JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY VOL. 76, NO. 9, 2020

PUBLISHED BY ELSEVIER

Bicuspid Aortic Valve Morphology and Outcomes After Transcatheter Aortic Valve Replacement

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ABSTRACT

BACKGROUND Bicuspid aortic stenosis accounts for almost 50% of patients undergoing surgical aortic valve replacement in the younger patients. Expanding the indication of transcatheter aortic valve replacement (TAVR) toward lower-risk and younger populations will lead to increased use of TAVR for patients with bicuspid aortic valve (BAV) stenosis despite the exclusion of bicuspid anatomy in all pivotal clinical trials.

OBJECTIVES This study sought to evaluate the association of BAV morphology and outcomes of TAVR with the new-generation devices.

METHODS Patients with BAV confirmed by central core laboratory computed tomography (CT) analysis were included from the international multicenter BAV TAVR registry. BAV morphology including the number of raphe, calcification grade in raphe, and leaflet calcium volume were assessed with CT analysis in a masked fashion. Primary outcomes were all-cause mortality at 1 and 2 years, and secondary outcomes included 30-day major endpoints and procedural complications.

RESULTS A total of 1,034 CT-confirmed BAV patients with a mean age of 74.7 years and Society of Thoracic Surgeons score of 3.7% underwent TAVR with contemporary devices (n = 740 with Sapien 3; n = 188 with Evolut R/Pro; n = 106 with others). All-cause 30-day, 1-year, and 2-year mortality was 2.0%, 6.7%, and 12.5%, respectively. Multivariable analysis identified calcified raphe and excess leaflet calcification (defined as more than median calcium volume) as independent predictors of 2-year all-cause mortality. Both calcified raphe plus excess leaflet calcification were found in 269 patients (26.0%), and they had significantly higher 2-year all-cause mortality than those with 1 or none of these morphological features (25.7% vs. 9.5% vs. 5.9%; log-rank $p < 0.001$). Patients with both morphological features had higher rates of aortic root injury ($p < 0.001$), moderate-to-severe paravalvular regurgitation ($p = 0.002$), and 30-day mortality ($p = 0.016$).

CONCLUSIONS Outcomes of TAVR in bicuspid aortic stenosis depend on valve morphology. Calcified raphe and excess leaflet calcification were associated with increased risk of procedural complications and midterm mortality. (Bicuspid Aortic Valve Stenosis Transcatheter Aortic Valve Replacement Registry; NCT03836521)
(J Am Coll Cardiol 2020;76:1018–30) © 2020 by the American College of Cardiology Foundation.

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ISSN 0735-1097/$36.00 https://doi.org/10.1016/j.jacc.2020.07.005

Bicuspid aortic valve (BAV) is the most common congenital cardiac anomaly in adults and accounts for 50% of patients requiring surgical valve replacement in the younger population (1–4). A series of randomized trials of transcatheter aortic valve replacement (TAVR) has demonstrated that TAVR is noninferior or superior to surgery regardless of patient risk profile (5–12). These results have accelerated the global trend of TAVR use in younger patients, leading to the increasing number of TAVR candidates with bicuspid anatomy (13). However, these pivotal randomized trials excluded bicuspid aortic stenosis due to the perceived anatomic challenges for TAVR. Previous registries have shown comparable outcomes of TAVR between bicuspid and tricuspid aortic stenosis patients (14,15), but these registries were comprised of patients diagnosed with BAV by each site and were limited in detailed information regarding various BAV morphologies, which may affect the outcomes after TAVR.

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BAV encompasses various aortic valve morphologies such as presence of raphe, extent and location of calcification, and dilated ascending aorta (aortopathy). In contrast to surgery, where the native valve is excised, the valve function and procedural complications after TAVR are more likely to be affected by native aortic valve anatomy. Bicuspid aortic valve has been traditionally diagnosed with transthoracic echocardiography,

ABBREVIATIONS AND ACRONYMS

BAV = bicuspid aortic valve

CI = confidence interval

CT = computed tomography

STS = Society of Thoracic Surgeons

TAVR = transcatheter aortic valve replacement

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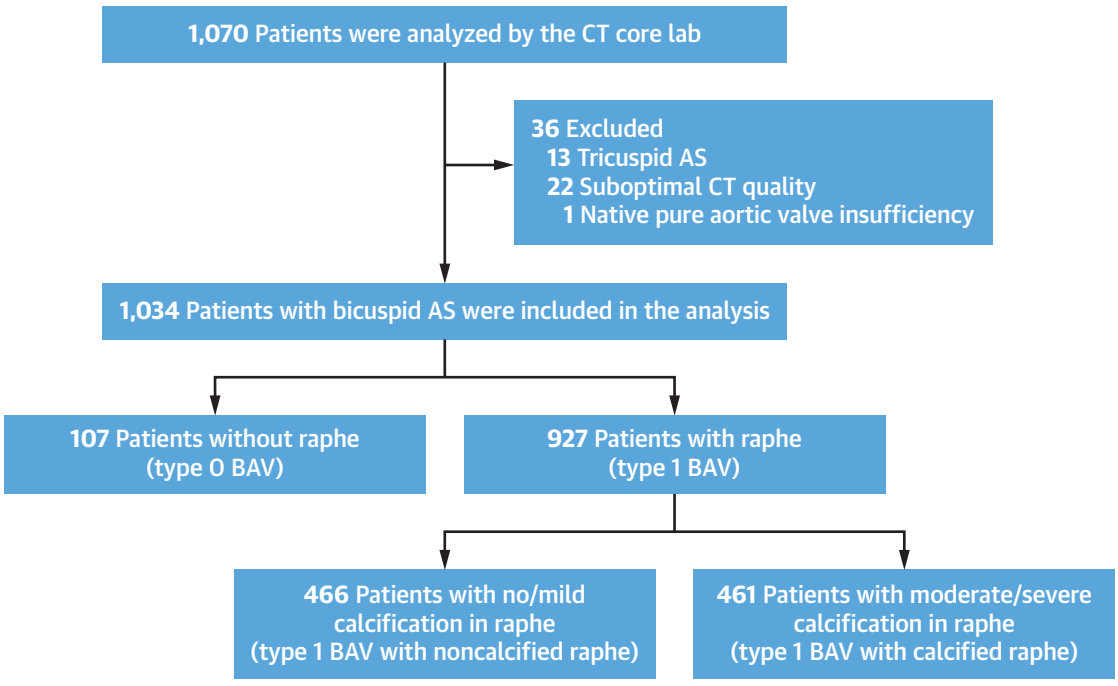
The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the *JACC* author instructions page.

Manuscript received April 3, 2020; revised manuscript received June 9, 2020, accepted July 2, 2020.

