

A Bicuspid Aortic Valve Imaging Classification for the TAVR Era

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ABSTRACT

OBJECTIVES This study sought to evaluate transcatheter aortic valve replacement (TAVR) in bicuspid aortic valve (BAV) aortic stenosis (AS), with a particular emphasis on TAVR-directed bicuspid aortic valve imaging (BAVi) of morphological classification.

BACKGROUND TAVR has been used to treat BAV-AS but with heterogeneous outcomes and uncertainty regarding the relevance of morphology.

METHODS In 14 centers in the United States, Canada, Europe, and Asia, 130 BAV-AS patients underwent TAVR. Baseline cardiac computed tomography (CT) was analyzed by a dedicated Corelab. Outcomes were assessed in line with Valve Academic Research Consortium criteria.

RESULTS Bicommissural BAV (vs. tricommissural) accounted for 68.9% of those treated in North America, 88.9% in Europe, and 95.5% in Asia ($p = 0.003$). For bicommissural bicuspid, non-raphe type (vs. raphe type) BAV accounted for 11.9% of those treated in North America, 9.4% in Europe, and 61.9% in Asia ($p < 0.001$). Overall rates of 30-day mortality (3.8%) and cerebrovascular events (3.2%) were favorable and similar among anatomical subsets. The rate of new permanent pacemaker insertion was high (26.2%) and similar between balloon-expandable (BE) and self-expanding (SE) designs (BE: 25.5% vs. SE: 26.9%; $p = 0.83$); there was a trend to greater permanent pacemaker insertion in BE TAVR in the presence of coronary cusp fusion BAV morphology. Paravalvular aortic regurgitation (PAR) \geq moderate was 18.1% overall but lower at 11.5% in those with pre-procedural CT. In the absence of pre-procedural CT, there was an excess of PAR in BE TAVR that was not the case in those with a pre-procedural CT; SE TAVR required more post-dilation. Predictors of PAR included intercommissural distance for bicommissural bicuspid (odd ratio [OR]: 1.37; 95% confidence interval [CI]: 1.02 to 1.84; $p = 0.036$) and lack of a baseline CT for annular measurement (OR: 3.03; 95% CI: 1.20 to 7.69; $p = 0.018$).

CONCLUSIONS In this multicenter study, TAVR achieved favorable outcomes in patients with pre-procedural CT, with the exception of high permanent pacemaker rates for all devices and shapes. (J Am Coll Cardiol Img 2016;■:■-■)
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**ABBREVIATIONS
AND ACRONYMS****BAV** = bicuspid aortic valve**CT** = computed tomography**HU** = Hounsfield unit**MPR** = multiplanar reformatted**PAR** = paravalvular
regurgitation**PPM** = permanent pacemaker**TAV** = trileaflet aortic valve**TAVR** = transcatheter aortic
valve replacement

Bicuspid aortic valve (BAV) disease is the most common congenital cardiac abnormality in humans and is a significant risk factor for premature aortic valve disease, most commonly aortic stenosis (AS) (1). Some surgical series have demonstrated that BAV is much more common than previously appreciated, even in the elderly (2). Moreover, with favorable data for transcatheter aortic valve replacement (TAVR) in high- and extreme-risk cohorts well-established in trileaflet aortic valve (TAV) stenosis (3–7), TAVR is currently being evaluated

in younger age groups at intermediate surgical risk (8), whose frequency of BAV is even more common; indeed, some series in Asia have reported an incidence of BAV in up to half of patients presenting with TAVR (9). Limited data exist for outcomes from TAVR in BAV and, despite promising single-center series (10–13), a recently published multicenter series raised concerns about an excess of bioprosthetic regurgitation (14). We sought to further evaluate outcomes of TAVR in BAV, in line with Valve Academic Research Consortium (VARC-2) criteria (15), with particular emphasis on the potential role of pre-procedural imaging to identify morphological subtypes and stratify risk of complications with a TAVR-directed bicuspid aortic valve imaging (BAVi) morphological classification.

METHODS

STUDY POPULATION. One hundred thirty consecutive patients with severe native AS (aortic valve area was determined by echocardiography $<1\text{ cm}^2$) and BAV leaflet morphology undergoing TAVR were enrolled from 14 centers across Canada, China, France, Hong Kong, Italy, Germany, and the United

States. Edward Sapien, Sapien XT, and Sapien 3 transcatheter heart valves (Edwards Lifesciences, Irvine, California) and Corevalve (Medtronic, Inc., Minneapolis, Minnesota) transcatheters were implanted using standard techniques (3,6).

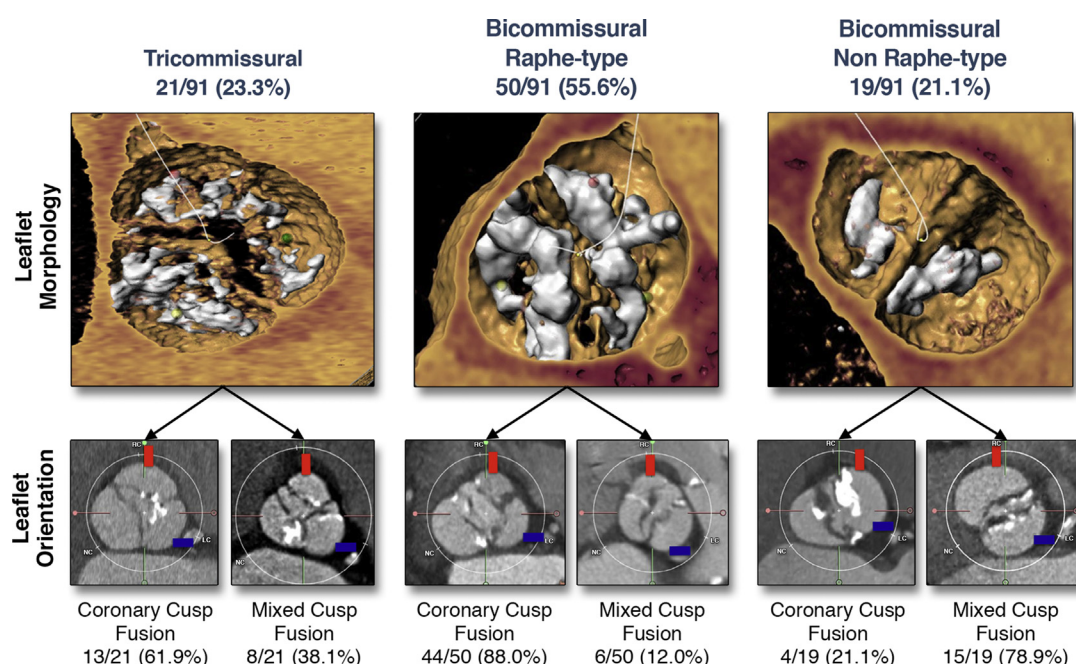
**MULTIDETECTOR COMPUTED TOMOGRAPHY ACQUISITION
AND ANALYSES.**

Computed tomography (CT) scans were performed using several different scanners, 64-slice or higher. Multiple CT scan protocols incorporating electrocardiography gating were used according to site-specific practice. In total, 91 of 130 patients (70%) had a baseline contrast cardiac CT performed, which were all assessed by dedicated TAVR CT Corelab (Cedars-Sinai Heart Institute). A systolic phase was evaluated wherever available. All analyses were overseen and confirmed by a single expert reader (H.J.). For annular and atrioventricular dimensions, curved multiplanar reconstruction analyses were performed using software specifically customized for valve analysis (3mensio Valves version 7.0 software, 3-mensio Medical Imaging BV, Bilthoven, the Netherlands). Further details of CT analyses are described in the [Online Methods](#). BAV morphology was delineated by the CT Corelab if a contrast CT was available and by the treating site if only echocardiographic imaging was performed.

