Transcatheter aortic valve replacement in bicuspid aortic valve disease

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ABSTRACT

Background

Limited information exists describing the results of transcatheter aortic valve (TAV) replacement in patients with bicuspid aortic valve (BAV) disease (TAV-in-BAV).

Objectives

This study sought to evaluate clinical outcomes of a large cohort of patients undergoing TAV-in-BAV.

Methods

We retrospectively collected baseline characteristics, procedural data, and clinical follow-up findings from 12 centers in Europe and Canada that had performed TAV-in-BAV.

Results

A total of 139 patients underwent TAV-in-BAV with the balloon-expandable transcatheter heart valve (THV) (n = 48) or self-expandable THV (n = 91) systems. Patient mean age and Society of Thoracic Surgeons predicted risk of mortality scores were 78.0 ± 8.9 years and 4.9 ± 3.4%, respectively. BAV stenosis occurred in 65.5%, regurgitation in 0.7%, and mixed disease in 33.8% of patients. Incidence of type 0 BAV was 26.7%; type 1 BAV was 68.3%; and type 2 BAV was 5.0%. Multislice computed tomography (MSCT)-based TAV sizing was used in 63.5% of patients (77.1% balloon-expandable THV vs. 56.0% self-expandable THV, p = 0.02). Procedural mortality was 3.6%, with TAV embolization in 2.2% and conversion to surgery in 2.2%. The mean aortic gradient decreased from 48.7 ± 16.5 mm Hg to 11.4 ± 9.9 mm Hg (p < 0.0001). Post-implantation aortic regurgitation (AR) grade ≥2 occurred in 28.4% (19.6% balloon-expandable THV vs. 32.2% self-expandable THV, p = 0.11) but was prevalent in only 17.4% when MSCT-based TAV sizing was performed (16.7% balloon-expandable THV vs. 17.6% self-expandable THV, p = 0.99). MSCT sizing was associated with reduced AR on multivariate analysis (odds ratio [OR]: 0.19, 95% confidence intervals [CI]: 0.08 to 0.45; p < 0.0001). Thirty-day device safety, success, and efficacy were noted in 79.1%, 89.9%, and 84.9% of patients, respectively. One-year mortality was 17.5%. Major vascular complications were associated with increased 1-year mortality (OR: 5.66, 95% CI: 1.21 to 26.43; p = 0.03).

Conclusions

TAV-in-BAV is feasible with encouraging short- and intermediate-term clinical outcomes. Importantly, a high incidence of post-implantation AR is observed, which appears to be mitigated by MSCT-based TAV sizing. Given the suboptimal echocardiographic results, further study is required to evaluate long-term efficacy.

Keywords: aortic stenosis, aortic valve replacement, bicuspid aortic valve, transcatheter aortic valve implantation, transcatheter aortic valve replacement

Bicuspid aortic valve (BAV) is a heritable disease affecting 0.5% to 2% of the general population, with a strong male predilection (1–3). BAV stenosis and/or regurgitation is the most common indication for surgical aortic valve replacement (SAVR) in patients <70 years of age. Nonetheless, a recent study that examined surgically excised aortic valves observed that one-fifth of patients older than 80 years of age had underlying bicuspid pathology; echocardiography had identified only two-thirds of these patients as having bicuspid morphology (4). BAV has been excluded from the landmark clinical trials involving transcatheter AVR (TAVR) (5,6). Theoretically, abnormal cusp fusion, pronounced asymmetry of the valve orifice and annulus, heavily calcified and fibrotic leaflets, and calcified raphe (**Figure 1**) could have adverse effects on the expansion of transcatheter aortic valves (TAV), ultimately leading to paravalvular aortic regurgitation (AR) and poor hemodynamic function (7–9). The small number of published case reports and series describing the feasibility of TAV implantation in BAV stenosis (TAV-in-BAV) have been limited in their demonstration of safety and efficacy (10–16). Given the possibility that there are a significant number of elderly patients with BAV stenosis currently undergoing TAVR and that there is a shift toward treating younger patients with TAVR, a better understanding of the clinical outcomes of patients subjected to TAV-in-BAV is necessary (17,18).

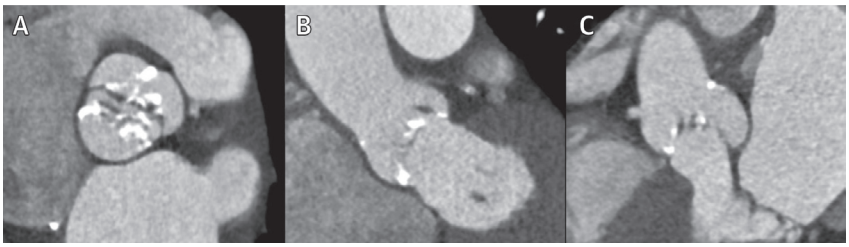


FIGURE 1 Bicuspid Aortic Valve Stenosis
Multislice computed tomography of a type 1 (left-right) bicuspid aortic valve. Axial **(A)**, sagittal **(B)**, and coronal **(C)** images demonstrate the asymmetrical nature of the bicuspid aortic root.