FIGURE 1 Study Flow Chart



Baseline computed tomographic (CT) images were analyzed. After excluding patients with tricuspid aortic stenosis (AS), suboptimal image quality, or aortic insufficiency, 1,034 patients with confirmed bicuspid anatomy were included in the analysis. BAV = bicuspid aortic valve.

while computed tomography (CT) scans provides detailed spatial information of bicuspid morphology with higher diagnostic accuracy (16–18). Nevertheless, little is known about the association between various BAV phenotypes and TAVR outcomes. This knowledge gap makes it difficult to optimize treatment for patients with bicuspid aortic stenosis, creating an unmet need for a risk assessment method. Therefore, in this study, we aimed to evaluate the clinical outcomes of patients undergoing TAVR for BAV using CT-based diagnosis and assessment of bicuspid anatomy and identify the morphological features that place patients at high risk for adverse outcomes.

METHODS

STUDY DESIGN AND PATIENT POPULATION. The International Bicuspid Aortic Valve Stenosis Registry was established in collaboration with 24 cardiovascular centers across 8 countries (Denmark, France, Germany, Israel, Italy, the Netherlands, Switzerland, and the United States). Consecutive patients with BAV undergoing TAVR using the new-generation devices for symptomatic severe aortic valve stenosis and available CT scans were enrolled, and those with adjudicated bicuspid anatomy by central core laboratory were included in this study. We collected data retrospectively for cases performed before participation in the registry and prospectively thereafter. All inconsistencies were resolved directly with local investigators and on-site data monitoring. This study was approved by the institutional review board of each institution, and all patients provided written informed consent for TAVR and the use of anonymous clinical, procedural, and follow-up data for research. For retrospective analysis of clinically acquired and anonymized data, the institutional review board of some institutions waived the need for written patient informed consent. Patients were selected for TAVR after discussions by the multidisciplinary heart team of each institution, and the access site and type of transcatheter heart valves were determined thereafter. All centers adopted a transfemoral-first approach policy with criteria for performing a non-transfemoral approach based on the heart team's consideration of the size, calcification, and atheroma of the aorto-iliofemoral artery. All TAVR procedures were conducted in accordance with local guidelines using standard techniques via transfemoral, transapical, trans-subclavian, transaortic, or transcaval access, and contemporary devices (Sapien 3

[Edwards Lifesciences, Irvine, California], Evolut R/Evolut R Pro [Medtronic, Minneapolis, Minnesota], Acurate [Boston Scientific, Marlborough, Massachusetts], Lotus/Edge [Boston Scientific], or Portico [Abbott Structural Heart, St. Paul, Minnesota]) were implanted (19–23).

OUTCOMES AND DEFINITIONS. The primary outcomes of the present study were all-cause mortality at 1 and 2 years. Secondary outcomes were cardiovascular mortality and 30-day major clinical endpoints using the Valve Academic Research Consortium (VARC) 2 criteria (24). The composite endpoint of aortic root injury, moderate or severe paravalvular regurgitation, stroke, or mortality at 30 days was assessed. Other endpoints included new permanent pacemaker insertion, procedure- and device-related complications, and echocardiographic assessment of the valve and cardiac function at discharge. No echocardiographic core laboratory was used, and all echocardiographic data were site reported. The severity of regurgitation was qualitatively assessed and graded using transthoracic echocardiography at each institution according to established guidelines (24).

DATA COLLECTION. All CT scans were centrally collected and analyzed by a dedicated core laboratory at Cedars-Sinai Heart Institute. Data collection by a dedicated case report form included baseline clinical, echocardiographic, and procedural data as well as clinical follow-up data at pre-specified time points (1, 6, and 12 months, and yearly thereafter). Follow-up was obtained by clinical visits and/or through telephone contacts. Referring cardiologists, general practitioners, and patients were contacted whenever necessary for further information. All data provided by each institution were anonymized, centrally collected, and assessed for quality.

BICUSPID AORTIC VALVE. All CT scans were analyzed at Cedars-Sinai Heart Institute (Los Angeles, California) by a dedicated core laboratory blinded to patient information and outcome data. Diagnosis and assessment of bicuspid anatomy were performed with CT images based on the classification described by Sievers et al. (25) according to the presence and number of raphes (no raphe type as type 0, and raphe type as type 1) as well as spatial position of raphe. For type 1 BAV, calcification in raphe was assessed in the sagittal plane through the raphe (2-dimensional) and maximum-intensity projection view (3-dimensional) with grading as none, mild (spotty calcification in raphe not extending more than one-half of the raphe), moderate (bulky calcification or linear calcification extending more than one-half of the raphe), or severe (bulky and linear calcification covering the entire raphe) (Supplemental Appendix) (18). Patients with moderate or severe calcification in raphe were categorized as having calcified raphe. The quantity and distribution of calcification were analyzed with calcium volume measurement using an 850-HU threshold (26). Left ventricular outflow tract calcification was graded as none, mild, moderate, or severe (18). The leaflet with calcium volume more than median value in the entire cohort was categorized as excess leaflet calcification. Intraobserver and interobserver agreement for the calcification in raphe and leaflet calcium volume were satisfactory (intraclass correlation coefficient: 0.993 [$p < 0.001$] and 0. 980

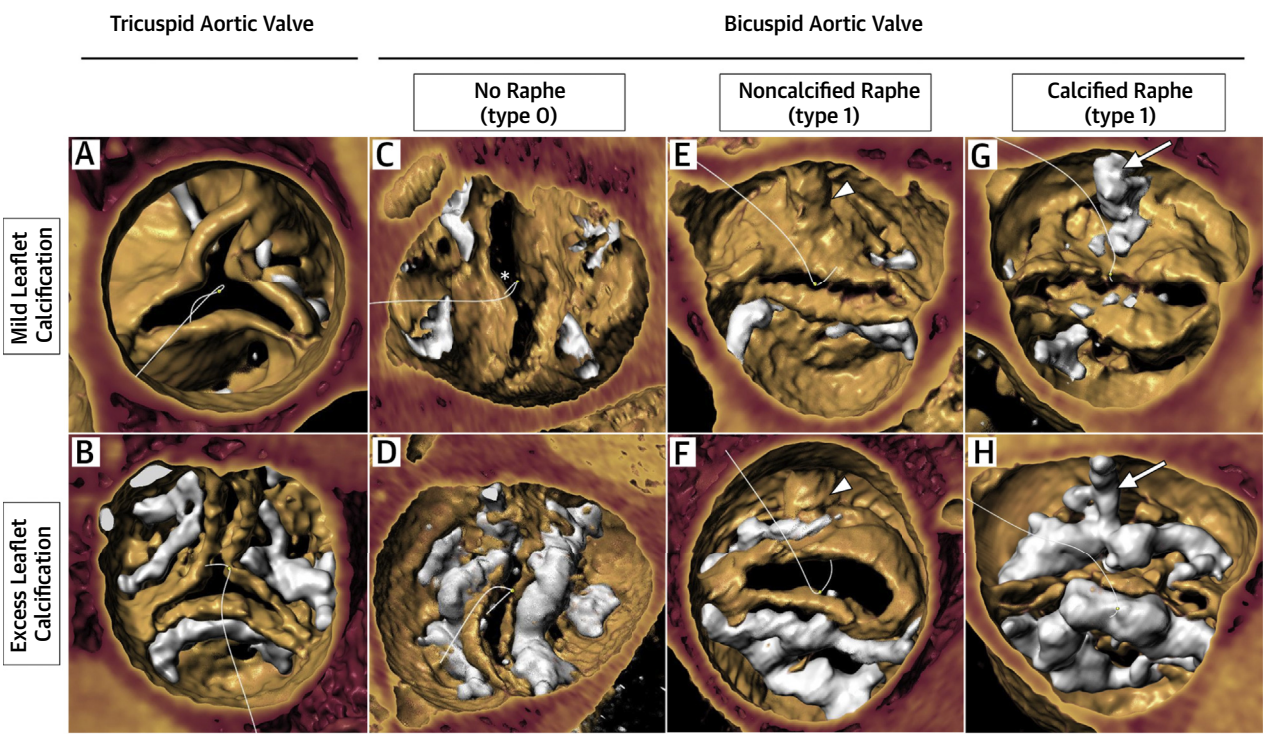
TABLE 1 Baseline Characteristics (n = 1,034)