BAV MORPHOLOGY ANALYSIS. Several classifications of BAV morphology exist, including that of Sievers and Schmidtke (16) and that of the BAV consortium (1) ([Online Figure 1](#)). A novel TAVR-directed and simplified non-numerical classifications based on heterogeneous leaflet morphologies and on leaflet orientation were also used ([Figure 1](#)). This classification specified 3 BAV morphologies as tri-commissural (1 commissure completely fused between 2 cusps, often referred to as “functional” or

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FIGURE 1 Proposed TAVR-Specific BAV Classification

(Top panel) Leaflet morphology is classified on the basis of number of commissures (2 or 3) and, in the presence of 2 commissures, the presence or absence of a raphe. This classification yields tricommissural, bicommisural raphe type, and bicommisural non-raphe types. **(Bottom panel)** Leaflet orientation is classified on the basis of cusp fusion, which is either coronary cusp fusion or mixed non-coronary–coronary cusp fusion. Take off of the right coronary artery is indicated by the red line; take off of the left coronary artery is indicated by the blue line. Values, for example, 21 of 91 (23.3%), are overall frequency of BAV treated with TAVR relative to overall TAVR cases. BAV = bicuspid aortic valve; TAVR = transcatheter aortic valve replacement.

“acquired” [functional/acquired] BAV by the surgical and interventional community [in this morphology, fusion is not seen in the basal third of the sinus and occurs at or close to the commissural level ([Online Figure 2](#))]; bicommisural raphe type (in which 2 cusps fused by a fibrous or calcified ridge of various heights, does not reach the height of the commissure [in this morphology, fusion of cusps occurs at or proximal to the basal third of the sinus ([Figure 1](#)), and the raphe may also vary in terms of calcification and vertical height ([Online Figure 2](#))]); and bicommisural non-raphe type (2 cusps completely fused from their basal origin by no visible seam [in this morphology, there are only 2 commissures with no raphe or third commissure ([Figure 1](#))]). Leaflet orientation was simplified as coronary cusp fusion (comparable to Sievers left-right for raphe type or antero-posterior for non-raphe type) or mixed coronary and noncoronary (coronary/noncoronary) cusp fusion (compare with Sievers right-non or non-left for raphe type or lateral for non-raphe type) ([17](#)).

STUDY OUTCOMES. Study outcomes were site reported using VARC-2 criteria ([15](#)). Criteria included

acute procedural, periprocedural, and 30-day outcomes. Paravalvular aortic regurgitation (PAR) and central aortic regurgitation were site reported by pre-discharge transthoracic echocardiography (TTE), in line with VARC-2 criteria.

STATISTICAL ANALYSIS. Statistics were analyzed using SPSS software (PASW version 20, SPSS Inc., Chicago, Illinois). Normality of distributions for continuous variables was tested using the Shapiro-Wilks test, and data were analyzed appropriately thereafter. Kaplan-Meier survival curves were compared for balloon-expandable (BE) versus self-expanding (SE) prostheses in BAV; data were truncated at 6 months, given the limited number of BAV cases with follow-up beyond this time point (approximately one-half). Further statistical details are described in [Online Methods](#).

RESULTS

CLINICAL CHARACTERISTICS AND OUTCOMES. A total of 130 patients with bicuspid valve stenosis were treated with internationally available devices from

Edwards Lifesciences and Medtronic in 14 centers in Canada, United States, Europe, and Asia between April 2005 and October 2014 (Online Figure 1). The overall frequency of iBAV treated with TAVR relative to overall TAVR cases was 130 of 5,130 (2.5%) but varied widely and ranged from 0.32% in Padova, Italy, to 66.7% in Chengdu, China, with a median of 2.3%. Overall, age was 76.6 ± 10.4 years, and median Society of Thoracic Surgeons (STS) score (mortality) was 4.7 (interquartile range [IQR]: 3.0 to 7.3). Other clinical characteristics are shown in Table 1. Procedural characteristics are shown in Table 2, and acute outcomes to 30 days are shown in Table 3 and Table 4. There were 2 procedural deaths: 1 annular rupture in a non-raphe type bicuspid with Sapien XT (48.1% oversizing by area and left ventricular outflow tract calcium present) and a low (deep) Corevalve implant in a heavily calcified non-raphe type bicuspid requiring conversion to surgery (no baseline CT available).

BICUSPID MORPHOLOGY, CT CHARACTERISTICS, AND CLINICAL OUTCOMES. BAV morphology was classified as tricommissural, bicommissural raphe type, or bicommissural non-raphe type (Figure 1). Sievers and BAVcon (Bicuspid Aortic Valve consortium) classifications were also used for those shapes with a baseline CT available to the Corelab (Online Figure 1).

A total of 91 patients underwent contrast CT (80 of adequate quality for annular sizing) and had bicuspid morphology delineated by the CT Corelab. In 29 patients, the treating site, using TEE, reported the morphology. An additional 10 patients had only baseline TTE reported by the site to identify bicuspid morphology, and in 3 of these reports, they were definitively bicommissural, and in 7 their bicuspid morphology was unclear and classified as “indeterminate.” This overall assessment, using Corelab adjudicated CT whenever available, yielded 24 of 130 tricommissural bicuspid (18.5%), 74 of 130 bicommissural (56.9%) raphe type bicuspid, 21 of 130 bicommissural (16.2%) non-raphe type bicuspid, 4 of 130 bicommissural, indeterminate subtypes (3.1%), and 7 of 130 bicuspid (4.4%) with indeterminate morphology. Outcomes of this overall population are shown in Table 4 and are discussed further below.

Of all BAV, bicommissural (vs. tricommissural) accounted for 68.9% of those treated in North America, 88.9% of those treated in Europe, and 95.5% of those treated in Asia ($p = 0.003$). Of bicommissural BAV, non-raphe type (vs. raphe type) accounted for 11.9% of those treated in North America, 9.4% of those treated in Europe, and 61.9% of those treated in Asia ($p < 0.001$). The age of BAV patients was 76.2 ± 12.1 years in North America, 78.6 ± 8.7 years in Europe, and 73.7 ± 7.3 years in Asia; age was significantly different between European and Asian BAV patients ($p = 0.027$) but not among the other groups.