This multicenter study sought to assess the safety and efficacy of TAV-in-BAV in a large group of patients. More specifically, we sought to assess hemodynamic, echocardiographic, and clinical outcomes, along with the association between BAV morphology and TAV prosthesis type on these aforementioned outcomes.

METHODS

Participating centers and patients

The TAV-in-BAV registry, a multinational collaboration of interventional cardiologists and cardiac surgeons from high-volume TAVR centers, collected data from patients who underwent TAV-in-BAV from 12 participating centers in Europe and Canada (Online Table 1). Data

have been prospectively collected since October 2013. Patient selection for TAV-in- BAV was performed at an institutional level, following consideration of the risk profile of each case and discussions by the Heart Team. In each case, centers submitted a dedicated case report form detailing patient baseline characteristics, echocardiographic and/or multislice computed tomographic (MSCT) data, procedural information, and scheduled clinical follow-up.

Bicuspid aortic valve

BAV was defined as a spectrum of abnormal aortic valve morphology consisting of 2 functional cusps with less than 3 zones of parallel apposition between cusps (19). BAV classification was assigned according to the number and spatial orientation of the raphe (**Figure 2**). Type 0, commonly referred to as "pure BAV," has 2 normally developed cusps, sinuses, and commissures and no raphe. Type 1 has 3 anlagen, 2 underdeveloped, and 1 fully developed cusps, 1 underdeveloped commissure, 2 fully developed commissures, and 1 raphe whose orientation in relation to the sinuses defined subcategorization (left-right; right-non; and left-non). Type 2 has 3 anlagen, 2 underdeveloped cusps, 1 fully developed cusp, 2 underdeveloped commissures, 1 fully developed commissure, and 2 raphe (19). Consistent with findings by prior publications, cases of commissural fusion with a raphe <3 mm long were not considered to represent BAV (20). All participating sites retrospectively confirmed the diagnosis and classification of BAV using multimodal imaging: transthoracic and transesophageal echocardiography (TEE) and MSCT. When both TEE and MSCT were performed, cases were excluded if the diagnosis of BAV was not consistent or remained speculative.

Endpoints and definitions

Procedural, 30-day mortality and other major clinical endpoints were defined according to the updated Valve Academic Research Consortium (VARC) criteria (21). Of particular interest were the composite clinical endpoints of valve efficacy, safety, and success (21). Post-implant AR represented an important nonclinical endpoint (22). Regurgitation was defined as the sum of transvalvular and paravalvular regurgitation following prosthesis implantation and removal of the stiff guidewire. At each institution, the severity of regurgitation was qualitatively assessed and graded using TEE according to established guidelines (23,24). Regurgitation was categorized as paravalvular, transvalvular, or mixed and was classified as none (0), trace (I), mild (II), moderate (III), or severe (IV) (23,24).

The dimensions of the aortic valve annulus were measured using TEE or MSCT. TAV sizing was thus defined as either TEE- or MSCT-based. The ellipticity ratio was determined using the formula "long/short-axis" in patients who underwent MSCT analysis. The cover index describes the amount of transcatheter heart valve (THV) oversizing relative to native aortic annulus and was defined by the formula: ([{prosthesis diameter – annulus diameter}/prosthesis diameter] ×100) (25,26).