Age, yrs	74.7 ± 9.3
Male	610 (59.0)
NYHA functional class III or IV	736 (71.2)
STS score, %	3.7 ± 3.3
Hypertension	823 (79.6)
Diabetes mellitus	264 (25.5)
Creatinine, μmol/l	1.1 ± 0.9
Peripheral vascular disease	147 (14.2)
Prior cerebrovascular accident	121 (11.7)
Chronic lung disease	93 (9.0)
Prior myocardial infarction	119 (11.5)
Prior percutaneous coronary intervention	201 (19.4)
Prior coronary artery bypass surgery	80 (7.7)
Prior atrial fibrillation	187 (18.1)
Prior pacemaker	68 (6.6)
Aortic valve gradient, mm Hg	47.5 ± 16.5
Aortic valve area, cm^2	0.7 ± 0.2
LVEF, %	53.5 ± 15.3
Aortic regurgitation ≥moderate	116 (11.2)
Mitral regurgitation ≥moderate	97 (9.4)
Type of bicuspid aortic valve	
No raphe (type 0)	107 (10.3)
Raphe (type 1)	927 (89.7)
Calcified raphe	461 (44.6)
Noncalcified raphe	466 (45.1)
Calcification volume in leaflet, mm^3	382 (182–695)
Left ventricular outflow tract calcification ≥moderate	128 (12.4)
Ascending aorta diameter, mm	38.8 ± 5.3
≥40 mm	436 (42.2)
≥45 mm	128 (12.4)
≥50 mm	23 (2.2)
Transfemoral access	975 (94.3)
Device	
Sapien 3	740 (71.6)
Evolut R/Pro	188 (18.2)
Lotus/Edge	47 (4.5)
Acurate	40 (3.9)
Portico	19 (1.8)

Values are mean ± SD, n (%), or median (interquartile range).

LVEF = left ventricular ejection fraction; NYHA = New York Heart Association; STS = Society of Thoracic Surgeons.