The only significant differences in baseline characteristics between tricommissural versus bicommissural BAV were that patients with tricommissural BAV were older, 81.2 ± 10.4 years of age versus 75.7 ± 10.3 years of age, respectively ($p = 0.026$), and taller, 170.6 ± 8.6 cm versus 164.4 ± 19.4 cm, respectively ($p = 0.021$) (Online Table 1). The only significant differences in baseline characteristics between raphe type versus non-raphe type bicommissural BAV were that patients with raphe type were heavier, 70.3 ± 17.6 kg versus 60.4 ± 11.3 kg, respectively ($p = 0.003$), and had more renal impairment (29.7% vs. 5.0%, respectively; $p = 0.033$) (Online Table 1).

Analyses of the 91 cases who did have pre-procedural CT scans available (Table 5) showed,

TABLE 1 Baseline Characteristics

	All BAV TAVR (n = 130)	BAV TAVR by Device		p Value
		BE TAVR (n = 70)	SE TAVR (n = 60)	
Age, yrs	76.6 (10.4)	76.2 (11.6)	77.0 (9.0)	0.65
Weight, kg	70.1 (18.3)	75.1 (21.3)	64.1 (11.5)	0.001
Height, cm	165.5 (17.6)	168.0 (10.1)	162.4 (23.3)	0.088
Males	80 (61.5)	43/70 (61.4)	37/60 (61.7)	>0.99
STS mortality	4.7 (3.0-7.3)	4.7 (2.8-7.4)	4.7 (3.3-7.2)	0.64
Frailty	35/93 (37.6)	22/46 (47.8)	13/47 (27.7)	0.055
Baseline NYHA functional class III-IV	105/130 (80.7)	55/70 (78.6)	50/60 (83.3)	0.56
Previous PCI	18/130 (13.8)	12/70 (17.1)	6/60 (10.0)	0.31
Previous CABG	14/130 (10.8)	11/70 (15.7)	3/60 (5.0)	0.086
Baseline renal impairment	27/111 (24.3)	13/51 (25.5)	14/60 (23.3)	0.83
Diabetes	35/129 (27.1)	21/70 (30.0)	14/59 (23.7)	0.55
Pulmonary disease	50/129 (38.8)	33/70 (47.1)	17/59 (50)	0.046
Cerebrovascular disease	19/130 (14.6)	13/70 (18.6)	6/60 (10.0)	0.22
Atrial fibrillation baseline	40/129 (31.0)	21/70 (30.0)	19/59 (32.2)	0.85
PPM baseline	19/130 (14.6)	11/70 (15.7)	8/60 (13.3)	0.81
Porcelain aorta	5/111 (4.5)	4/51 (7.8)	1/60 (1.7)	0.18
Echocardiographic variables				
Baseline mean gradient	49.5 (41.0-60.0)	46.0 (38.0-58.0)	52.5 (44.0-63.5)	0.014
AVA baseline	0.64 (0.52-0.80)	0.62 (0.50-0.77)	0.64 (0.60-0.85)	0.23
Severe AR	7/130 (5.4)	4/70 (5.7)	3/60 (5.0)	>0.99
Severe MR	9/130 (6.9)	7/70 (10.0)	2/60 (3.3)	0.18
EF baseline <50%	33/130 (25.4)	18/70 (25.7)	15/60 (25.0)	>0.99

Values are n (%), n/N (%), or median (interquartile range).

AR = aortic regurgitation; AVA = aortic valve area; BAV = bicuspid aortic valve; BE = balloon-expandable; CABG = coronary artery bypass graft; EF = ejection fraction; MR = mitral regurgitation; NYHA = New York Heart Association; PCI = percutaneous coronary intervention; PPM = permanent pacemaker; SE = self-expanding; STS = Society of Thoracic Surgeons; TAVR = transcatheter aortic valve replacement.

aside from leaflet morphology, there were additional clear anatomical differences between tricommissural (so-called functional/acquired) and bicommissural (raphe or non-raphe type) bicuspid (Table 5). Bicommissural bicuspid had similar annular dimensions but significantly larger intercommissural distances, sinotubular junctions, and ascending aorta dimensions. They also tended toward greater valvular calcification by contrast (HU-850) volume. In comparison to raphe type bicommissural bicuspid, non-raphe type bicommissural bicuspid had smaller annuli and larger sinuses of Valsalva, and nonsignificant trends to taller sinuses, larger sinotubular junctions and aortic dimensions, and more valvular calcification (Table 5).

There were no significant differences in periprocedural and 30-day outcomes between bicommissural and tricommissural bicuspid (Table 4); however, there was a trend to twice the rate of post-dilation (21.6% vs. 12.5%, respectively; $p = 0.40$). There were no significant differences in most periprocedural and 30-day outcomes between non-raphe type and raphe type bicommissural bicuspid; there were statistical differences in procedural mortality (9.5% vs. 0.0%, respectively; $p = 0.047$), although this was driven by just 2 cases, and there were no statistical difference at 30 days.

TABLE 2 Procedural Characteristics

	BAV TAVR (n = 130)	BAV TAVR by Device		p Value
		BE TAVR (n = 70)	SE TAVR (n = 60)	
Procedure access				0.017
Transfemoral	114/130 (87.7)	59/70 (84.3)	55/60 (91.7)	
Alternative access	16/130 (13.3)	11/70 (15.7)	5/60 (8.3)	
Prosthesis				NA
Sapien	17 (13.1)	17/70 (24.3)	—	
Sapien XT	45 (34.6)	45/70 (64.3)	—	
Sapien 3	8 (6.2)	8/70 (11.4)	—	
Corevalve	60 (46.2)	—	60/60 (100)	
Prosthesis size*				0.39
Small	26/128 (20.3)	11/70 (15.7)	15/58 (25.9)	
Medium	64/128 (50.0)	38/70 (54.3)	26/58 (44.8)	
Large	38/128 (29.7)	21/70 (30.0)	17/58 (29.3)	
Balloon pre-dilation performed	116/127 (91.3)	64/67 (95.5)	52/60 (86.7)	0.11
Balloon post-dilation performed	24/128 (18.8)	7/69 (10.1)	17/59 (28.8)	0.011

Values are n/N (%). *Small BE = 23 mm or SE = 23 to 26 mm; medium BE = 26 mm or SE = 29 mm; large BE = 29 mm or SE = 31 mm.
NA = not available; other abbreviations as in Table 1.

