in 23-mm, 26-mm, and 29-mm sizes and is implanted via a 16-F InLine Sheath. The Evolut PRO valve shares the same design as the Evolut R valve, except for the addition of an outer pericardial tissue wrap, which has been shown to decrease paravalvular leak (12).

ECHOCARDIOGRAPHIC ANALYSIS. All echocardiographic assessments are performed based on standard practices and are site reported. Baseline, post-procedural, and 1-year echocardiographic measurements are analyzed. Echocardiographic data in the

TABLE 1 Baseline Characteristics

	Unadjusted Dataset				Adjusted Dataset			
	Bicuspid Group (n = 932)	Tricuspid Group (n = 26,154)	p Value	ASD*	Bicuspid Group (n = 929)	Tricuspid Group (n = 929)	p Value	ASD*
Age, yrs	72.9 ± 10.3	81.0 ± 7.6	<0.001	0.892	73.0 ± 10.3	72.6 ± 10.8	0.43	0.037
Male	515 (55.3)	12,205 (46.7)	<0.001	0.172	512 (55.1)	508 (54.7)	0.85	0.009
STS PROM, %	5.3 ± 4.2	6.9 ± 4.8	<0.001	0.357	5.3 ± 4.2	5.2 ± 4.1	0.63	0.022
NYHA functional class III or IV	702 (75.7)	19,585 (75.5)	0.86	0.006	705 (75.9)	710 (76.4)	0.79	0.013
Diabetes mellitus	328 (35.2)	10,048 (38.5)	0.04	0.068	328 (35.3)	341 (36.7)	0.53	0.029
Serum creatinine >2.0 mg/dl	63 (6.8)	2,107 (8.1)	0.15	0.050	63 (6.8)	69 (7.4)	0.59	0.025
Hypertension	788 (84.5)	23,853 (91.4)	<0.001	0.210	786 (84.6)	806 (86.8)	0.19	0.062
Peripheral vascular disease	238 (25.5)	7,542 (28.9)	0.03	0.075	238 (25.6)	262 (28.2)	0.21	0.058
Prior stroke	81 (8.7)	3,023 (11.6)	0.007	0.096	81 (8.7)	71 (7.6)	0.40	0.039
Chronic lung disease	438 (47.1)	10,623 (40.9)	<0.001	0.126	436 (46.9)	442 (47.6)	0.78	0.013
Current/recent smoker†	145 (15.6)	1,477 (5.7)	<0.001	0.326	143 (15.4)	160 (17.2)	0.29	0.050
Home oxygen	105 (11.3)	2,367 (9.1)	0.02	0.073	105 (11.3)	94 (10.1)	0.41	0.038
Immunocompromised	86 (9.2)	2,307 (8.8)	0.68	0.014	86 (9.3)	99 (10.7)	0.31	0.047
Cardiac history								
Previous coronary intervention	262 (28.1)	8,975 (34.4)	<0.001	0.136	262 (28.2)	264 (28.4)	0.92	0.005
Prior coronary bypass grafting	140 (15.0)	5,495 (21.1)	<0.001	0.158	140 (15.1)	163 (17.5)	0.15	0.067
Atrial fibrillation/atrial flutter	270 (29.0)	9,802 (37.6)	<0.001	0.183	269 (29.0)	248 (26.7)	0.28	0.051
Pre-existing pacemaker/ defibrillator	112 (12.1)	4,529 (17.4)	<0.001	0.150	112 (12.1)	128 (13.8)	0.27	0.051
Frailty								
Body mass index <21 kg/m^2	98 (10.5)	2,357 (9.0)	0.12	0.051	98 (10.6)	90 (9.7)	0.54	0.029
Albumin <3.3 g/dl	145 (17.7)	3,787 (16.3)	0.26	0.040	143 (17.6)	130 (15.5)	0.26	0.055
5-m gait speed >6 s	392 (55.1)	13,642 (68.5)	<0.001	0.280	391 (55.1)	456 (61.5)	0.01	0.128
Prohibitive anatomic factors								
Annular calcification	757 (81.7)	21,215 (82.1)	0.71	0.013	756 (81.8)	769 (84.1)	0.19	0.062
Porcelain aorta	30 (3.2)	808 (3.1)	0.82	0.007	30 (3.2)	30 (3.2)	>0.99	0.000
Hostile chest	53 (5.7)	1,540 (5.9)	0.79	0.009	53 (5.7)	80 (8.6)	0.02	0.113
Baseline echo characteristics								
Aortic valve area, cm^2	0.69 ± 0.19	0.69 ± 0.18	0.43	0.027	0.69 ± 0.19	0.69 ± 0.18	0.53	0.030
Maximum aortic valve velocity, m/s	4.2 ± 0.8	4.1 ± 0.7	<0.001	0.171	4.2 ± 0.8	4.2 ± 0.7	0.93	0.004
Mean aortic valve gradient, mm Hg	45.2 ± 16.1	42.3 ± 14.5	<0.001	0.192	45.2 ± 16.0	45.8 ± 15.4	0.44	0.036
Annular size, mm	25.1 ± 3.5	24.1 ± 3.0	<0.001	0.290	25.0 ± 3.4	24.7 ± 3.2	0.07	0.084
Left ventricular ejection fraction, %	52.7 ± 15.5	55.6 ± 13.4	<0.001	0.197	52.8 ± 15.4	52.9 ± 15.1	0.85	0.009
Moderate-to-severe aortic regurgitation	143 (15.4)	3,761 (14.5)	0.43	0.026	142 (15.3)	150 (16.1)	0.61	0.024
Moderate-to-severe mitral regurgitation	155 (16.8)	6,189 (23.8)	<0.001	0.175	155 (16.7)	166 (17.9)	0.50	0.031
Severe tricuspid regurgitation	20 (2.2)	979 (3.8)	0.01	0.095	20 (2.2)	15 (1.6)	0.39	0.040