FIGURE 2 Various Aortic Valve Morphology

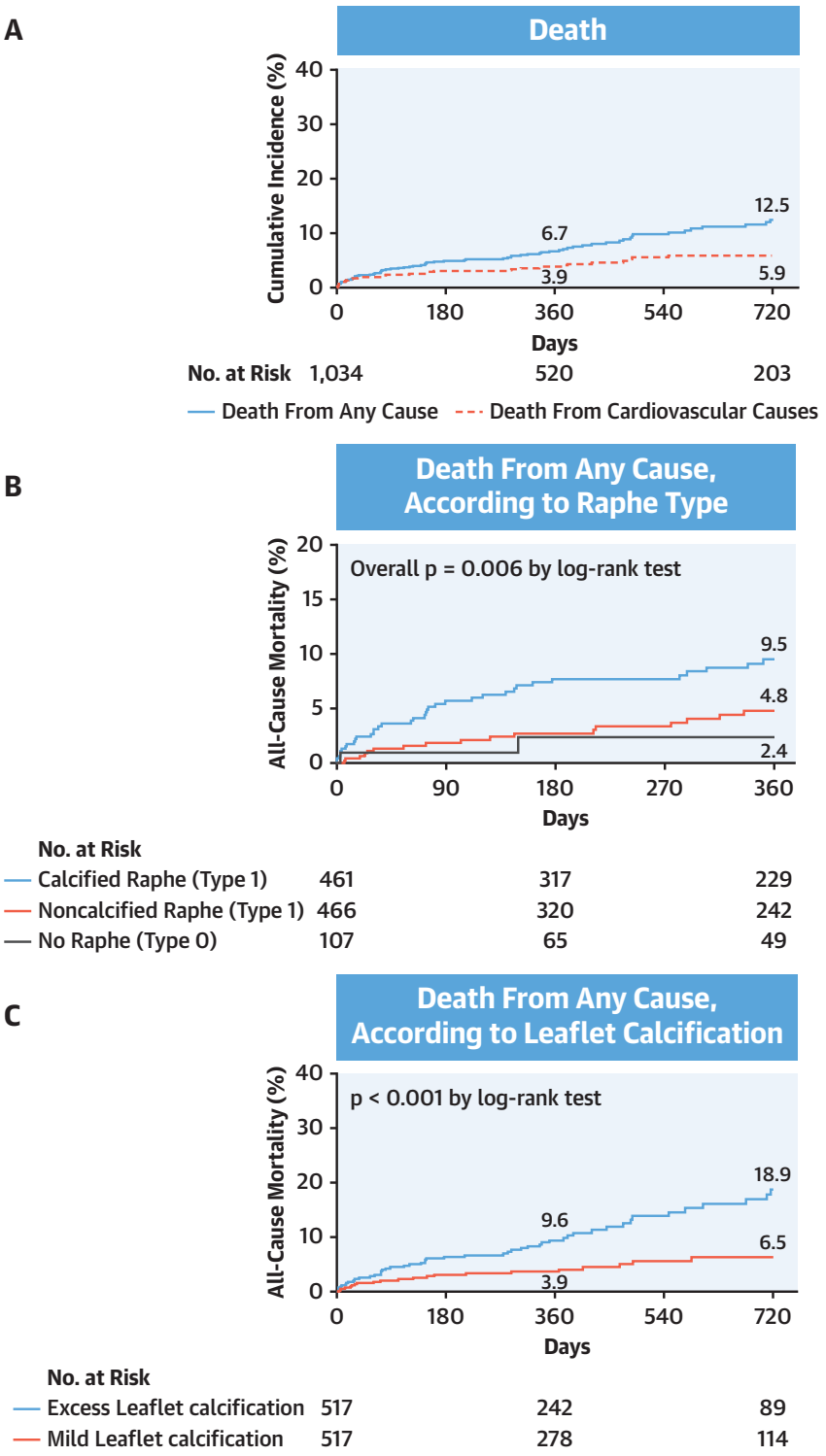


Various aortic valve morphology on volume-rendered computed tomography for tricuspid **(A and B)** and bicuspid aortic valve stenosis **(C to H)** are shown. The characteristic "fish mouth" opening of the valve **(asterisk)** is appreciated in bicuspid aortic valve. Bicuspid aortic valve is categorized as no raphe type **(C and D)** and raphe type **(E to H).** Raphe type is further categorized as noncalcified raphe type **(E and F)** and calcified raphe type **(G and H)**. **Arrowheads** indicate noncalcified raphe, and **arrows** indicate calcified raphe. **(Top)** Aortic valve with mild leaflet calcification; **(bottom)** aortic valves with excess leaflet calcification.

[$p < 0.001$] for calcification in raphe; 0.999 [$p < 0.001$] and 0.999 [$p < 0.001$] for leaflet calcium volume, respectively). Details are described in the Supplemental Appendix. Maximal diameter of the ascending aorta was measured, and patients with diameter ≥40 mm were categorized as having aortopathy.

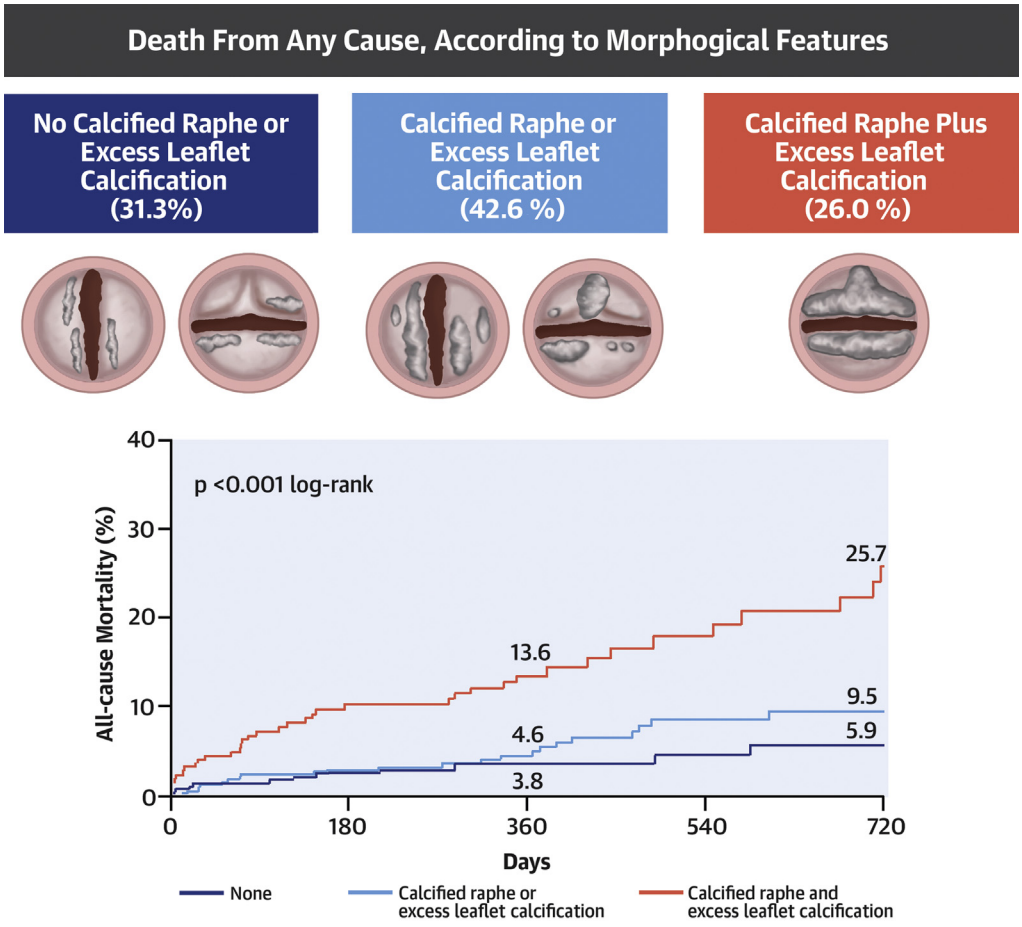
STATISTICAL ANALYSIS. Continuous variables are presented as means and standard deviations or medians and interquartile ranges. Categorical variables are provided with percentages. We compared continuous variables between 2 groups with the Student's *t*-test or Mann-Whitney *U* test, and we compared categorical variables with the chi-square or Fisher exact test. Comparisons of continuous variables among 3 groups were performed with the analysis of variance or Kruskal-Wallis test as appropriate. Cumulative rates of death at 1 and 2 years as well as aortic valve reintervention at 2 years were calculated using the Kaplan-Meier survival analysis, and the log-rank test was used for comparison across the groups. Univariable Cox regression models were used to evaluate correlates of all-cause mortality. Statistically significant variables with a p value <0.10 by univariable analysis were included in the multivariable model. The final model was determined by forward and backward elimination procedures with a threshold p value <0.10. The proportional hazard assumption was confirmed by examination of log (−log [survival]) curves and by testing of partial (Schoenfeld) residuals, and no relevant violations were found. The estimated hazard ratio with 95% confidence interval (CI) was provided by the Cox model. Baseline characteristics and outcomes were also assessed in patients with or without aortopathy defined as ascending aorta diameter ≥40 or 45 mm, respectively. All statistical analyses were performed using SPSS software version 24.0 (SPSS, Inc., Armonk, New York) and Stata version 14.2 (StataCorp, College Station, Texas). A 2-sided p value of <0.05 was considered to be statistically significant.

FIGURE 3 Time-to-Event Curves for the Primary Endpoint and Other Selected Endpoints



(A) All-cause mortality (the primary endpoint) and cardiovascular mortality. **(B and C)** All-cause mortality stratified by raphe and leaflet calcification, respectively. Event rates were calculated with the use of Kaplan-Meier methods and were compared with the log-rank test.

CENTRAL ILLUSTRATION **Death From Any Cause According to Morphological Features**



Yoon, S.-H. et al. J Am Coll Cardiol. 2020;76(9):1018-30.

(Top) Schematic presentations of various bicuspid aortic valve morphology. Bicuspid aortic valve with no morphological features (calcified raphe or excess leaflet calcification), either, or both of these features. **(Bottom)** All-cause mortality according to the morphological features. Event rates were calculated with the use of Kaplan-Meier methods and were compared with the log-rank test.