OUTCOME AFTER TAVR IN BAV ACCORDING TO PROSTHESIS TYPE. There was significantly higher post-dilation with the SE prosthesis versus that for the BE prostheses (28.8% vs. 10.1%, respectively; $p = 0.011$), although the SE prosthesis group had

TABLE 3 Procedural and 30-Day Outcomes by Valve Type and Availability of CT at baseline

	BAV TAVR (n = 130)	BE TAVR (n = 70)	SE TAVR (n = 60)	p	No Pre-Procedural CT* (n = 50)	Pre-Procedural CT* (n = 80)	p Value
Procedural Outcomes							
Procedural death	2/130 (1.5)	1/70 (1.4)	1/60 (1.7)	>0.99	2/50 (4.0)	2/80 (2.5)	0.64
Prosthesis embolization	2/130 (1.5)	2/70 (2.9)	0/60 (0)	0.5	1/50 (2.0)	1/80 (1.3)	>0.99
Transcatheter-valve-in-transcatheter-valve	4/130 (3.1)	1/70 (1.4)	3/60 (5.4)	0.34	2/50 (4.0)	2/80 (2.5)	0.64
Tamponade	3/129 (2.3)	2/69 (2.9)	1/60 (1.7)	>0.99	0/50 (0)	3/80 (3.8)	0.29
Aortic root injury	3/129 (2.3)	3/69 (4.3)	0/60 (0)	0.25	2/49 (4.1)	1/80 (1.3)	0.56
Coronary compromise	0/129 (0)	0/69 (0)	0/60	NA	0/49 (0)	0/80 (0)	NA
Conversion to surgery	4/129 (3.1)	2/69 (2.9)	2/60 (3.3)	>0.99	3/49 (6.1)	1/80 (1.3)	0.15
Balloon post-dilation	24/128 (18.8)	7/69 (10.1)	17/59 (28.8)	0.011	10/49 (20.4)	14/79 (17.7)	0.82
Pre-discharge TTE							
Paravalvular AR				0.27			0.003
None/Trace	43/127 (33.9)	24/68 (35.3)	19/59 (32.2)		9/49 (18.4)	34/78 (43.6)	
Mild	61/127 (48.0)	28/68 (41.2)	33/59 (55.9)		26/49 (53.1)	35/78 (44.9)	
Moderate	19/127 (15.0)	13/68 (19.1)	6/59 (10.2)		10/49 (20.4)	9/78 (11.5)	
Severe	4/127 (3.1)	3/68 (4.4)	1/59 (1.7)		4/49 (8.2)	0/78 (0)	
Mean AV gradient	9.3 (7.0-13.0)	10.0 (7.0-13.3)	9.0 (7.0-13.0)	0.58	10.7 (7.0-13.0)	9.0 (7.0-13.0)	0.43
30-day outcomes							
Death	5/130 (3.8)	2/70 (2.9)	3/60 (5.0)	0.66	2/50 (4.0)	3/80 (3.8)	>0.99
Cerebrovascular event	4/127 (3.2)	3/67 (4.5)	1/60 (1.7)	0.3	0/49 (0)	4/78 (5.1)	0.27
Acute kidney injury \geq stage 3	1/114 (0.9)	1/68 (1.5)	0/46 (0)	>0.99	0/35 (0)	1/79 (1.3)	>0.99
New permanent pacemaker	28/107 (26.2)	14/55 (25.5)	14/52 (26.9)	0.83	10/43 (23.3)	18/64 (28.1)	0.66

Values are n/N (%) or median (interquartile range). *Of interpretable quality for annular measurement.
Abbreviations as in Table 1.

TABLE 4 Procedural and 30 Day Outcomes by BAV Morphology*

	Tricommissural* BAV (n = 24)	Bicommissural* BAV (n = 99)	p Value	Bicommissural Non-Raphe Subtype† (n = 21)	Bicommissural Raphe Subtype (n = 74)	p Value
Procedural outcomes						
Procedural death	0/24 (0)	2/99 (2.0)	>0.99	2/21 (9.5)	0/74 (0)	0.047
Prosthesis embolization	0/24 (0)	2/99 (2.0)	>0.99	0/21 (0)	2/74 (2.7)	>0.99
Transcatheter-valve-in-transcatheter-valve	0/24 (0)	4/99 (4.0)	>0.99	2/21 (9.5)	2/74 (2.7)	0.21
Tamponade	1/24 (4.2)	2/98 (2.0)	0.49	1/21 (4.8)	1/73 (1.4)	0.4
Aortic root injury	0/24 (0)	2/98 (2.0)	>0.99	1/21 (4.8)	1/73 (1.4)	0.4
Coronary compromise	0 (0)	0 (0)	>0.99	0/21 (0)	0/73 (0)	>0.99
Conversion to surgery	1/24 (4.2)	2/98 (2.0)	0.49	1/21 (4.8)	1/73 (1.4)	0.4
Balloon post-dilation	3/24 (12.5)	21/97 (21.6)	0.4	4/21 (19.0)	16/72 (22.2)	>0.99
Pre-discharge TTE			0.48			0.57
Paravalvular AR grade						
None/Trace	9/21 (42.9)	31/96 (32.3)		8/20 (40.0)	23/72 (31.9)	
Mild	8/21 (38.1)	48/96 (50.0)		9/20 (45.0)	35/72 (48.6)	
Moderate	4/21 (19.0)	13/96 (13.5)		2/20 (10.0)	11/72 (15.3)	
Severe	0/21 (0)	4/96 (4.2)		1/20 (5.0)	3/72 (4.2)	
Mean AV gradient	8 (7-13)	10 (7.4-13)		10 (7-14)	9.5 (7.8-13)	>0.99
30-day outcomes						
Death	1/24 (4.2)	4/99 (4.0)	>0.99	2/21 (9.5)	2/74 (2.7)	0.21
Cerebrovascular event	1/24 (4.2)	3/96 (3.1)	>0.99	0/20 (0)	3/72 (4.2)	0.39
Acute kidney injury ≥ stage 3	0/24 (0)	1/83 (1.2)	>0.99	0/19 (0)	1/63 (1.6)	>0.99
New permanent pacemaker	5/19 (26.3)	21/81 (25.9)	>0.99	4/18 (22.2)	16/60 (26.7)	>0.99

Values are n/N (%) or median (interquartile range). *Morphology based on all available data (n = 130). CT was analyzed by Corelab wherever available. 7 of 130 indeterminate BAV morphology, only TTE available; in 4 bicommissural cases, calcification prevented definitive delineation of raphe or non-raphe subtype.