Values are mean ± SD or n (%), unless otherwise indicated. *As proportion. †Within the most recent year.
ASD = absolute standardized difference. NYHA = New York Heart Association; STS PROM = Society of Thoracic Surgeons Predicted Risk of Mortality.

TVT Registry are self-reported and not independently adjudicated.

ENDPOINTS. Data included in this report are based on version 2.1 of the TVT Registry data collection form. Baseline characteristics, demographics, medical history, procedural characteristics, and in-hospital, 30-day, and 1-year outcomes are reported. Device success was defined based on the original Valve Academic Research Consortium definitions (14).

PROPENSITY MATCHING AND STATISTICAL METHODS. To account for intrinsic differences in the bicuspid and tricuspid aortic valve stenosis patient populations, a propensity score model was developed using a multivariable logistic regression with 28 baseline characteristics selected based on previous reports and clinical judgment (Supplemental Table 1). Missing data for the 28 variables was imputed; continuous variables were imputed by the median of nonmissing cases and categorical variables were imputed by the mode of nonmissing cases of baseline variables. A 5-to-1 digits greedy 1:1 matching algorithm was used to form a propensity-matched cohort for analysis (15). Absolute standardized differences (ASDs) were calculated to evaluate the balance before and after matching, with values <10% used to

indicate no meaningful imbalance. In-hospital outcomes are reported as frequencies, and comparisons between groups were performed using the chi-square test. Continuous variables are reported as mean ± SD or median (interquartile range [IQR]) as appropriate and were compared using the independent samples *t* test for mean comparisons or Wilcoxon rank sum test for median comparisons. Categorical variables are reported as counts and percentages and were compared using the chi-square test or Fisher exact test. Safety outcomes at 30 days and 1 year are reported as Kaplan-Meier estimates and compared using the log-rank test. Time-to-event analyses were applied to the full cohort (929 matched pairs), in which patients without complete 1-year follow-up were right-censored. For patients who had an adverse event at 30 days, but for whom 1-year follow-up was not completed or missed, their events were included in the 1-year clinical outcomes. A p value of <0.05 was considered statistically significant. All statistical analyses were performed using SAS software version 9.4 (SAS Institute, Cary, North Carolina).

RESULTS

BASELINE CHARACTERISTICS. A total of 932 patients with bicuspid aortic valve stenosis underwent TAVR using the Evolut R or Evolut PRO valve, who were propensity matched with a group of 26,154 patients with tricuspid valve morphology who underwent routine TAVR over the same period, resulting in 929 data pairs (Figure 1). Baseline characteristics for the unadjusted and the adjusted datasets are shown in Table 1. Within the unadjusted cohorts, there were significant differences in baseline characteristics. Patients with bicuspid aortic valve stenosis undergoing TAVR were younger (72.9 ± 10.3 vs. 81.0 ± 7.6 years; p < 0.001), were more frequently men (55.3% vs. 46.7%; p < 0.001), had lower Society of Thoracic Surgeons Predicted Risk of Mortality scores (5.3 ± 4.2% vs. 6.9 ± 4.8%; p < 0.001), were more likely to be a current smoker, and had lower rates of comorbid cardiovascular conditions (prior coronary revascularization, hypertension, diabetes, and peripheral vascular disease). Patients with bicuspid aortic valves tended to have a larger annular size (25.1 ± 3.5 mm vs. 24.1 ± 3.0 mm; p < 0.001) and higher mean aortic valve gradients (45.2 ± 16.1 mm Hg vs. 42.3 ± 14.5 mm Hg; p < 0.001), although there was no difference in baseline valve areas (0.69 cm^2 for both groups). After propensity score matching, the groups were well balanced with ASD <0.10 across all measured baseline characteristics, except fewer bicuspid patients had a 5-m gait speed >6 s (55.1% vs. 61.5%; p = 0.01, ASD = 0.128) and fewer were determined to have a hostile mediastinum (5.7% vs. 8.6%; p = 0.01, ASD = 0.113).