RESULTS

PATIENTS. A total of 1,070 patients undergoing TAVR using the contemporary devices across 24 participating centers between October 2012 and October 2019 were enrolled from the international multicenter BAV TAVR Registry. After excluding 36 patients (13 patients with tricuspid aortic valve; 22 suboptimal quality CT images; and 1 with native pure aortic insufficiency), 1,034 patients with bicuspid anatomy confirmed by central core laboratory CT analysis were included in this study (**Figure 1**). Of the study population, 610 patients (59.0%) were men, and the mean age was 74.7 years. The mean Society of Thoracic Surgeons (STS) score was 3.7%, and 708 patients (68.5%) had an STS score <4%. BAV without raphe (type 0) was observed in 107 patients (10.3%), and BAV with raphe (type 1) was observed in 927 patients (89.7%). Among patients with raphe, 461 (44.6%) had calcified raphe (**Table 1, Figure 2**). The median calcium volume was 382 mm^3, and aortopathy was observed in 436 patients (42.2%). Most procedures were performed via transfemoral access (94.3%). The Sapien 3 was the most frequently used valve (71.6%), followed by Evolut R/Pro (18.2%). Baseline characteristics according to type of raphe and aortopathy are summarized in Supplemental Tables 1 and 2.

PRIMARY ENDPOINT. Over a median follow-up period of 360 days (interquartile range: 100 to 575 days), 86 patients died in the entire cohort. All-

TABLE 2 Independent Correlates of All-Cause Mortality

	Univariate Model		Multivariate Model	
	HR (95% CI)	p Value	HR (95% CI)	p Value
Age, per increase of 1 yr	1.05 (1.02–1.08)	0.002		
Male	1.11 (0.70–1.77)	0.66		
NYHA functional class III or IV	0.87 (0.53–1.45)	0.60		
STS score, per increase of 1%	1.07 (1.03–1.11)	<0.001	1.06 (1.02–1.09)	0.002
Peripheral vascular disease	2.15 (1.28–3.63)	0.004		
Previous cerebrovascular accident	1.12 (0.58–2.18)	0.74		
Chronic pulmonary disease	1.02 (0.44–2.35)	0.96		
Prior myocardial infarction	1.39 (0.75–2.59)	0.29		
Prior CABG	0.47 (0.15–1.49)	0.20		
Prior atrial fibrillation	1.82 (1.09–3.04)	0.023	1.92 (1.15–3.23)	0.013
Aortic regurgitation ≥moderate at baseline	0.43 (0.16–1.19)	0.10		
Mitral regurgitation ≥moderate at baseline	1.40 (0.72–2.73)	0.32		
LVEF at baseline, per increase of 10%	1.05 (0.90–1.23)	0.56		
Raphe type (type 1 noncalcified raphe as control)		0.002		0.006
Calcified raphe	2.07 (1.27–3.38)	0.004	1.91 (1.17–3.14)	0.01
No raphe	0.39 (0.09–1.65)	0.20	0.39 (0.09–1.65)	0.20
Excess leaflet calcification	2.57 (1.56–4.23)	<0.001	2.33 (1.41–3.85)	0.001
Aortopathy (ascending aorta diameter ≥45 mm)	1.72 (0.96–3.08)	0.068		
Nontransfemoral access	2.13 (1.09–4.16)	0.026	2.32 (1.18–4.53)	0.014

CABG = coronary artery bypass grafting; CI = confidence interval; HR = hazard ratio; other abbreviations as in Table 1.

cause mortality at 1 and 2 years was 5.9% and 12.5%, respectively. Patients with raphe had higher 2-year all-cause mortality compared to those without raphe (13.5% vs. 2.4%; log-rank p = 0.04) (Supplemental Figure 1). With stratification according to calcification in raphe, type 1 calcified raphe group had significantly higher 2-year all-cause mortality than type 1 noncalcified raphe or type 0 groups (17.7% vs. 9.3% vs. 2.4%; log-rank p = 0.001). Patients with excess leaflet calcification had significantly higher 2-year all-cause mortality than those with mild leaflet calcification (18.9% vs. 6.5%; log-rank p < 0.001) (**Figure 3**). Furthermore, 2-year all-cause mortality was significantly higher in patients with both calcified raphe plus excess leaflet calcification compared with those with one or none of these morphological features (25.7% vs. 9.5% vs. 5.9%; log-rank p < 0.001) (**Central Illustration**).

On multivariable analysis, the factors that had a significant association with 2-year mortality were STS score (hazard ratio per 1% increase: 1.06; 95% CI: 1.02 to 1.09; p = 0.002), prior atrial fibrillation (hazard ratio: 1.92; 95% CI: 1.15 to 3.23; p = 0.013), presence of calcified raphe (hazard ratio compared to noncalcified raphe: 1.91; 95% CI: 1.17 to 3.14; p = 0.01), excess leaflet calcification (hazard ratio: 2.33; 95% CI: 1.41 to 3.85; p = 0.001), and nontransfemoral access (hazard ratio: 2.32; 95% CI: 1.18 to 4.53; p = 0.014) (**Table 2**). Neither number of raphe (presence or absence of raphe) nor aortopathy (ascending aorta diameter ≥40 or 45 mm) were independently associated with 2-year mortality (Supplemental Table 3, Supplemental Figure 2).

OTHER CLINICAL ENDPOINTS. Baseline characteristics and procedural and clinical outcomes according to morphological features (calcified raphe and excess leaflet calcification) were summarized in **Table 3** and Supplemental Table 4. Conversion to surgery occurred in 9 patients (0.9%), but no coronary obstructions were observed. Aortic root injury occurred more frequently in patients with both calcified raphe plus excess leaflet calcification than those with 1 or none of these morphological features (4.5% vs. 0.7% vs. 0.9%; p < 0.001), but there was no significant difference in second valve implantation among the 3 groups. Mean gradient did not significantly differ among the 3 groups, whereas there were statistically significant differences in effective orifice area and left ventricular ejection fraction at discharge. Moderate-to-severe paravalvular regurgitation was more frequent in patients with both calcified raphe plus excess leaflet calcification (6.5% vs. 2.5% vs. 1.6%; p = 0.002), so was mild or greater paravalvular regurgitation (**Figure 4**). The incidences of all-cause 30-day mortality and composite endpoint were significantly higher in this group (p = 0.016 and