TABLE 5 Corelab CT Evaluation of BAV Morphology*

	Tricommissural BAV (n = 21)	Bicommissural* BAV (n = 70)	p Value	Bicommissural Non-Raphe Type (n = 19)	Bicommissural Raphe Type (n = 50)	p Value
Aortic root angle, degrees	51.9 ± 8.4	50.3 ± 11.3	0.5	50.1 ± 10.6	50.8 ± 11.4	0.79
Calcium volume at HU-850 threshold, mm ³	274 (134-472)	400 (211-625)	0.10	479 (174-986)	377 (211-586)	0.46
Mean annular major dimension, mm	27.6 ± 2.9	27.6 ± 3.3	0.96	25.6 ± 3.1	38.3 ± 3.0	0.004
Mean annular minor dimension, mm	22.2 ± 2.2	22.3 ± 2.8	0.82	21.1 ± 2.9	22.7 ± 2.7	0.076
Mean aortic annulus diameter, mm	24.9 ± 2.3	25.0 ± 2.6	0.94	23.4 ± 2.5	25.5 ± 2.4	0.006
Annular eccentricity index, mm (minor/major)	0.81 (0.07)	0.82 (0.11)	0.66	0.84 (0.11)	0.81 (0.11)	0.41
Annular area, mm ²	472.5 (80.3)	486.4 (97.5)	0.57	434.4 (92.7)	505.0 (93.3)	0.015
Annular perimeter, mm	78.2 (6.7)	79.4 (8.1)	0.52	75.0 (8.1)	80.9 (7.5)	0.016
LVOT calcium present	5/21 (23.8)	29/70 (40.0)	0.21	5/19 (26.3)	22/50 (44.0)	0.27
Commissural calcium present	5/21 (23.8)	16/70 (22.9)	>0.99	7/19 (36.8)	9/50 (18.0)	0.12
Mean sinus of Valsalva diameter, mm	33.5 ± 3.4	35.2 ± 3.9	0.056	38.5 ± 3.3	34.0 ± 3.4	<0.001
Sinus of Valsalva height, mm	25.4 (3.7)	25.0 (5.0)	0.68	26.4 (5.1)	24.4 (4.8)	0.14
Intercommissural distance, mm	24.3 (2.9)	28.7 (3.6)	<0.001	27.8 (4.5)	29.1 (3.1)	0.18
STJ diameter, mm	29.5 (3.8)	32.4 (4.7)	0.006	33.5 (6.0)	32.0 (4.2)	0.25
Aortic diameter at 40 mm from annulus, mm	33.9 (3.0)	37.9 (5.2)	<0.001	38.8 (5.8)	37.7 (5.0)	0.47
Maximal mean aortic diameter, mm	36.0 (3.5)	40.9 (5.9)	<0.001	42.5 (6.4)	40.5 (6.5)	0.25
LM height, mm	15.2 (3.0)	14.8 (3.9)	0.61	15.5 (4.3)	14.5 (3.6)	0.34
RCA height, mm	19.0 (4.0)	17.3 (3.5)	0.098	17.9 (2.9)	17.1 (3.7)	0.31

Values are mean ± SD, median (IQR), or n/N (%). *Analysis of the only 91 cases with available contrast CT scans classified by BAV morphology; 1 case was classified as bicommissural but was of indeterminate subtype. **Bold** indicates statistical significance.

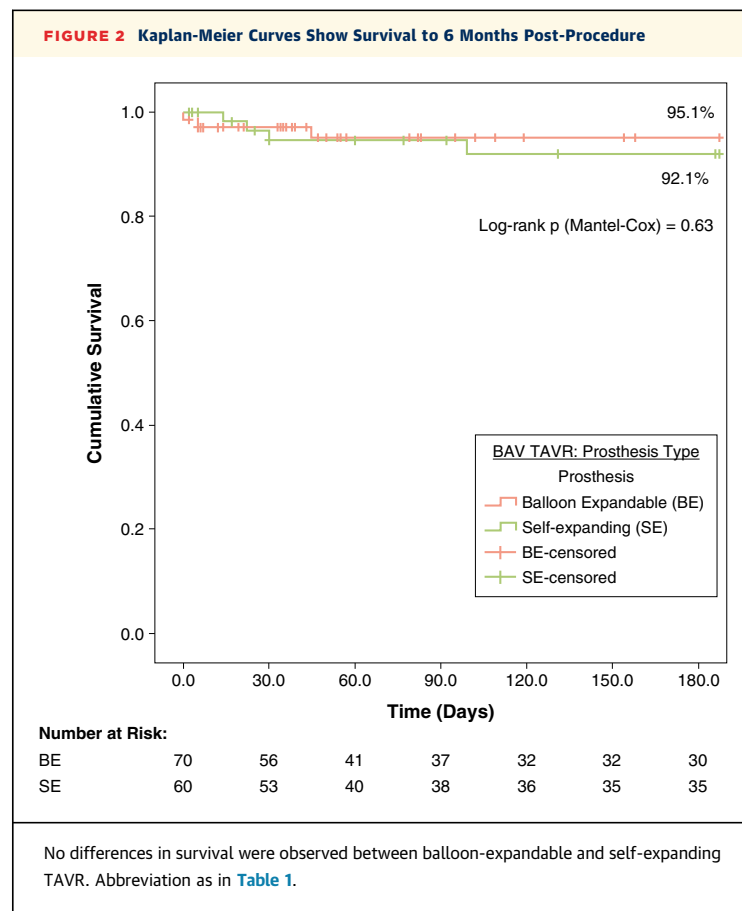
LM = left main; LVOT = left ventricle outflow tract; RCA = right coronary artery; STJ = sino-tubular junction.

higher mean baseline aortic valve gradients (52.5 vs. 46.0 mm Hg, respectively; $p = 0.014$). There were no significant differences in clinical endpoints including 30-day mortality (BE vs. SE, 2.9% vs. 5.0%, respectively; $p = 0.66$), and new permanent pacemaker (PPM) implantation (BE vs. SE, 25.5% vs. 26.9%, respectively; $p = 0.83$). For the 7 sites with BE TAVR, the median rate of new PPMs after BE TAVR was 20%. There were limited survival data available beyond 6 months, but Kaplan-Meier curves suggested similar intermediate-term survival over this time frame (Figure 2).

On pre-discharge TTE, there were similar mean bioprosthetic gradients after TAVR median of 10.0 mm Hg (IQR: 7.0 to 13.3, with BE vs. median of 9.0 mm Hg; IQR: 7.0 to 13.0; $p = 0.58$). There was a trend toward higher rates of PAR with BE than with SE prostheses (\geq moderate PAR: 23.5% vs. 11.9%, respectively; $p = 0.11$) (Figure 3) but not in those with a pre-procedural CT (\geq moderate PAR: 8.7% vs. 15.6%, respectively; $p = 0.48$). There were no cases of \geq moderate PAR with the Sapien 3 prosthesis (0 of 8 cases). There was also a nonsignificant trend to more, largely milder central AR (in all but 1 SE case with moderate central AR), on pre-discharge TTE with SE versus BE (\geq mild 8.5% vs. 1.5%, respectively; $p = 0.098$). Limited CT scans were available post-TAVR but clear differences in stent-frame expansion were observed with varying BAV anatomy that could influence valve function (Figure 4).