TABLE 2 Procedural Characteristics and In-Hospital Adverse Events for the Adjusted Cohort

	Bicuspid Group (n = 929)	Tricuspid Group (n = 929)	p Value
General anesthesia	546 (58.8)	538 (58.0)	0.73
Access route			0.94
Iliofemoral	853 (91.8)	854 (91.9)	
Subclavian	44 (4.7)	44 (4.7)	
Direct aortic	9 (1.0)	12 (1.3)	
Valve size implanted			
23 mm	26 (2.8)	27 (2.9)	0.89
26 mm	215 (23.3)	208 (22.5)	0.70
29 mm	434 (47.0)	461 (49.9)	0.21
34 mm	248 (26.9)	227 (24.6)	0.26
Valve type implanted			0.84
Evolut R	664 (71.5)	660 (71.0)	
Evolut PRO	265 (28.5)	269 (29.0)	
Device success*	893 (96.5)	887 (96.4)	0.88
Conversion to open heart surgery	6 (0.6)	2 (0.2)	0.29
Procedure time, min	113.6 ± 61.0	105.1 ± 51.2	0.001
In-hospital events			
All-cause mortality	16 (1.7)	7 (0.8)	0.06
Lab/operating room death	4 (0.4)	0 (0.0)	0.12
Stroke	27 (2.9)	24 (2.6)	0.67
Myocardial infarction	0 (0.0)	2 (0.2)	0.50
Coronary obstruction	2 (0.2)	1 (0.1)	>0.99
Bleeding at access site	17 (1.8)	10 (1.1)	0.17
Major vascular complication	11 (1.2)	11 (1.2)	>0.99
New requirement for dialysis	8 (0.9)	3 (0.3)	0.23
Permanent pacemaker†	133 (14.3)	115 (12.4)	0.22
Atrial fibrillation	16 (1.7)	20 (2.2)	0.50
Post-procedural length of stay, days	2.0 (2.0-4.0)	2.0 (2.0-4.0)	0.58
Discharged home	798 (87.4)	810 (87.9)	0.77

Values are n (%), mean ± SD, or median (interquartile range). *Per Valve Academic Research Consortium (14). †Includes patients with prior pacemaker.