TABLE 3 Procedural and Clinical Outcomes According to Valve Morphology

		Morphological Features			
	Overall (N = 1,034)	None (n = 324)	Calcified Raphe or Excess Leaflet Calc (n = 441)	Calcified Raphe Plus Excess Leaflet Calc (n = 269)	p Value
Procedural outcomes					
Conversion to surgery	9 (0.9)	1 (0.3)	2 (0.5)	6 (2.2)	0.028
Coronary obstruction	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	–
Aortic root injury	18 (1.7)	3 (0.9)	3 (0.7)	12 (4.5)	<0.001
Implantation of second valve	14 (1.4)	4 (1.2)	3 (0.7)	7 (2.6)	0.10
Echocardiographic findings					
Aortic valve gradient, mm Hg	10.6 ± 5.0	10.8 ± 5.4	10.4 ± 4.3	10.9 ± 5.6	0.37
Effective orifice area, cm^2	1.7 ± 0.5	1.7 ± 0.4	1.7 ± 0.5	1.8 ± 0.5	0.053
LVEF, %	56.3 ± 14.0	59.0 ± 13.3	55.3 ± 14.1	54.5 ± 14.4	<0.001
Paravalvular regurgitation ≥mild*	291 (28.6)	63 (19.8)	130 (29.7)	98 (37.3)	<0.001
Paravalvular regurgitation ≥moderate*	33 (3.2)	5 (1.6)	11 (2.5)	17 (6.5)	0.002
Clinical outcomes					
Death at 30 days					
From any cause	21 (2.0)	5 (1.5)	5 (1.1)	11 (4.1)	0.016
From cardiac cause	17 (1.6)	4 (1.2)	3 (0.7)	10 (3.7)	0.009
Death at 1 yr					
From any cause	55 (6.7)	10 (3.8)	16 (4.6)	29 (13.6)	<0.001
From cardiac cause	33 (3.9)	6 (2.2)	6 (2.7)	21 (9.6)	<0.001
Death at 2 yrs					
From any cause	74 (12.5)	12 (5.9)	24 (9.5)	38 (25.7)	<0.001
From cardiac cause	40 (5.9)	6 (2.2)	9 (3.6)	25 (14.4)	<0.001
Stroke	28 (2.7)	9 (2.8)	12 (2.7)	7 (2.6)	>0.99
Major vascular complication	34 (3.3)	8 (2.5)	12 (2.7)	14 (5.2)	0.12
Bleeding (life-threatening or major)	37 (3.6)	10 (3.1)	14 (3.2)	13 (4.9)	0.46
Acute kidney injury (stage 2 or 3)	20 (1.9)	7 (2.2)	6 (1.4)	7 (2.6)	0.43
Composite endpoint	86 (8.3)	20 (6.2)	28 (6.3)	38 (14.1)	<0.001
Aortic valve reintervention	5 (0.7)	2 (0.9)	2 (0.6)	1 (0.4)	0.91
New permanent pacemaker†	118 (12.2)	31 (10.3)	50 (11.9)	37 (15.1)	0.23

Values are n (%) or mean ± SD. *1,018 patients with available echocardiographic data were included in the analysis. †966 patients without prior permanent pacemaker were included in the analysis.

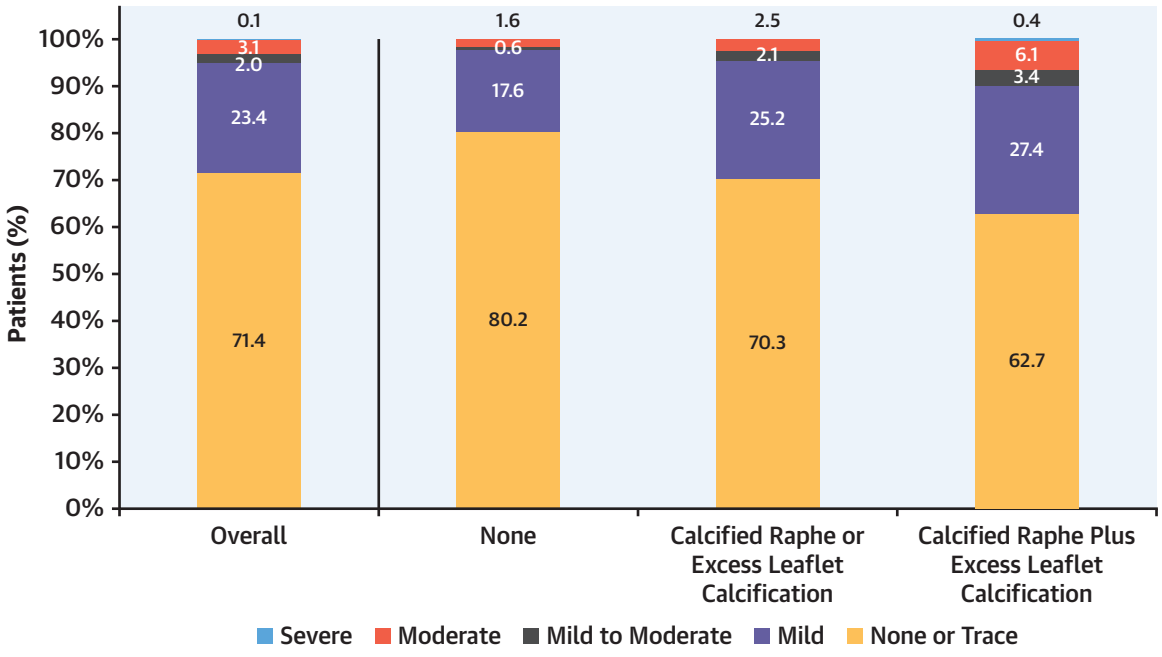
LVEF = left ventricular ejection fraction.

$p < 0.001$, respectively). Aortic reintervention occurred in 5 (0.7%) patients at 2 years. Outcomes according to raphe type and aortopathy were shown in Supplemental Tables 5 and 6. Patients with ascending aorta diameter 45 mm or more tended to have more frequent moderate or severe paravalvular regurgitation (6.3% vs. 2.8%; $p = 0.054$), and significantly higher rates of 30-day mortality and 1- and 2-year cardiovascular mortality. On multivariate analysis, ascending aorta diameter 45 mm or more was not independently associated with cardiovascular mortality (Supplemental Table 7).

DISCUSSION

This is the first large-scale study of patients with bicuspid aortic stenosis who had high resolution pre-procedural CT scans and an independent core laboratory analysis used for the diagnosis and assessment of bicuspid morphology. In our study of 1,034 patients with bicuspid anatomy, we found that overall outcomes of TAVR were acceptable despite technical challenges, and morphological features of bicuspid aortic valve such as calcified raphe and excess leaflet calcification were independently associated with increased 2-year all-cause mortality. Aortopathy was commonly observed in our cohort, but was not independently associated with increased all-cause and cardiovascular mortality. Patients with combined calcified raphe and excessive leaflet calcium were the highest risk phenotype associated with more frequent procedural complications, such as aortic root injury and paravalvular regurgitation, and a 3-fold higher mortality. In our cohort, one-quarter

FIGURE 4 Paravalvular Aortic Regurgitation Stratified by Morphological Features



Rates of paravalvular regurgitation according to morphological features.

of BAV patients had unfavorable morphological features, with both calcified raphe plus excess leaflet calcification representing the highest-risk phenotype. Conversely, the remaining three-quarters of BAV patients without the high-risk phenotype had favorable procedural outcomes and midterm mortality. These findings in conjunction with surgical risk assessment can help triage patients appropriately to transcatheter versus surgical valve replacement to optimize clinical outcomes.