TABLE 1 Baseline Characteristics

Characteristic	All Patients (n = 139)	Sapien (n = 48)	CoreValve (n = 91)	p Value
Age, yrs	78.0 ± 8.9	77.6 ± 9.7	78.2 ± 8.4	0.71
Males	78 (56.1)	30 (62.5)	48 (52.7)	0.29
BMI, kg/m^2	25.7 ± 5.8	26.5 ± 6.9	25.3 ± 5.2	0.25
Diabetes mellitus	34 (24.5)	14 (29.2)	20 (22.0)	0.41
NYHA functional class	3.0 ± 0.6	3.0 ± 0.5	2.9 ± 0.6	0.33
NYHA functional class III/IV	114 (82.0)	44 (91.7)	70 (76.9)	0.04
Previous MI	26 (18.7)	9 (18.8)	17 (18.7)	0.99
Previous PCI	30 (21.6)	9 (18.8)	21 (23.1)	0.67
Previous CABG	14 (10.1)	5 (10.4)	9 (9.9)	0.99
Peripheral vascular disease	17 (12.2)	6 (12.5)	11 (12.1)	0.99
Previous stroke	8 (5.8)	4 (8.3)	4 (4.4)	0.45
Atrial fibrillation	34 (24.5)	7 (14.6)	27 (29.7)	0.06
Pulmonary hypertension*	34 (24.5)	10 (20.8)	24 (26.4)	0.68
eGFR, ml/min	61.0 ± 25.4	61.2 ± 21.2	60.9 ± 27.2	0.95
eGFR, ≤60 ml/min	70 (50.4)	23 (47.9)	47 (51.6)	0.74
STS PROM	4.9 ± 3.4	5.0 ± 3.9	4.8 ± 3.1	0.96
Logistic EuroSCORE	14.8 ± 10.6	15.3 ± 10.7	14.5 ± 10.7	0.68
EuroSCORE II	4.6 ± 3.6	5.3 ± 4.0	4.3 ± 3.4	0.12
Echocardiography				
Aortic valve mean gradient, mm Hg	48.7 ± 16.5	49.9 ± 15.5	48.1 ± 17.1	0.54
Aortic valve area, cm^2	0.6 ± 0.2	0.7 ± 0.2	0.6 ± 0.2	0.006
Estimated annulus diameter, mm	23.2 ± 2.3	24.2 ± 2.4	23.2 ± 3.7	0.09
LV ejection fraction, %	50.4 ± 14.6	50.9 ± 14.1	50.1 ± 14.9	0.76
LV ejection fraction, ≤40%	41 (29.5)	13 (27.1)	28 (30.8)	0.70
MSCT aortic annulus dimensions†				
Mean diameter, mm	24.5 ± 3.4	24.0 ± 2.2	24.7 ± 3.9	0.25
Long diameter, mm	27.6 ± 2.8	27.0 ± 2.7	28.0 ± 2.8	0.09
Short diameter, mm	22.2 ± 2.5	21.6 ± 2.3	22.7 ± 2.5	0.04
Ellipticity ratio	1.25 ± 0.12	1.26 ± 0.12	1.24 ± 0.12	0.44

Values are mean ± SD or n (%). p Values represent comparisons between the balloon-expandable and self-expandable valve prostheses.

* Pulmonary artery systolic pressure ≥60 mm Hg.

† Total of 88 patients underwent MSCT analysis.

BMI = body mass index; CABG = coronary artery bypass graft; eGFR = estimated glomerular filtration rate; LV = left ventricle; MI = myocardial infarction; MSCT = multislice computed tomography; NYHA = New York Heart Association; PCI = percutaneous coronary intervention; PROM = predicted risk of mortality; STS = Society of Thoracic Surgeons.

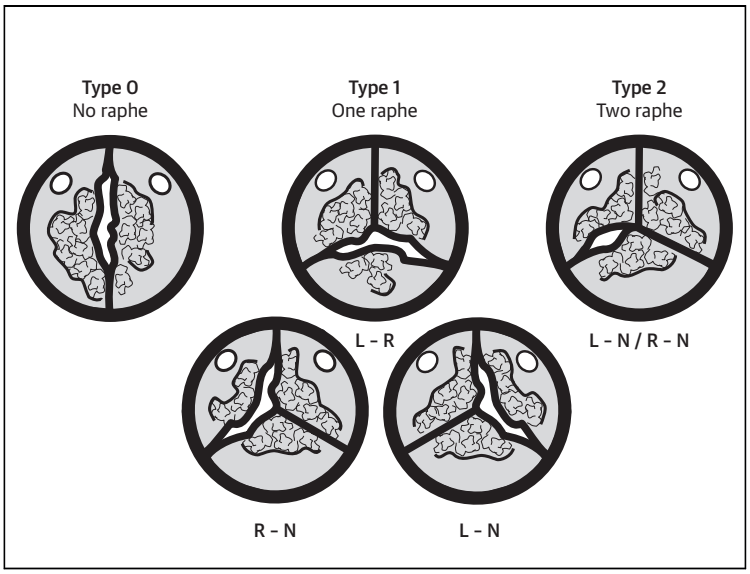


FIGURE 2 Classification of BAV
Classification of BAV according to the description of Sievers et al. (19). BAV = bicuspid aortic valve; L = left coronary cusp; N = non coronary cusp; R = right coronary cusp.

Statistics

Continuous variables are presented as mean ± SD, medians, and ranges and were compared using Student *t* test, Mann-Whitney test, or paired *t* test for repeated measures. Categorical variables are presented as frequencies and percentages and were compared using the chi-square or Fisher exact test. Rates of 1-year mortality were shown using Kaplan- Meier curves, and between-group differences were analyzed with the log-rank test. Logistic regression was performed with the entire cohort to identify possible predictors of 1-year survival and post-implantation AR. All variables that could plausibly be associated with these outcomes were evaluated in a univariate approach, and then factors with a p value of <0.08 in the univariate analysis were combined in a multivariate logistic regression model. A p value of <0.05 was considered significant. Analyses were performed using SPSS version 20.0 (IBM Corp., Armonk, New York).