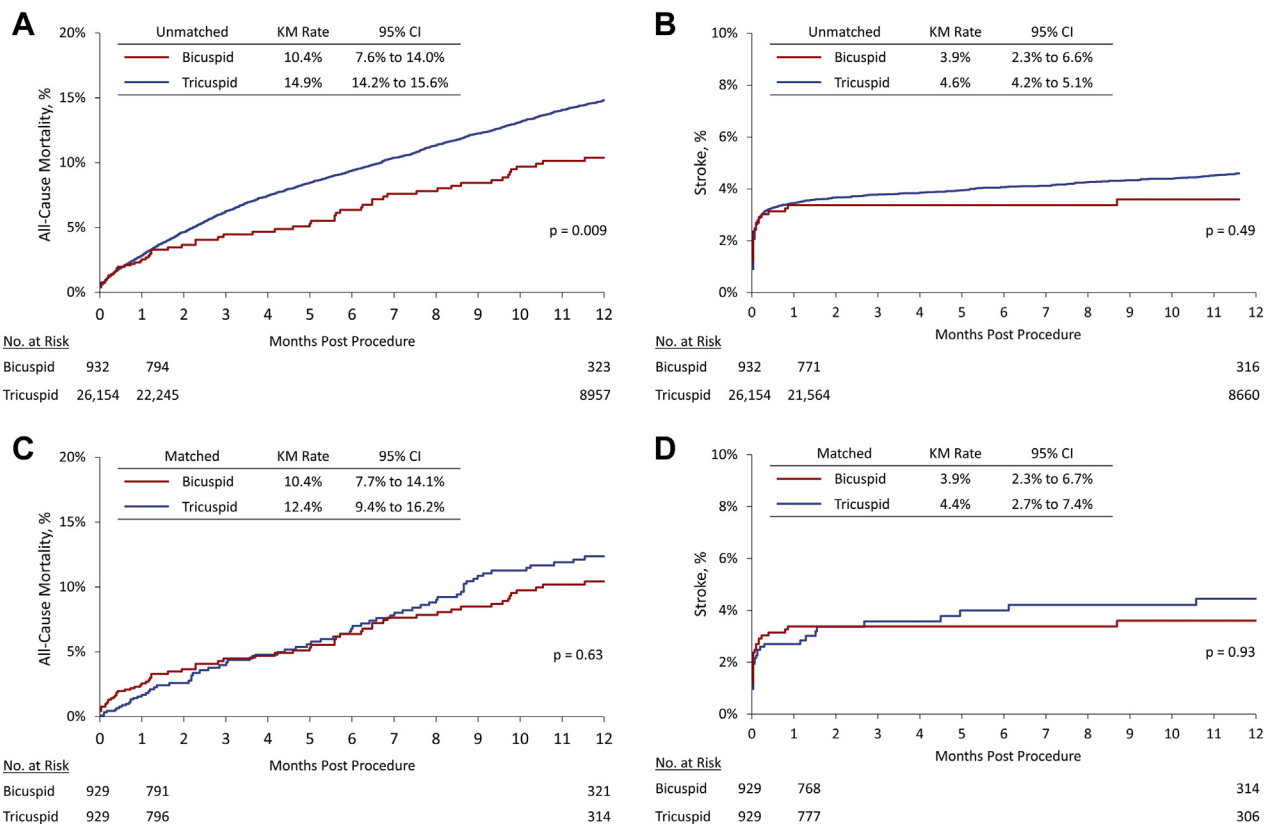
PROCEDURAL CHARACTERISTICS AND IN HOSPITAL OUTCOMES. Among the propensity score-matched patients, there were no significant differences in procedural characteristics except for procedure time, which was longer for patients with bicuspid valves than for those with tricuspid valves (113.6 ± 61.0 min vs. 105.1 ± 51.2 min; p = 0.001). The type of anesthesia used (general anesthesia in ~58%) and route of valve delivery (iliofemoral approach in ~92%) did not differ between the groups. The size and type of valve implanted, as well as device success rates, were also not different between the 2 groups. Most valves implanted were 29 mm in size (47.0% in bicuspid vs. 49.9% in tricuspid; p = 0.21), followed by 34 mm

TABLE 3 Clinical Outcomes at 30 Days and 1 Year for the Adjusted Cohort

	30 Days			1 Year		
	Bicuspid Group	Tricuspid Group	p Value	Bicuspid Group	Tricuspid Group	p Value
All-cause mortality	23 (2.6)	15 (1.7)	0.18	62 (10.4)	69 (12.4)	0.63
Stroke	31 (3.4)	25 (2.7)	0.41	33 (3.9)	34 (4.4)	0.93
Myocardial infarction	2 (0.2)	3 (0.3)	0.66	4 (0.7)	5 (0.8)	0.75
Life-threatening bleeding*	1 (0.1)	1 (0.1)	0.99	2 (0.3)	2 (0.3)	0.98
Valve thrombosis	0 (0.0)	1 (0.1)	0.32	0 (0.0)	1 (0.1)	0.32
Pacemaker implantation†	141 (15.4)	126 (13.7)	0.30	145 (16.4)	136 (15.9)	0.52
Percutaneous coronary intervention	2 (0.2)	1 (0.1)	0.56	3 (0.5)	4 (0.8)	0.72
Aortic valve reintervention	7 (0.8)	1 (0.1)	0.03	11 (1.7)	2 (0.3)	0.01
Valve-related readmission	10 (1.1)	6 (0.7)	0.31	23 (3.8)	18 (3.1)	0.40

Values are n (%). *After index hospitalization. †Includes patients with prior pacemaker.

FIGURE 2 All-Cause Mortality and Stroke to 1 Year



Kaplan-Meier (KM) estimates of **(A)** all-cause mortality and **(B)** stroke at 1 year for patients in the unadjusted cohort, and **(C)** all-cause mortality and **(D)** stroke for the adjusted cohort. Log-rank test p values are presented. CI = confidence interval.