Although the Sievers' classification using the number and location of raphe has been widely used to understand the various BAV morphology (25), successful outcomes of TAVR may be more dependent on factors such as overall calcium burden and presence of calcified raphe, which can prevent optimal device expansion. In our cohort, the majority of BAV patients (89.7%) had raphe and approximately one-half of them showed calcification in raphe. Outcomes of the no raphe group (type 0 BAV) were excellent despite challenges in annulus measurement and optimal valve implantation. Increased procedural experience and use of multimodality imaging might play a significant role (27). The presence of raphe itself was not independently associated with increased 2-year all-cause mortality. In fact, the type 1 calcified raphe group showed worse outcomes, suggesting categorization according to presence of calcified raphe, rather than the number of raphe, would add prognostic value in bicuspid patients undergoing TAVR. Furthermore, quantification of leaflet calcification helped identify the highest-risk phenotype with both calcified raphe and excessive leaflet calcification.

Procedural complication rates varied significantly among different bicuspid valve phenotypes. Aortic root injury is a life-threatening complication, occurring in 1.7% of the overall cohort. This rose up to 4.5% in patients with both calcified raphe plus excessive leaflet calcification. Similarly, the overall rate of moderate to severe paravalvular regurgitation was 3.2%, which increased to 6.5% in patients with these 2 morphological features. This hostile BAV anatomy may hinder the expansion and sealing of transcatheter heart valve within aortic annulus, leading to significant paravalvular regurgitation. Attempts to decrease the paravalvular regurgitation by selection

of larger transcatheter valves or performing balloon post-dilation may also have resulted in aortic root injury. Conversely, patients without the highest-risk phenotype showed excellent procedural outcomes. For adoption of TAVR in the young and low-risk patients with bicuspid anatomy, TAVR outcomes must comply with performance benchmarks set by outcomes of surgical aortic valve replacement in the recent intermediate- or low-risk trials (9–12): early mortality around 1%, major vascular complications, and moderate-severe paravalvular regurgitation <5%. In addition, catastrophic events such as aortic root injury must occur in <1% of patients. In our study, TAVR with the new-generation devices for intermediate- and low-risk patients with bicuspid anatomy met these standards when they did not have the highest-risk phenotype. This may support the safety and efficacy of TAVR for selected bicuspid anatomy, whereas high complication rates were noted among patients with the highest-risk phenotype, suggesting the limitation of TAVR with the current technology.

Due to the higher rates of procedural complications and associated poorer outcomes (28,29), patients with both calcified raphe plus excess leaflet calcification had significantly higher 2-year all-cause mortality. The 2-year all-cause mortality after TAVR using the contemporary devices were 9.5% and 5.9% among patients with 1 or none of the anatomical risk factors, which are acceptable based on those of low- and intermediate-risk randomized trials (4.5% from low-risk and 16.7% from intermediate-risk trials) (8,12). In contrast, 2-year all-cause mortality was 25.7% among BAV patients with the highest-risk phenotype in patients undergoing contemporary TAVR. Surgical outcomes are generally not affected by aortic valve structure, and hence, TAVR should be avoided for patients with the highest-risk phenotype unless the patients are at very high risk for surgery.

The decision whether TAVR or surgery has been generally made by multiple factors. Now that a series of randomized trials showed the noninferiority or superiority of TAVR irrespective of clinical risk profile, the decision whether TAVR or surgery will rely more on the suitability for each treatment. Anatomic factors such as porcelain aorta preclude surgery, whereas poor femoral access, severe left ventricular outflow tract calcification, or low take-off coronary artery require cautious procedural planning for TAVR (29,30). The assessment of these factors has been already integrated into clinical practice to provide optimal individual treatment. Nonetheless, our study sounds the alarm in patients with bicuspid anatomy. Our findings suggest TAVR should not be withheld or recommended simply because of BAV. CT assessment of bicuspid aortic valve morphology may help differentiate patients with high-risk and favorable phenotypes. For the further expansion of TAVR toward BAV population, we need randomized trials of TAVR in the BAV population, for which patients with favorable bicuspid phenotypes would be a reasonable target. Until then, our findings might provide information for better patient selection for TAVR and help to guide the optimal therapy in patients with bicuspid anatomy.

STUDY LIMITATIONS. First, this study had the inherent limitations of an observational study without center-independent adjudication of adverse events and an independent core laboratory to assess paravalvular regurgitation severity. Second, calcium volume measurement with contrast CT scan, although not the gold standard for assessment of aortic valve calcification, has been validated in multiple studies (18,26) and, in addition, allows assessment of the distribution of calcification. Third, the average age was 75 years, and as such, the extrapolation of our findings to the younger bicuspid patients should be carefully considered. Fourth, although aortopathy was not independently associated with increased 2-year all-cause and cardiovascular mortality in our cohort, long-term risks of aortic aneurysm formation and aortic dissection after TAVR are unknown. Fifth, device selection was not randomized but was at the operator's discretion, and patient selection as well as operator experience may have affected the observed outcomes. Sixth, we did not assess long-term clinical outcomes and valve durability; relatively high rates of mild or greater paravalvular regurgitation may affect long-term outcomes. Post-procedural CT findings of eccentric and suboptimal expansion of transcatheter heart valves in bicuspid anatomy raises the concerns about increased risk of future valve deterioration (31). Therefore, particularly for younger patients, the decision regarding whether to proceed with TAVR or surgery should be weighed against the potential long-term risk of aortic valve reintervention.

CONCLUSIONS

Outcomes of TAVR in bicuspid aortic stenosis depend on valve morphology. Calcified raphe and

excess leaflet calcification were associated with increased risk of procedural complications and midterm mortality. These data suggest caution against generalization of the excellent outcomes of recent low-risk TAVR clinical trials to all bicuspid aortic stenosis patients and call for taking into account the anatomical risk assessed by computed tomography in conjunction with surgical risk to decide between transcatheter or surgical valve replacement options.

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PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: BAV morphology such as calcified raphe and excess leaflet calcification were associated with worse procedural and mid-term clinical outcomes after TAVR. Assessment of bicuspid aortic valve anatomy by CT can identify patients likely to gain greatest benefit from TAVR.

TRANSLATIONAL OUTLOOK: Randomized clinical trials are needed to compare the outcomes of TAVR and surgical aortic valve replacement in patients with bicuspid aortic valve stenosis of various morphologies.

REFERENCES

1. Fedak PW, Verma S, David TE, Leask RL, Weisel RD, Butany J. Clinical and pathophysiological implications of a bicuspid aortic valve. Circulation 2002;106:900–4.