RESULTS

Patients

A total of 139 elderly patients underwent TAV-in-BAV across 12 participating centers between April 2005 and January 2014. Isolated stenoses occurred in 91 patients (65.5%), isolated

regurgitation in 1 patient (0.7%), and mixed disease in 47 patients (33.8%). The baseline demographics of the study patients are outlined in **Table 1**. The mean age was 78.0 ± 8.9 years, and the mean Society of Thoracic Surgeons (STS) predicted risk of mortality (PROM) score was 4.9 ± 3.4%.

Bicuspid morphology

Evaluation of the morphology of the aortic valve was performed using TEE in all patients. MSCT was performed for the purpose of sizing the TAV in 88 cases (63.3%). Among these patients, the annuli were elliptical with an average ellipticity ratio of 1.25 ± 0.12. The BAV type was definitively established in 120 patients (86.3%) and remained uncertain in 19 patients (13.7%), despite multimodal imaging. Among patients with a confirmed BAV type (**Table 2**), 32 patients (26.7%) were type 0, 82 (68.3%) were type 1 (left-right: n = 60; right-non: n = 15; and left-non: n = 7), and 6 (5.0%) were type 2. Diameter of the aortic sinuses (mean: 34.7 ± 3.3 mm; range: 29 to 41 mm), root (mean: 32.7 ± 5.8 mm; range: 22 to 41 mm), and ascending aorta (mean: 35.9 ± 6.1 mm; range: 25 to 46 mm) indicated that no patient had significant ascending aortopathy.

Procedures

Table 3 outlines the procedural characteristics and results of the TAV-in-BAV procedures. A balloon-expandable THV (SapienXT, Edwards Lifesciences, Inc., Irvine, California) (**Figure 3**) and self-expandable THV (CoreValve, Medtronic, Inc., Minneapolis, Minnesota) (**Figure 4**) were used in 48 patients (34.5%) and 91 patients (65.5%), respectively. Transfemoral vascular access was performed in 78.5% of cases, and pre-implantation balloon aortic valvuloplasty was performed in 98.6% of cases. A TAV was subsequently implanted in 137 cases (98.6%). Of 2 patients who did not receive a TAV, 1 case had severe aortic incompetence and fatal cardiogenic shock following balloon valvuloplasty (balloon-to-annulus ratio: 0.9), and in 1 case, the balloon-expandable valve failed to cross the native aortic valve. The mean diameter of the transcatheter valve was 27.8 ±

TABLE 2 Bicuspid Aortic Valve Type

Valve Type	All Patients (n = 120)	Sapien (n = 40)	CoreValve (n = 80)	p Value
Type 0	32 (26.7)	8 (20.0)	24 (30.0)	0.28
Type 1	82 (68.3)	31 (77.5)	51 (63.8)	0.15
LR	60 (50.0)	26 (65.0)	34 (42.5)	
RN	15 (12.5)	2 (5.0)	13 (16.3)	
LN	7 (5.8)	3 (7.5)	4 (5.0)	
Type 2				
LR/RN	6 (5.0)	1 (2.5)	5 (6.2)	0.66

Values are n (%). Classification of bicuspid aortic valve morphology according to Sievers et al. (19).
LN = left - non; LR = left - right; RN = right - non.

2.2 mm and was significantly smaller in patients receiving the balloon-expandable valve than in those receiving the self-expandable THV (26.3 ± 2.2 mm vs. 28.5 ± 1.8 mm, respectively; p = 0.0002). Similarly, the cover index was significantly smaller in patients treated with the balloon-expandable THV (8.9 ± 5.7% vs 16.3 ± 9.8%, respectively; p < 0.0001). Post-implantation balloon dilation was required in 25 cases (18.1%; balloon-expandable THV n = 5; self-expandable THV n = 20), and there were 3 (2.2%) episodes of TAV embolization (balloon-expandable THV n = 2; self-expandable THV: n = 1). A second TAV was implanted in 5 patients (3.6%; balloon-expandable THV n = 1; self-expandable THV n = 4), and 3 cases (2.2%) were converted to SAVR (balloon-expandable THV n = 2; self-expandable THV n = 1). SAVR was required for 1 annular rupture, 1 balloon-expandable THV embolization, and 1 self-expandable THV malposition. Procedural mortality occurred in 5 patients (3.5%) and was attributed to cardiac tamponade resulting from guidewire perforation of the left ventricle (n = 2), major vascular complication, annular rupture, and the case of severe AR following balloon aortic valvuloplasty, as described previously.