TABLE 4 Echocardiographic Measures for the Matched Cohorts

	Post-Procedure			1 Year*		
	Bicuspid Group	Tricuspid Group	p Value	Bicuspid Group	Tricuspid Group	p Value
Aortic valve area, cm^2†	1.91 ± 0.64 (669)	1.93 ± 0.63 (721)	0.74	NA	NA	
Maximum aortic valve velocity, m/s†	2.1 ± 0.6 (780)	2.0 ± 0.6 (807)	0.03	NA	NA	
Mean aortic valve gradient, mm Hg	9.7 ± 5.2 (833)	9.0 ± 5.0 (841)	0.002	9.4 ± 5.2 (292)	8.9 ± 5.1 (307)	0.22
Mean aortic valve gradient ≥20 mm Hg	49 (5.9)	27 (3.2)	0.009	NA	NA	
Left ventricular ejection fraction, %	NA	NA		54.1 ± 12.7 (297)	56.4 ± 11.9 (311)	0.02
Aortic regurgitation	840	845	0.04	296	311	0.42
None	343 (40.8)	383 (45.3)		155 (52.4)	148 (47.6)	
Trace	242 (28.8)	227 (26.9)		54 (18.2)	69 (22.2)	
Mild	208 (24.8)	217 (25.7)		73 (24.7)	82 (26.4)	
Moderate or severe	47 (5.6)	18 (2.1)	<0.001	14 (4.7)	12 (3.9)	0.60

Values are mean ± SD (n), n (%), or n. *Includes patients with evaluable echocardiograms. †Only measured post-procedure.
NA = not analyzed.

(26.9% in bicuspid vs. 24.6% in tricuspid; p = 0.26) and 26 mm (23.3% in bicuspid vs. 22.5% in tricuspid; p = 0.70). Only a small percentage of patients received a 23-mm valve (2.8% in bicuspid vs. 2.9% in tricuspid; p = 0.89). The median post-procedural length of stay was similar for the 2 groups (2.0 [IQR: 2.0 to 4.0] vs. 2.0 [IQR: 2.0 to 4.0]; p = 0.58) (Table 2).

There were no significant differences for in-hospital events including mortality, stroke, coronary obstruction, pacemaker implantations, vascular complication, or post-procedural length of stay between the 2 groups. The median follow-up was 79.0 (IQR: 34.0 to 373.0) days for the bicuspid group and 168.0 (IQR: 34.0 to 377.0) days for the tricuspid group (p = 0.60).

THIRTY-DAY AND 1-YEAR CLINICAL OUTCOMES. There was no significant difference in all-cause mortality between the bicuspid and tricuspid groups at 30 days (2.6% vs. 1.7%; p = 0.18) or 1 year (10.4% vs. 12.1%; p = 0.63). The incidence of stroke was also not different at 30 days (3.4% vs. 2.7%; p = 0.41) or 1 year (3.9% vs. 4.4%; p = 0.93). There was no significant difference in the incidence of pacemaker implantation, coronary intervention, or life-threatening bleeding between the bicuspid and tricuspid propensity-matched groups (Table 3). There were more patients in the bicuspid group who required aortic valve reintervention as compared with the tricuspid group at both 30 days (0.8% vs. 0.1%; p = 0.03) and 1 year (1.7% vs. 0.3%; p = 0.01). The cumulative incidences for all-cause mortality and stroke at 1 year for both the propensity-matched and unmatched groups are shown in Figure 2 and the Central Illustration.