2. Siu SC, Silversides CK. Bicuspid aortic valve disease. J Am Coll Cardiol 2010;55:2789–800.

3. Michelena HI, Desjardins VA, Avierinos JF, et al. Natural history of asymptomatic patients with normally functioning or minimally dysfunctional bicuspid aortic valve in the community. Circulation 2008;117:2776–84.

4. Ward C. Clinical significance of the bicuspid aortic valve. Heart 2000;83:81–5.

5. Leon MB, Smith CR, Mack M, et al. Transcatheter aortic-valve implantation for aortic stenosis in patients who cannot undergo surgery. N Engl J Med 2010:1597–607.

6. Smith CR, Leon MB, Mack MJ, et al. Transcatheter versus surgical aortic-valve replacement in high-risk patients. N Engl J Med 2011;364:2187–98.

7. Adams DH, Popma JJ, Reardon MJ, et al. Transcatheter aortic-valve replacement with a self-expanding prosthesis. N Engl J Med 2014; 370:1790–8.

8. Leon MB, Smith CR, Mack MJ, et al. Transcatheter or surgical aortic-valve replacement in intermediate-risk patients. N Engl J Med 2016; 374:1609–20.

9. Reardon MJ, Van Mieghem NM, Popma JJ, et al. Surgical or transcatheter aortic-valve replacement in intermediate-risk patients. N Engl J Med 2017; 376:1321–31.

10. Thourani VH, Kodali S, Makkar RR, et al. Transcatheter aortic valve replacement versus surgical valve replacement in intermediate-risk patients: a propensity score analysis. Lancet 2016;387:2218–25.

11. Mack MJ, Leon MB, Thourani VH, et al. Transcatheter aortic-valve replacement with a balloon-expandable valve in low-risk patients. N Engl J Med 2019;380:1695–705.

12. Popma JJ, Deeb GM, Yakubov SJ, et al. Transcatheter aortic-valve replacement with a self-expanding valve in low-risk patients. N Engl J Med 2019;380:1706–15.

13. Hira RS, Vemulapalli S, Li Z, et al. Trends and outcomes of off-label use of transcatheter aortic valve replacement: insights from the NCDR STS/ACC TVT Registry. JAMA Cardiol 2017;2:846–54.

14. Yoon SH, Bleiziffer S, De Backer O, et al. Outcomes in transcatheter aortic valve replacement for bicuspid versus tricuspid aortic valve stenosis. J Am Coll Cardiol 2017;69:2579–89.

15. Makkar RR, Yoon S-H, Leon MB, Chakravarty T. Association between transcatheter aortic valve replacement for bicuspid vs tricuspid aortic stenosis and mortality or stroke. JAMA 2019;321:2193–202.

16. Hayashida K, Bouvier E, Lefevre T, et al. Transcatheter aortic valve implantation for patients with severe bicuspid aortic valve stenosis. Circ Cardiovasc Interv 2013;6:284–91.

17. Tanaka R, Yoshioka K, Niinuma H, Ohsawa S, Okabayashi H, Ehara S. Diagnostic value of cardiac CT in the evaluation of bicuspid aortic stenosis: comparison with echocardiography and operative findings. AJR Am J Roentgenol 2010; 195:895–9.

18. Blanke P, Weir-McCall JR, Achenbach S, et al. Computed tomography imaging in the context of transcatheter aortic valve implantation (TAVI)/transcatheter aortic valve replacement (TAVR): an expert consensus document of the Society of Cardiovascular Computed Tomography. J Am Coll Cardiol Img 2019;12:1–24.

19. Webb J, Gerosa G, Lefevre T, et al. Multicenter evaluation of a next-generation balloon-expandable transcatheter aortic valve. J Am Coll Cardiol 2014;64:2235–43.

20. Grube E, Van Mieghem NM, Bleiziffer S, et al. Clinical outcomes with a repositionable self-expanding transcatheter aortic valve prosthesis: the international FORWARD Study. J Am Coll Cardiol 2017;70:845–53.

21. Am IT, Walters DL, Dumonteil N, et al. Transcatheter aortic valve replacement for severe symptomatic aortic stenosis using a repositionable valve system: 30-day primary endpoint results from the REPRISE II study. J Am Coll Cardiol 2014;64:1339–48.

22. Kim W-K, Hengstenberg C, Hilker M, et al. The SAVI-TF registry: 1-year outcomes of the European post-market registry using the ACURATE neo transcatheter heart valve under real-world conditions in 1,000 patients. J Am Coll Cardiol Intv 2018;11:1368–74.

23. Willson AB, Rodes-Cabau J, Wood DA, et al. Transcatheter aortic valve replacement with the St. Jude Medical Portico valve: first-in-human experience. J Am Coll Cardiol 2012;60:581–6.

24. Kappetein AP, Head SJ, Genereux P, et al. Updated standardized endpoint definitions for transcatheter aortic valve implantation: the Valve Academic Research Consortium-2 consensus document. J Am Coll Cardiol 2012;60:1438–54.

25. Sievers HH, Schmidtke C. A classification system for the bicuspid aortic valve from 304 surgical specimens. J Thorac Cardiovasc Surg 2007;133:1226–33.

26. Jilaihawi H, Makkar RR, Kashif M, et al. A revised methodology for aortic-valvar complex calcium quantification for transcatheter aortic valve implantation. Eur Heart J Cardiovasc Imaging 2014;15:1324–32.

27. Bax JJ, Delgado V, Hahn RT, et al. Transcatheter aortic valve replacement: role of multimodality imaging in common and complex clinical scenarios. J Am Coll Cardiol Img 2020;13:124–39.

28. Kodali S, Pibarot P, Douglas PS, et al. Paravalvular regurgitation after transcatheter aortic valve replacement with the Edwards sapien valve in the PARTNER trial: characterizing patients and impact on outcomes. Eur Heart J 2015;36:449–56.

29. Barbanti M, Yang TH, Rodes Cabau J, et al. Anatomical and procedural features associated with aortic root rupture during balloon-expandable transcatheter aortic valve replacement. Circulation 2013;128:244–53.

30. Ribeiro HB, Webb JG, Makkar RR, et al. Predictive factors, management, and clinical outcomes of coronary obstruction following transcatheter aortic valve implantation: insights from a large multicenter registry. J Am Coll Cardiol 2013;62:1552–62.

31. Kawamori H, Yoon SH, Chakravarty T, et al. Computed tomography characteristics of the aortic valve and the geometry of SAPIEN 3 -transcatheter heart valve in patients with bicuspid aortic valve disease. Eur Heart J Cardiovasc Imaging 2018;19:1408–18.

KEY WORDS aortic stenosis, bicuspid aortic valve, transcatheter aortic valve implantation

APPENDIX For supplemental tables and figures, please see the online version of this paper.