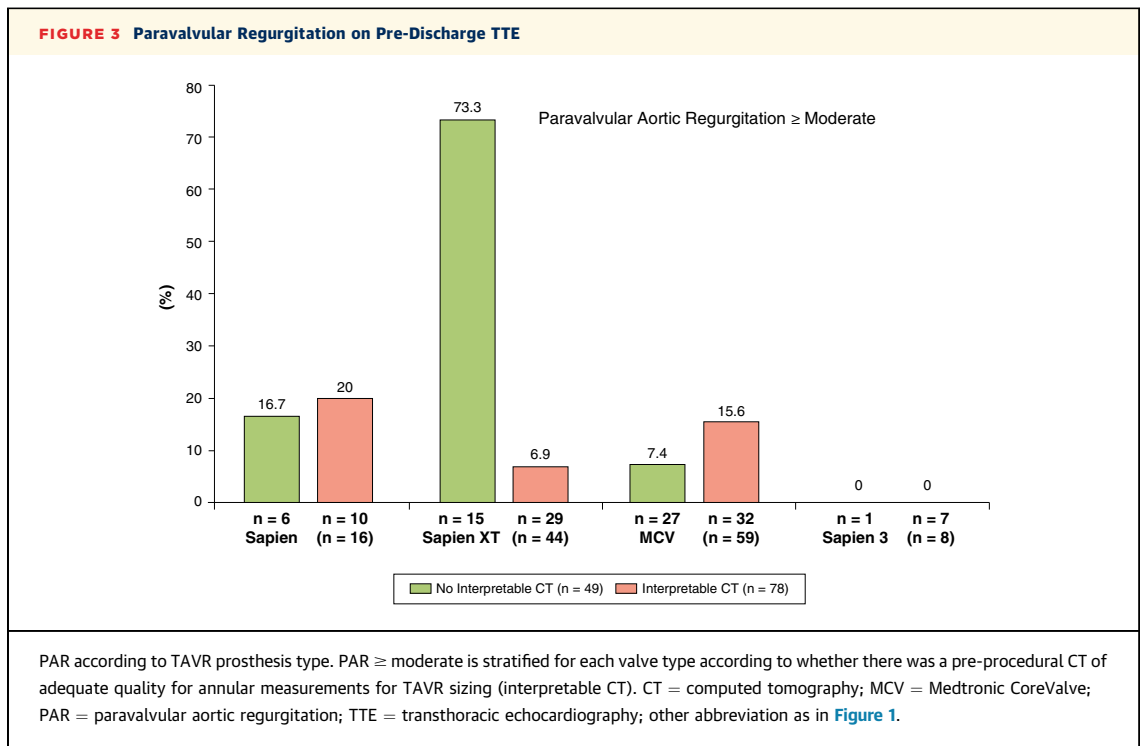
PREDICTORS OF ADVERSE OUTCOME AFTER BAV TAVR. Predictors of new PPM implantation (28 cases) and \geq moderate PAR (23 cases) were studied from all the available baseline clinical, echocardiographic, and CT parameters. The study was insufficiently powered to study predictors of cumulative mortality events ($n = 18$) but, notably, there were 2 cases of late fatal aortic dissection (beyond 30 days post-procedure), without baseline CT or any anatomical data on aortic dimension.

The only significant predictor of new PPM implantation identified was low device implantation, as interpreted by the treating center (OR: 5.21; 95% confidence interval [CI]: 1.33 to 20.39; $p = 0.017$). However, low device implantation was only significant for the prediction of PPM implantation for the SE TAVR design, with low device implantation OR was 10.0 (95% CI: 1.94 to 51.54; $p = 0.006$; $p > 0.99$ for BE TAVR). Low SE device implants had a rate of new PPM of 66.7% versus 16.7% for implants that were not reported as low ($p = 0.006$). For BE TAVR, a specific CT parameter was studied that could contribute to a posterior direction of device expansion, coronary



cuspid fusion (Figure 1, Table 4); these bicuspid valves with either Sievers left-right fusion (raphe type but also functional) or Sievers antero-posterior orientation (non-raphe type) accounted for 62 of 91 patients (68.1%) with discernible CT data. There were no differences in coronary cuspid fusion versus mixed non-coronary or coronary cuspid fusion for new PPM after TAVR with the SE device (25% [4 of 16] vs. 25% [5 of 20], respectively; $p > 0.99$). However, for the BE TAVR, there was new PPM in 9 of 29 (31.0%) of those with coronary cuspid fusion versus 1 of 7 (12.5%) in those with mixed cuspid fusion, although there were insufficient numbers to show significance ($p = 0.40$). A relationship with % prosthesis oversizing by area and new pacemaker could not be demonstrated ($p = 0.15$), and valve leaflet calcification was not predictive of new pacemaker ($p = 0.91$).

Predictors of \geq moderate PAR included inter-commissural distance (for bicommissural bicuspid only, OR: 1.37; 95% CI: 1.02 to 1.84; $p = 0.036$ and $p = 0.36$ not for tricommissural bicuspid). Calcium volume by HU-850 score ($p = 0.38$) or undersizing by CT ($p = 0.32$) did not predict PAR. However, the latter



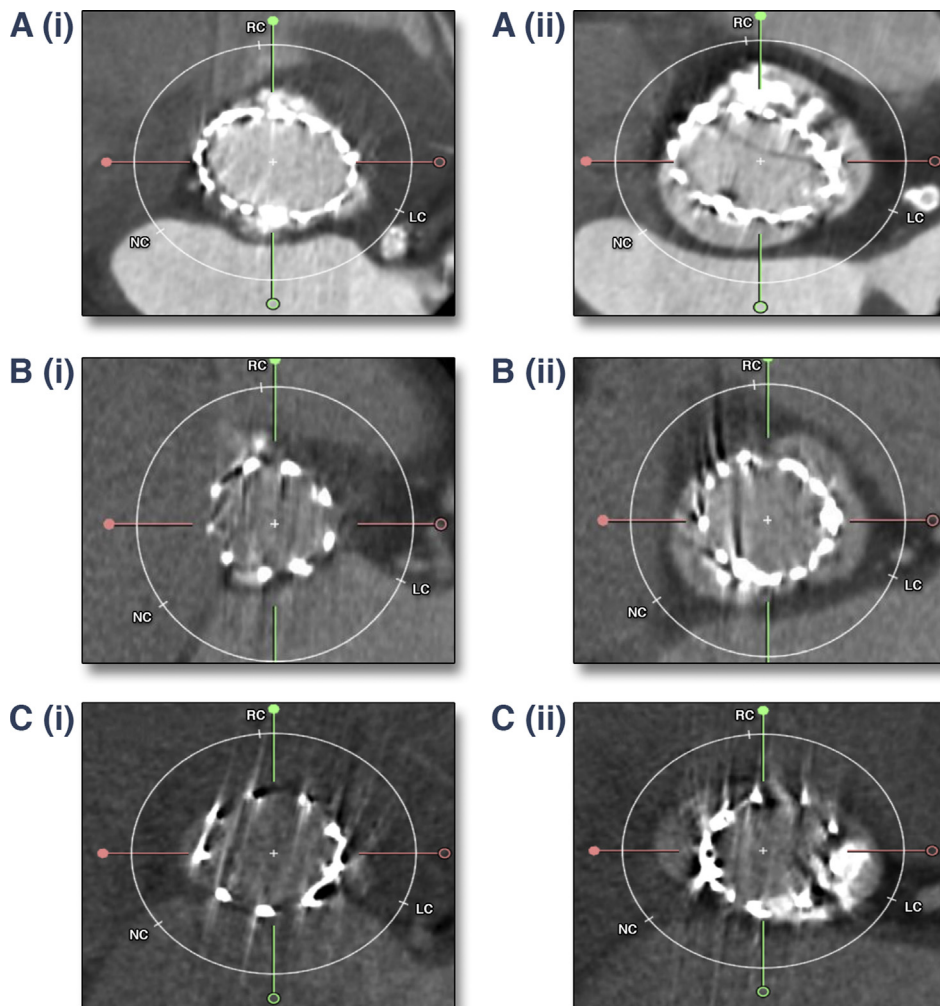
endpoint was attributable to the observation that the majority, that is, 87.5% (70 of 80) of those with CTs of adequate quality for definitive Corelab annular measurement had well-sized prostheses according to manufacturer-directed guidelines; there was a nonsignificant trend to more ≥moderate PAR with undersizing by CT: 2 of 10 (20%) versus 7 of 68 (10.3%), respectively ($p = 0.32$). Increasing prosthesis size per millimeter (OR: 0.8; 95% CI: 0.65 to 0.98; $p = 0.034$) and availability of a contrast CT pre-TAVR of adequate quality for annular measurement (OR: 0.33; 95% CI: 0.13 to 0.83; $p = 0.018$) were protective against PAR. Mild PAR was nonprognostically significant in that it did not predict cumulative mortality (hazard ratio [HR]: 0.66; 95% CI: 0.19 to 2.34; $p = 0.73$), and there was a nonsignificant trend to greater mortality with ≥moderate PAR (HR: 2.09; 95% CI: 0.70 to 6.24; $p = 0.19$).