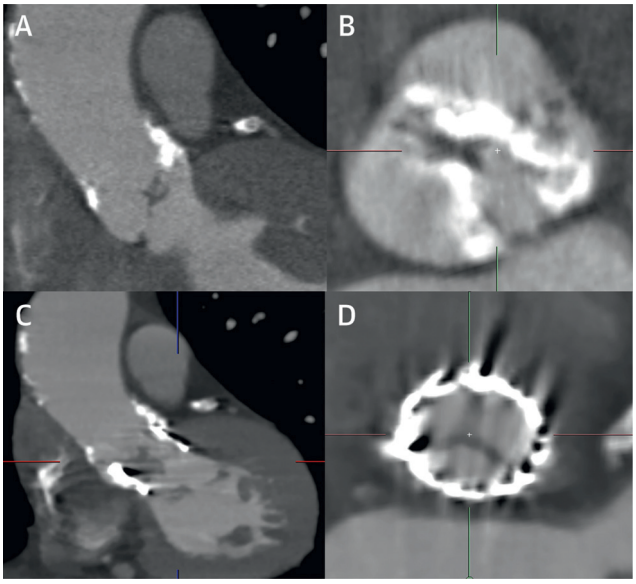


FIGURE 3 Newer Generation Balloon-Expandable TAV-in-BAV
TAV-in-BAV with a newer generation 29-mm balloon-expandable THV (Sapien XT, Edwards Lifesciences). **(A and B)** Multislice computed tomography of bicuspid aortic valve stenosis (type 1, RN). **(C and D)** Same patient after implantation with the newer generation balloon-expandable valve. RN = right - non; TAV-in-BAV = transcatheter aortic valve in bicuspid aortic valve; THV = transcatheter heart valve.

TABLE 3 Procedural Information and Outcomes

Characteristic	All Patients (n = 139)	Sapien (n = 48)	CoreValve (n = 91)	p Value
TAV size, mm	27.8 ± 2.2	26.3 ± 2.2	28.5 ± 1.8	0.0002
23 mm	10 (7.2)	10 (20.8)	–	–
26 mm	50 (36.0)	23 (47.9)	27 (29.7)	0.04
29 mm	59 (42.4)	15 (31.3)	44 (48.4)	0.07
31 mm	20 (14.4)	–	20 (22.0)	–
MSCT cover index, %	13.2 ± 9.1	8.9 ± 5.7	16.3 ± 9.8	<0.0001
MSCT-based TAV sizing	88 (63.3)	37 (77.1)	51 (56.0)	0.02
Vascular access				
Femoral	109 (78.5)	30 (62.5)	79 (86.8)	0.002
Subclavian	5 (3.6)	–	5 (5.5)	–
Apical	12 (8.6)	12 (25.0)	–	–
Aortic	12 (8.6)	6 (12.5)	6 (6.6)	–
Carotid	1 (0.7)	–	1 (1.1)	–
General anesthesia	85 (61.1)	33 (68.8)	52 (57.1)	0.20
Balloon predilation	137 (98.6)	51 (100.0)	89 (97.8)	0.54
Predilation balloon size, mm	22.5 ± 2.1	21.9 ± 2.2	22.9 ± 2.0	0.008
Balloon postdilation*	25 (18.1)	5 (10.6)	20 (22.2)	0.11
Postdilation balloon size, mm*	26.5 ± 2.3	24.7 ± 2.5	26.8 ± 2.1	0.07
TAV malposition*	9 (6.5)	2 (4.3)	7 (7.8)	0.72
TAV embolization*	3 (2.2)	2 (4.3)	1 (1.1)	0.27
Need for 2nd TAV*	5 (3.6)	1 (2.1)	4 (4.4)	0.66
Tamponade	5 (3.6)	0	5 (5.7)	0.16
Aortic root rupture	1 (0.7)	1 (2.1)	0	–
Conversion to SAVR	3 (2.2)	2 (4.2)	1 (1.1)	0.30
Postimplantation echocardiography				
Aortic regurgitation, grade (1–4)*	1.1 ± 0.9	1.0 ± 0.9	1.1 ± 0.9	0.53
≥Grade 2	38 (28.4)	9 (19.6)	29 (32.2)	0.11
≥Grade 3	8 (6.0)	3 (6.5)	5 (5.5)	0.99
Aortic valve gradient, mm Hg*	11.4 ± 9.9	11.7 ± 8.7	11.3 ± 10.4	0.82
Aortic valve area, cm^2*	1.7 ± 0.5	1.6 ± 0.4	1.7 ± 0.5	0.23
Contrast media, ml	174 ± 88	176 ± 118	172 ± 81.5	0.17
Fluoroscopy duration, min	20 (14–28)	14 (9–25)	20 (15–29)	0.004

Values are mean ± SD, n (%), or median (interquartile range). p values represent comparisons between the Edwards Sapien and Medtronic CoreValve prostheses.

* Refers to 137 patients who received a TAV.

MSCT = multislice computed tomography; SAVR = surgical aortic valve replacement; TAV = transcatheter aortic valve.