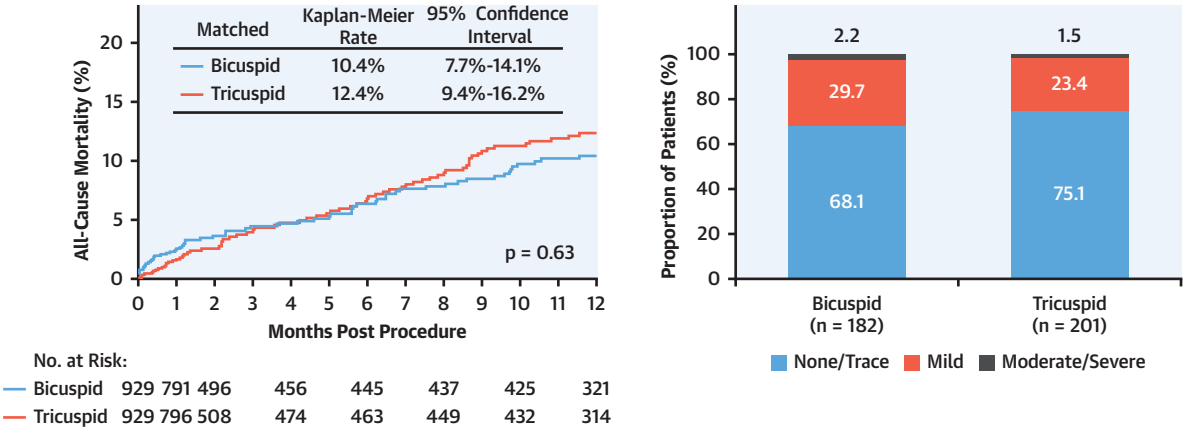
VALVE FUNCTION. Valve hemodynamics were excellent for bicuspid and tricuspid patients post-procedure and at 1 year (Table 4). Post-procedural effective valve area was 1.9 cm^2 in both groups. Mean gradients for the bicuspid group were slightly higher post-procedure as compared with tricuspid patients (9.7 ± 5.2 mm Hg vs. 9.0 ± 5.0 mm Hg; p = 0.002) but were not statistically different at 1 year (9.4 ± 5.2 mm Hg vs. 8.9 ± 5.1 mm Hg; p = 0.22). Post-procedure moderate or severe aortic regurgitation (AR) was more prevalent in patients with bicuspid aortic valves (5.6% vs. 2.1%; p < 0.001) at 30 days. Examining by valve type, Evolut PRO versus prior-generation Evolut R (Table 5, Central Illustration), there was significantly less moderate or severe AR seen in patients who were implanted with the Evolut PRO valve. In addition, in patients implanted with the Evolut PRO valve, there was no difference seen in greater than mild AR at 30 days between the bicuspid and tricuspid groups (2.2% bicuspid vs. 1.5% tricuspid; p = 0.71).

TABLE 5 Total Aortic Regurgitation at 30 Days for Patients With Bicuspid and Tricuspid Valves and by Implanted Valve Type

	Bicuspid Group (n = 662)			Tricuspid Group (n = 697)		
Measurement	Evolut R (n = 480)	Evolut PRO (n = 182)	p Value	Evolut R (n = 496)	Evolut PRO (n = 201)	p Value
Total aortic regurgitation			0.38*			0.002*
None	182 (37.9)	68 (37.4)		179 (36.1)	89 (44.3)	
Trace/trivial	123 (25.6)	56 (30.8)		126 (25.4)	62 (30.8)	
Mild	138 (28.8)	54 (29.7)		165 (33.3)	47 (23.4)	
Moderate	35 (7.3)	4 (2.2)		24 (4.8)	3 (1.5)	
Severe	2 (0.4)	0 (0.0)		2 (0.4)	0 (0.0)	
Moderate/severe	37 (7.7)	4 (2.2)	0.007†	26 (5.2)	3 (1.5)	0.02†

Values are n (%). *Calculated from Cochran-Mantel-Haenszel statistics. †Fisher exact test.

CENTRAL ILLUSTRATION Key Outcomes



Forrest, J.K. et al. J Am Coll Cardiol Intv. 2020;13(15):1749–59.

(Left) All-cause mortality at 1 year for matched patients. **(Right)** Aortic regurgitation at 30 days for bicuspid and tricuspid patient groups implanted with the Evolut PRO valve.

QUALITY OF LIFE. Quality of life as assessed via the Kansas City Cardiomyopathy Questionnaire improved significantly from baseline to 1 year following TAVR with a >32-point increase for each group ($p < 0.001$ for both) (**Table 6**). New York Heart Association functional class at baseline and 1 year is shown in **Figure 3**. Improvement in New York Heart Association functional class at 1 year occurred in most patients in both groups (75.1% of bicuspid patients and 78.7% of tricuspid patients; $p = 0.35$) (Supplemental Figure 1).

DISCUSSION

This study represents the first analysis from the TVT Registry evaluating TAVR using a supra-annular, repositionable, self-expanding valve in patients with bicuspid aortic valve stenosis. In this analysis, among 929 pairs of propensity-matched patients undergoing TAVR in the United States between July 2015 and September 2018, there was no significant difference in all-cause mortality or stroke at 30 days or 1 year between patients with bicuspid versus tricuspid aortic valve anatomy. However, there was a small but increased number of patients in the bicuspid group who required aortic valve reintervention as compared with the tricuspid group at 30 days and at 1 year.