DISCUSSION

The presented multicenter study identified 130 cases of BAV among a population of 5,130 patients undergoing TAVR (2.5%); it is likely that this frequency is understated given challenges in pre-procedural imaging and diagnosis. The study demonstrated acute procedural and 30-day outcomes from TAVR in BAV stenosis comparable to those reported for TAV stenosis (Table 6), with the notable exception of an

excess of new PPM implantation whose frequency was surprisingly similar between BE and SE designs. Moreover, previous concerns raised with an excess of significant aortic regurgitation in previous studies of TAVR in BAV compared to TAVR in TAV (Table 6) were not observed to the same extent in the present study, particularly when operators had adequate cross-sectional CT data available for device sizing. A simplified assessment of BAV morphology by CT Corelab evaluation demonstrated important baseline differences in aortic anatomy, mostly similar outcomes between subgroups but with some potential differences in predictive parameters for PAR (intercommissural distance in particular) that merit further evaluation.

PARAVALVULAR AR, PACEMAKER, AND IMPACT OF PROSTHESIS DESIGN. PAR is a critical determinant of outcome after TAVR and has received much attention. A recent multicenter study of TAVR in BAV disease by Mylotte et al. (14) reported outcomes in a predominantly self-expanding TAVR population and raised considerable concerns regarding post-TAVR AR, particularly when assessment for TAVR sizing did not use a cross-sectional CT assessment. Although our study also found CT prior to TAVR to be important to mitigating this endpoint, there were clear differences in the observed frequency of significant (≥moderate) PAR after TAVR, with similar

FIGURE 4 CT Post-TAVR in BAV

Limited scans were available post TAVR. Axial CT scans of deployed balloon-expandable Sapien XT prostheses are shown at (i) the prosthesis inflow level and at (ii) the mid sinus of Valsalva level in various bicuspid shapes: (A) bicommissural, raphe type, calcified raphe; severe PAR, no new PPM; (B) bicommissural, raphe type, noncalcified raphe; mild PAR, new PPM required; and (C) bicommissural, non-raphe type; moderate PAR, no new PPM required. Typically, circular expansion was seen at the inflow [B (i) and C (i)] with mild degrees of noncircularity at the mid sinus of Valsalva level [B (ii) and C (ii)]. In rare instances, extreme eccentricity of stent frame expansion was seen at both the inflow and the mid sinus of Valsalva level [A (i) and A (ii)]. PPM = permanent pacemaker; other abbreviations as in Figures 1 and 2.

rates of approximately 10% to those previously reported in TAV, albeit with an excess of mild, non-prognostically significant PAR. Like the former study, these data are reported with the caveat of site-reported non-Corelab-adjudicated echocardiography reports, but in contrast to the former study, we used conventional nomenclature for the assessment of PAR in line with VARC-2 guidelines, rather than the sum of transvalvular and paravalvular regurgitation following prosthesis implantation. There appeared to be an excess of PAR with the BE

versus the SE design but not in patients with a CT used prior to TAVR for procedural planning. Moreover, there was no >mild PAR with Sapien 3 ($n = 8$) in the present study, consistent with preliminary reports of excellent outcomes with this device in TAV disease (8).

Device differences for the endpoint of need for new PPM are well established for TAVR in TAV disease, ranging from 3.4% with Sapien (3) to 22.2% with the Corevalve (6). However, these differences were not observed for TAVR in BAV disease, where rates were

TABLE 6 Outcomes in Recent Studies of TAVR in Bicuspid and Tricuspid Aortic Stenosis

First Author/Study (Ref. #)	N	Age, yrs	Mean STS Score (%)	BE (%)	SE (%)	PVL > Mild (%)	New PPM (%)	30-Day Stroke (%)	30-Day Survival (%)
Bicuspid series									
Bauer et al. (21)	38	81	—	32	68	25	17	0	89
Kochman et al. (22)	28	78	—	18	82	32	29	0	96
Yousef et al. (23)	108	76	—	56	44	31	19	2.8	92
Mylotte et al. (14)	139	78	4.9	28	72	28.4†	23	2.2	95
Jilaihawi et al. (present study)	130	77	4.7	54	46	18.1	26	3.2†	96
Jilaihawi et al. (present study) Baseline CT* available	80	78	4.7	59	41	11.5	28.1	5.1‡	96
Tricuspid series									
Corevalve high risk (7)	390	83	7.3	0	100	7.8	19.8	4.9	97
Corevalve extreme risk (6)	489	83	10.3	0	100	11.4	19.8	4	92
CHOICE trial: BE (24)	121	82	2.9	100	0	1.6	17.3	5.8	96
CHOICE trial: SE (24)	117	80	3.9	0	100	5.8	37.6	1.6	95
NOTION study (25)	145	79	2.9	0	100	15.3†	34.1	1.4	98
Kodali et al. (5) S3 high-risk ACC	583	83	8.6	100	0	3.8	13	1.5	98
Kodali et al. (5) S3 intermediate risk ACC	1076	82	5.3	100	0	3.8	10.1	2.6	99

*Suitable for annular sizing. †Total aortic regurgitation. ‡Cerebrovascular event, stroke, or transient ischemic attack.

Abbreviations as in Table 1.