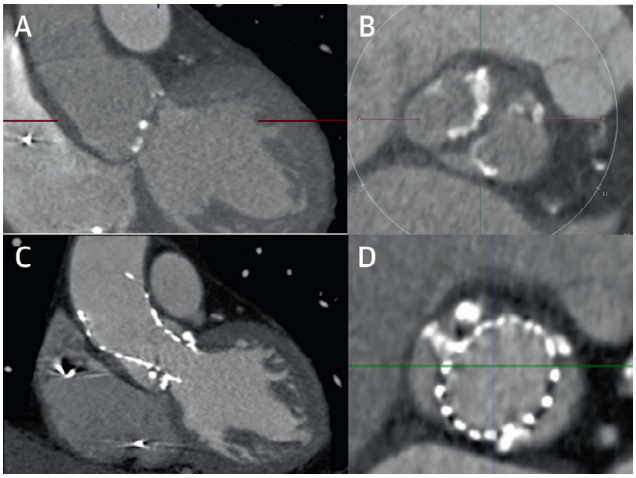


FIGURE 4 Self-Expandable TAV-in-BAV
TAV-in-BAV with a 29-mm self-expandable THV (CoreValve; Medtronic). **(A and B)** Multislice computed tomography of bicuspid aortic valve stenosis (type 1, LN). **(C and D)** Same patient with the self-expandable valve. LN = left - non; other abbreviations as in **Figure 3**.

Clinical outcomes

The median duration of hospital stay was 8 (interquartile range: 5 to 11) days (**Table 4**). The 30-day rates of death, myocardial infarction, and stroke were 5.0%, 2.2%, and 2.2%, respectively. Any instance of bleeding occurred in 37 patients (26.6%), life-threatening bleeding occurred in 10 patients (7.2%), and major vascular complications occurred in 9 patients (6.5%). Overall, 110 patients (79.1%) met the combined safety endpoint, and device success was observed in 125 patients (89.9%). At 30 days, the combined efficacy endpoint was achieved in 118 patients (84.9%).

Follow-up was available for all patients. At the time of data lock, 136 patients (97.8%) and 129 patients (92.8%) had reached 6- and 12-month follow-up examinations, respectively. The Kaplan-Meier survival curve is shown in the **Central Illustration**. There were 13 deaths (9.6%) at 6 months and 21 (17.5%) at 12 months; causes of death between 30 days and 1 year (n = 16) were congestive cardiac failure (n = 6), cancer (n = 3), unknown (n = 3), gastrointestinal hemorrhage (n = 1), stroke (n = 1), lung disease (n = 1), and a road traffic accident (n = 1). On multivariate analysis (**Table 5**), major vascular complications were associated with increased 1-year mortality (odds ratio [OR]: 5.66; 95% confidence interval [CI]: 1.21 to 26.43; p = 0.03). At 1 year, 60.4%, 30.2%, and 9.4% of patients were assessed at New York Heart Association (NYHA) functional class I, II, or III, respectively.

Post-procedural echocardiography

Among the 137 patients who received a TAV, the mean aortic valve gradient decreased from 48.7 ± 16.5 mm Hg at baseline to 11.4 ± 9.9 mm Hg at 30 days (p < 0.0001), whereas the

TABLE 4 Clinical Outcomes

Characteristic	All patients (n = 139)	Sapien (n = 48)	CoreValve (n = 91)	p Value
Hospital stay, days	8 (5, 11)	7 (4, 12)	8 (6, 11)	0.38
Mortality				
Procedural	5 (3.6)	1 (2.1)	4 (4.9)	0.66
At 30 days	7 (5.0)	3 (6.3)	4 (4.9)	0.69
At 6 months*	13 (9.6)	7 (14.6)	6 (6.6)	0.12
At 1 year†	21 (17.5)	10 (20.8)	11 (12.5)	0.12
Myocardial infarction	3 (2.2)	0	3 (3.3)	0.55
Periprocedural	3 (2.2)	0	3 (3.3)	–
Spontaneous	0	0	0	–
Stroke	3 (2.2)	1 (2.1)	2 (2.2)	0.99
Disabling	2 (1.4)	1 (2.1)	1 (1.1)	–
Non disabling	1 (0.8)	0	1 (1.1)	–
Bleeding	37 (26.6)	8 (16.7)	29 (31.9)	0.07
Minor	18 (12.9)	2 (4.2)	16 (17.6)	–
Major	9 (6.5)	4 (8.3)	5 (5.5)	–
Life-threatening	10 (7.2)	2 (4.2)	8 (8.8)	–
Acute kidney injury (stage 3)	3 (2.2)	1 (2.1)	2 (2.0)	0.99
Vascular complications	30 (21.6)	6 (12.5)	24 (26.4)	0.08
Minor	21 (15.1)	2 (4.2)	19 (20.9)	–
Major	9 (6.5)	4 (8.3)	5 (5.5)	–
New pacemaker	32 (23.2)	8 (16.7)	24 (26.7)	0.21
Device success	125 (89.9)	43 (89.6)	82 (90.1)	0.99
Combined safety endpoint	110 (79.1)	39 (82.2)	71 (78.0)	0.83
Combined efficacy endpoint	118 (84.9)	42 (87.5)	76 (84.5)	0.81