The primary focus of TAVR therapy in the initial large randomized clinical studies was for the treatment of higher-risk patients with severe aortic valve stenosis who had significant comorbidities. As a result, within these studies, patients undergoing TAVR tended to be older, and most had age-related degenerative tricuspid aortic valve disease. Although subsequent randomized trials have included patients at a progressively lower risk, the focus in these studies remained on patients with tricuspid aortic valve stenosis. Bicuspid aortic valve disease differs from tricuspid disease in not only the number of leaflets present, but also several other anatomic and pathophysiologic areas, including an increased incidence of aortopathy with dilation of the aortic root and ascending aorta, frequent atypical location of coronary artery ostia, asymmetric leaflet calcification, larger-sized annuli, and higher calcium scores with bulky leaflet calcification and fused raphe (16). Potentially as a result of these anatomic differences, the results of early-generation TAVR systems in patients with bicuspid aortic valve disease were notable for worse in-hospital outcomes, decreased device success, and an increased incidence of paravalvular leak, device malpositioning, and aortic injury (17,18). Modifications to address many of these issues have been made to subsequent generations of TAVR devices including improved sealing at the level of the annulus and the ability to recapture and reposition the valve to assist with obtaining the optimal implant depth prior to final release. In this study among propensity-matched cohorts, it is notable that there was no significant difference in device success and in 1-year rates of all-cause mortality, stroke, pacemakers, or aortic insufficiency.

The effect that bicuspid anatomy might have on valve expansion, hemodynamics, and aortic regurgitation or paravalvular leak because of the 2 commissures opening in a more elliptical fashion was certainly a concern when TAVR therapy was initially considered for patients with bicuspid aortic stenosis. Given that the hemodynamic profile of supra-annular self-expanding valves for patients with tricuspid aortic stenosis has been shown to be superior to intra-annular valves and is known to result in a lower incidence of patient-prosthesis mismatch (19,20), it is notable that these hemodynamics were maintained in patients with bicuspid anatomy with mean gradients at 30 days and at 1 year in both groups that were <10 mm Hg. Although the rates of significant aortic regurgitation were very low for both bicuspid and tricuspid patients (greater than mild leak being present in <5% of patients at 1 year), there was a significant difference between the 2 groups post-procedure. This increased incidence of aortic regurgitation may have contributed to the higher frequency of aortic valve reintervention for patients with a bicuspid valve, although this rate was generally low (0.8% at 30 days and 1.7% at 1 year). Importantly, in this study, less than one-third of the patients in each of the cohorts underwent TAVR using the Evolut PRO valve, which differs from the Evolut R valve due to the presence of an outer pericardial wrap added to the inflow portion of the valve, which has been shown to decrease paravalvular leak (12,21). Importantly, with the present-generation Evolut PRO valve, the rates of greater than mild AR were significantly less than with prior-generation Evolut R, and in bicuspid patients, the incidence of significant (greater than mild) AR was the same in bicuspid patients as it was for tricuspid patients.

Rates of early complications and 1-year outcomes in this analysis of TAVR in bicuspid aortic valves with a self-expanding valve system are similar to those seen by Makkar et al. (11) in their recently published analysis from the TVT Registry using the balloon expandable SAPIEN 3 valve. Although Makkar et al. did find a slightly higher incidence of stroke at 30 days for patients with bicuspid aortic valve, this difference was not significant at 1 year. In this study, the incidence of stroke (in-hospital, at 30 days, and at 1 year) was not statistically different between bicuspid and tricuspid valve patients undergoing TAVR and is consistent with another recent analysis by Elbadawi et al. (22) that analyzed data from the National Inpatient Sample. As such, it remains difficult to predict which patients undergoing TAVR are at higher risk for stroke and hence might benefit from cerebral embolic protection.

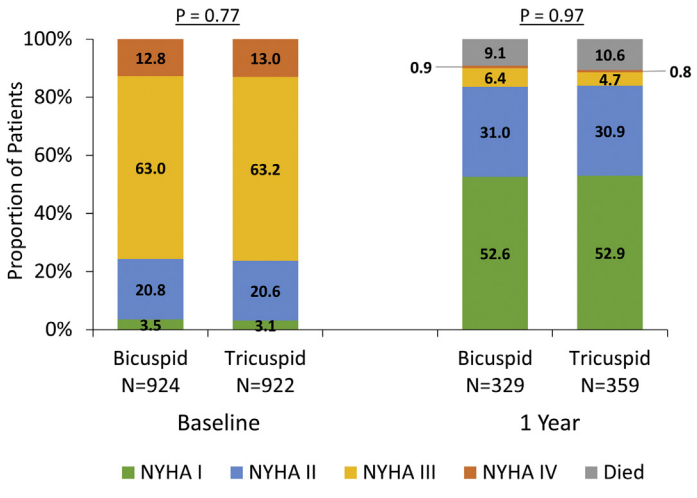
TABLE 6 Kansas City Cardiomyopathy Questionnaire

Measurement	Bicuspid Group	Tricuspid Group	p Value
Baseline	45.7 ± 25.3 (857)	45.4 ± 24.5 (875)	0.79
1 yr	78.9 ± 20.4 (293)	78.6 ± 21.6 (322)	0.87
Change from baseline	32.1 ± 26.0 (278)	32.9 ± 27.1 (310)	0.70
p value for change from baseline	<0.001	<0.001	

Values are mean ± SD (n).