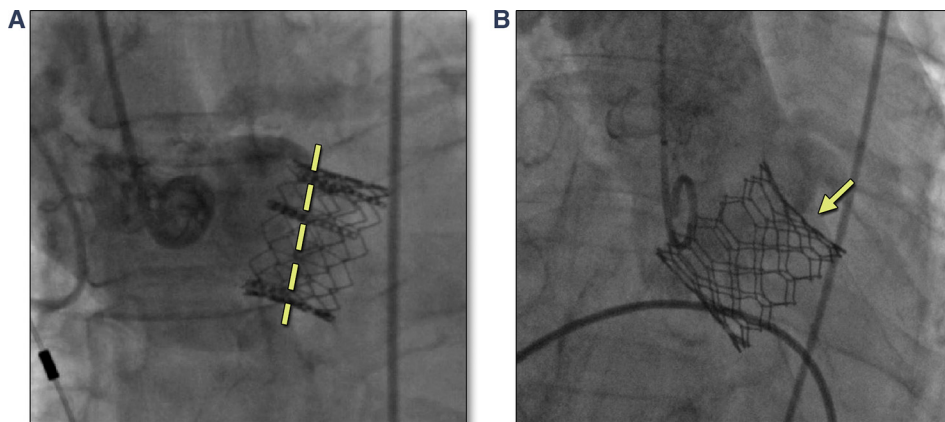
uniformly high, with 25.5% for the BE and 26.9% for the SE TAVR design. Mylotte et al. (14) also saw a higher than expected rate of new PPM with BE TAVR in BAV at 16.7%, which was not statistically significant to their SE TAVR in BAV cohort. We saw a possible relationship of new PPM implantation with orientation of leaflet fusion, in particular those with coronary cusp fusion. This could in some instances, particularly in the presence of a calcified raphe, direct device expansion posteriorly, toward the non-coronary cusp, close to the atrioventricular node (Figure 5), thus “crowding” the AV node. In TAV or alternative mixed cusp orientations of BAV disease, the commissural gaps may facilitate some redirection of tissue away from the atrioventricular node and act as “vents.” Data support such concepts but remain hypothesis-generating at this time.

In BAV morphology and outcomes, a valvular aortopathy is seen with varied phenotypes.

Bicuspid as a description is itself a misnomer, as several bicuspid morphologies have 3 cusps (e.g., those with a raphe or tricommissural bicuspid); bileaflet is more accurate. Several classifications have been previously described, most notably that of Sievers et al. (17), which makes distinctions on the basis of presence of a raphe and also the orientation of leaflet fusion but does not include tricommissural bicuspid and the BAV consortium (1), which makes distinctions only on the basis of orientation of leaflet fusion. It is important to recognize the huge variability observed in the CT Corelab assessment (Figure 1). The 3 broad bicuspid/bileaflet descriptive

subtypes specified were tricommissural, bicommissural raphe type, and bicommissural non-raphe type. The classification presented in the present study was designed as a simplified representation relevant to TAVR to take into account the interface of prosthesis and the aortic-valvular complex, at both the basal leaflet plane (presence or absence of a raphe) and at the commissural level (presence of 2 or 3 commissures). A raphe, particularly if calcified, may influence TAVR expansion and apposition at the annular level. Moreover, given that we have previously described the concept of a supra-annular, commissural seal mitigating PAR (18), the presence or absence of a third commissure may also influence TAVR apposition. The aforementioned potential influence of the orientation of leaflet fusion on PPM merits further investigation and suggests that this is also an important variable to be incorporated into the TAVR classification of BAV disease phenotypes. We also saw some relevance in the intercommissural distance for the prediction in PAR in bicommissural but not tricommissural BAV. It supports the further study of this parameter, often evaluated by expert TAVR operators in BAV.

The category of tricommissural BAV is an interesting one as such patients, from the data presented, appear not to have aortopathy, an important feature of congenital BAV disease. Although there has been no formal report of this subtype in the medical literature, experts in cardiac surgery and interventional cardiology widely employ the term “functional” or “acquired” BAV disease which, in

FIGURE 5 BAV TAVR Using Early and Next Generation Balloon-Expandable Prostheses

(A) Sapien in an angulated root with non-raphe type BAV morphology. The short device height is poorly suited to the tall sinus anatomy and makes positioning in the native annulus (**dashed line**) particularly challenging. No PAR was observed. **(B)** Sapien-3 expanded in a calcified raphe type BAV morphology. The device is constrained at the mid SOV level by at an area of lucency that represents a calcified raphe between the left and right coronary sinuses (**arrow**). No PAR was observed. A new permanent pacemaker was required. Abbreviations as in [Figures 1, 2, and 3](#).

contrast to bicommissural BAV disease, has traditionally been included in TAVR clinical trials. The commonly held belief is that tricommissural bicuspid are the result of focal commissural fusion and that this is an acquired pathology, resulting from a potentially rheumatic, fibrotic, or calcific process. The basis for this remains unclear but this entity, neglected in previous classifications of BAV disease, is distinct from TAV not only in its morphology but also with a possible excess of new PPM after TAVR. The fewer tricommissural BAV in Asia may be attributable to a younger population with less acquired and more congenital pathology. Genetic factors could be relevant to the excess of non-raphe versus raphe type bicommissural BAV in Asia.

Our data are in contrast to those of surgical AVR, which has shown no relationship between BAV phenotypes and clinical outcomes (19,20). Although the standard imaging technique for BAV diagnosis is transthoracic echocardiography, image resolution is such that this is inadequate to distinguish bicuspid subtypes. Although 2-dimensional TEE can offer adequate image resolution for the delineation of anatomy, it is highly operator-dependent; 3-dimensional TEE may be of incremental value but does not precisely delineate the eccentric patterns of calcification that may be seen with BAV anatomy. CT is thus the preferred modality for morphology delineation, calcium characterization, and quantification and can also optimally assess for aortopathy.

STUDY LIMITATIONS. Although this study incorporated a rigorous CT Corelab assessment of bicuspid morphology, around one-third of patients did not have a baseline CT performed and relied on site evaluation by TEE. Small numbers combined with a huge variety of bicuspid phenotypes observed means that anatomical influences on outcome observed are hypothesis-generating.

CONCLUSIONS

In this multicenter international study, regional anatomical differences were seen in BAV-AS undergoing TAVR and a previously neglected morphology of tricommissural (functional/acquired) BAV was clearly delineated. TAVR for BAV stenosis appeared not only feasible but achieved favorable rates of complications, with the exception of increased rates of predominantly mild paravalvular leak (particularly in the absence of baseline contrast CT scan) and PPM regardless of device design and leaflet morphology. Just as for TAVR in TAV, a CT-guided assessment should be an integral part of procedural planning, but is especially important given the heterogeneity of BAV morphological phenotypes that has significant potential to influence outcome.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: In an international multicenter study of TAVR in BAV stenosis, a systematic classification comprehensively characterized a broadly heterogeneous pattern of morphologies. TAVR achieved favorable outcomes in patients with a pre-procedural CT, with the exception of increased rates of PPM for all TAVR devices and BAV morphologies.

TRANSLATIONAL OUTLOOK: Additional studies are needed to explore the relevance of differences in BAV morphology in the setting of TAVR; this includes evidence

for regional anatomical heterogeneity, value of the intercommissural distance, comparisons of tricommissural versus bicommissural morphology, of raphe versus non-raphe bicommissural morphology, and of coronary versus mixed cusp fusion and specific features of the raphe such as calcification and height. A further granular understanding of these aspects is critical to the ongoing success of TAVR following expansion to intermediate and low surgical-risk populations, in whom BAV anatomy predominates.

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KEY WORDS aortic stenosis, aortic valve replacement, bicuspid aortic valve, transcatheter aortic valve implantation, transcatheter aortic valve replacement, TAVI, TAVR

APPENDIX For an expanded Methods section and supplementary figures and tables, please see the online version of this article.