mean aortic valve area increased from 0.6 ± 0.2 cm^2 at baseline to 1.7 ± 0.5 cm^2 at 30 days ($p < 0.0001$). Post-implantation AR grade ≥2 (paravalvular in 92% of cases) was present in 38 patients (28.4%) at 30 days. When only those patients with MSCT-based TAV sizing were considered, the incidence of AR grade ≥2 was 17.4%. On multivariate analysis, MSCT-based TAV sizing was independently associated with a reduction in the incidence of post-implantation AR grade ≥2 (OR: 0.19; 95% CI: 0.08 to 0.45; $p < 0.0001$) (**Table 6**). Male sex (OR: 4.29; 95% CI: 1.63 to 10.79; $p = 0.003$) was the only independent predictor of increased AR grade ≥2. AR grade ≥2 occurred in 13.3% of BAV type 0 patients, 34.2% of type 1, and 16.6% of type 2 (type 0 vs. type 1: $p = 0.03$).

TABLE 5 Predictors of 1-Year Survival

Characteristic	Univariate Analysis			Multivariate Analysis		
	Odds Ratio	95% CI	p Value	Odds Ratio	95% CI	p Value
Age	1.06	0.99–1.13	0.10			
Males	1.15	0.45–3.95	0.77			
STS PROM	1.06	0.94–1.19	0.38			
Mean aortic gradient	1.00	0.97–1.03	0.94			
Aortic valve area	0.08	0.01–1.50	0.09			
LV ejection fraction <40%	1.14	0.42–3.08	0.80			
Annulus size	1.03	0.88–1.19	0.74			
TAV size	0.94	0.77–1.16	0.59			
MSCT-based TAV sizing	1.32	0.49–3.55	0.58			
Bicuspid type 1	1.29	0.45–3.69	0.63			
CoreValve	0.44	0.17–1.15	0.08	0.38	0.14–1.04	0.06
Year of procedure	0.91	0.67–1.22	0.51			
Diabetes	0.53	0.14–1.93	0.33			
NYHA functional class II/III	2.57	0.56–11.85	0.23			
Pulmonary hypertension	1.85	0.67–5.11	0.24			
eGFR <60	1.44	0.56–3.69	0.45			
TAV malposition	4.29	0.89–20.80	0.07	5.05	0.93–27.31	0.06
TAV embolization	5.30	0.32–88.27	0.25			
Requirement for 2nd TAV	2.63	0.23–30.35	0.44			
Major vascular complications	1.12	1.40–26.81	0.02	5.66	1.21–26.42	0.03
New pacemaker	0.73	0.23–2.36	0.61			
AR grade ≥2	1.55	0.56–4.32	0.40			

AR = aortic regurgitation; CI = confidence interval; other abbreviations as in **Table 1**.

Prosthesis choice

Baseline characteristics among patients treated with the balloon-expandable THV were similar to those of patients who received the self-expandable THV, although NYHA functional class III or IV was more common in the balloon-expandable valve cohort (p = 0.04). MSCT-based TAV sizing was also performed more frequently in the balloon-expandable THV cohort (56.0% vs. 77.1%, respectively; p = 0.02), and the transfemoral approach was more common among self-expandable valve patients (p = 0.002). There was a trend toward an increased incidence of post-implantation AR grade ≥2 among the self-expandable valve-treated patients (19.6% vs. 32.2%, respectively; p = 0.11). When patients undergoing MSCT-based TAV sizing were considered, the incidence of AR grade ≥2 was similar between the 2 prostheses (6 of 37 [16.7%] vs. 9 of 50 [17.6%], respectively; p = 0.99). The choice of TAV was not associated with post-implantation AR in multivariate analysis. There were no significant differences in

TABLE 6 Predictors of Aortic Regurgitation Grade ≥2

Characteristic	Univariate Analysis			Multivariate Analysis		
	Odds Ratio	95% CI	p Value	Odds Ratio	95% CI	p Value
Age	0.95	0.96–1.03	0.63			
Males	3.50	1.50–8.20	0.004	4.29	1.63–10.79	0.003
STS PROM	0.85	0.75–1.04	0.05	0.88	0.75–1.04	0.13
Mean aortic gradient	0.99	0.97–1.02	0.61			
Aortic valve area	3.20	0.34–29.86	0.31			
LV ejection fraction <40%	1.40	0.62–3.14	0.41			
Annulus size	0.93	0.82–1.04	0.20			
TAV size	1.10	0.92–1.31	0.31			
MSCT-based TAV sizing	0.23	0.10–0.51	<0.0001	0.19	0.08–0.45	<0.0001
Bicuspid type 1	2.14	0.82–5.56	0.11			
CoreValve	1.93	0.82–4.54	0.13			
Year of procedure	0.78	0.60–1.03	0.08			

Abbreviations as in **Tables 1 and 5**.