In this TVT Registry analysis, only 3.4% of patients undergoing routine native valve TAVR had a bicuspid aortic valve. As the indications for TAVR have expanded to now include low-risk patients, and given that up to 50% of low-risk patients undergoing aortic valve replacement are known to have bicuspid aortic valve disease, heart teams across the United States are much more likely to have patients with bicuspid aortic valve disease referred for evaluation than they were previously (23). Although we continue to better understand sizing algorithms and implant techniques to optimize outcomes of TAVR in bicuspid aortic valve (16,24), surgical aortic valve replacement remains the only approved replacement strategy for low-risk patients with bicuspid aortic valve disease who require aortic valve replacement. Thus, although there is excellent randomized data demonstrating the safety and effectiveness of TAVR in low-risk surgical patients with tricuspid valve disease (3,4), and although this study contributes significantly to

FIGURE 3 New York Heart Association Functional Class at Baseline and 1 Year



New York Heart Association (NYHA) functional class symptoms at baseline and 1 year for patients with available data at both time points.

data showing similar results for TAVR in bicuspid and tricuspid disease, a definitive trial directly comparing surgery and transcatheter valve replacement for low-risk patients with bicuspid aortic valve stenosis is needed.

STUDY LIMITATIONS. Our study is limited by its retrospective and observational design, using the TVT Registry, in which data are site-reported, and anatomic classification and echocardiographic findings have been not adjudicated by a core laboratory. Within the TVT Registry, the Sievers classification (25) of bicuspid valve type is not recorded, and given the potential for selection bias within the registry, generalizations that these results reflect TAVR in all bicuspid valve anatomy cannot be made. Procedural data such as performing balloon pre-dilation, if repositioning of the valve was required, and thus potentially increased procedural time, and how the prosthesis was sized are also not available, which may play a role in outcomes. In addition, although propensity matching was performed, there are intrinsic differences in patients with bicuspid and tricuspid aortic valve disease that may not have been accounted for. Last, the percentage of patients with complete 1-year follow-up in the TVT Registry is much lower than it is in rigorous clinical studies, and many patients (45.7%) in our report were not yet eligible to have their 1-year data entered in the TVT Registry. Despite those patients being right-censored in all time-to-event analyses, there is a potential for event rates to change with complete follow-up.

CONCLUSIONS

For patients at increased risk for surgery with a bicuspid aortic valve, analysis from the TVT Registry among propensity-matched patients demonstrated that the 30-day and 1-year mortality, stroke, and quality-of-life improvement for patients undergoing TAVR are similar to those for patients who have a tricuspid aortic valve. Given intrinsic differences in bicuspid and tricuspid aortic valve anatomies and a lack of data around low-risk patients with bicuspid aortic valves, randomized studies evaluating TAVR in low-risk patients with bicuspid aortic valve disease are needed.

ADDRESS FOR CORRESPONDENCE: Dr. John K. Forrest, Yale School of Medicine, 789 Howard Avenue, Dana 3, Cardiology Section, New Haven, Connecticut 06519. E-mail: john.k.forrest@yale.edu. Twitter: @johnkforrest.

PERSPECTIVES

WHAT IS KNOWN? TAVR has shown safety and efficacy in patients with tricuspid aortic valve stenosis, but little data exist in TAVR using self-expanding valves in patients with bicuspid aortic valve stenosis.

WHAT IS NEW? These data from the TVT Registry indicate that TAVR with self-expanding valves in bicuspid aortic valve stenosis has similar outcomes in patient with increased surgical risk as compared with TAVR in tricuspid aortic stenosis.

WHAT IS NEXT? A better understanding of specific bicuspid anatomy and TAVR results as well as the performance of self-expanding TAVR in low-risk patients are needed.

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KEY WORDS bicuspid aortic valve, self-expanding transcatheter valve, transcatheter aortic valve replacement

APPENDIX For a supplemental table and figure, please see the online version of this paper.