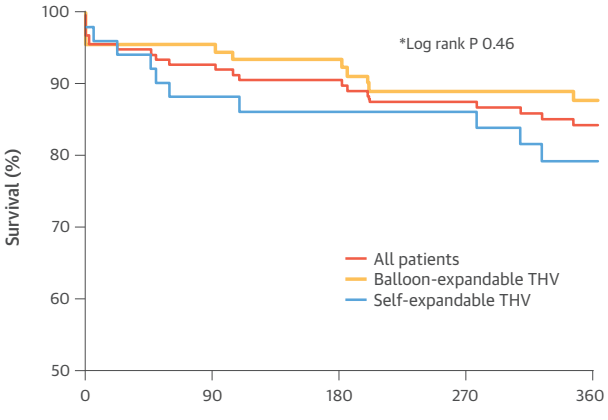
procedural outcomes between patients receiving the two types of valves. At 12 months, death occurred in 10 patients who received the balloon-expandable valve (20.8%) and in 11 self-expandable valve recipients (12.5%; log-rank: p = 0.46) (**Central Illustration**).

Values are n (%). Totals of 136* and 129† patients who reached 6-month or 1-year follow-up examination, respectively.

SAVR = surgical aortic valve replacement.

DISCUSSION

This is the first large multicenter analysis of TAV implantation in patients with significant BAV stenosis or regurgitation. We observed a 30-day mortality rate of 5%, a 30-day stoke rate of 2%, and a device success rate of 90%. One-year mortality was 17.5%, and the patients were NYHA functional class I or II. These results suggest that TAV-in-BAV is feasible and associated with encouraging short- and intermediate-term clinical outcomes. The current analysis, however, demonstrated a high incidence of post-implantation AR grade ≥2 (28.4%), although this was reduced to 17% in those with MSCT-based TAV sizing.



Patients at risk

All patients	139	130	125	114	106
Balloon-expandable THV	48	42	38	36	35
Self-expandable THV	91	88	85	78	73

Mylotte, D. et al. J Am Coll Cardiol. 2014; 64(22):2330–9.

Kaplan-Meier survival curve of patients undergoing transcatheter aortic valve in bicuspid aortic valve with the balloon-expandable THV (blue line) or self-expandable valve (orange line) prostheses. The p value is the log-rank comparison between the 2 valves. THV ¼ transcatheter heart valve.

Procedural safety and efficacy

Treatment of BAV disease with TAV technology is considered an off-label indication. Surgically excised bicuspid valves typically demonstrate leaflet fusion (raphe) and extensive nodular calcification. The histo-architectural distribution of calcific deposits in BAV leaflets is different from that of stenotic tricuspid valves (27). Extensive calcium deposition in the body of BAV leaflets and asymmetrical nature of the bicuspid aortic root could impair TAVR outcomes (19,28). Anecdotally, registry participants suggested that guidewire crossing and THV positioning were more difficult with bicuspid than tricuspid aortic valve stenosis. Nevertheless, the acute procedural results were acceptable, with acute TAV embolization occurring in 2.2%, conversion to SAVR in 2.2%, and encouraging 30-day rates of VARC-defined device success (89.9%), safety (79.1%), and efficacy (84.9%). These results are comparable to those reported for TAVR in tricuspid aortic stenosis (5,6,29–32).

Traditionally, TAVR has been reserved for patients at excessive or high risk for surgery (STS PROM >10%). More recently, it has been recognized that current risk models are ill equipped to accurately gauge risk among TAVR recipients (33). TAVR technology is therefore being applied to patients at lower predicted risk, following discussions by the institutional heart team. In our study, the expected 30-day mortality (STS PROM) was 4.9%, indicting an intermediate-risk cohort. We observed remarkable similarities between expected and observed (5.0%) 30-day mortality rates. Mortality continued to accrue, however, increasing

to 17.5% at 1 year. By comparison, Piazza et al. (34) performed a propensity-matched analysis comparing TAVR to SAVR among 205 intermediate-risk patient pairs (STS PROM 3% to 8%) with severe tricuspid aortic valve stenosis. They reported mortality in the TAVR and SAVR cohorts of 7.8 and 7.1%, respectively, at 30-days and 16.5 and 16.9%, respectively, at 1 year. One-year outcomes in the current study compare favorably to those reported for other TAV-in-BAV cohorts (11,15). The 1-year outcomes probably reflect the advanced age, heavy burden of comorbidities, and other adverse features inherent in TAVR cohorts that are not captured by current risk prediction models (33). The high rates of post-implantation AR also may have influenced 1-year mortality (22).

Post-implantation AR

In the current analysis, AR grade ≥2 occurred in 28.4% of patients. This rate is consistent with that reported in smaller TAV-in-BAV series (13–15) and compares poorly with reported rates (<20%) of AR following TAV for tricuspid aortic valve stenosis (30,35,36). Notably, the incidence of AR grade ≥2 was 17.4% when only patients who underwent MSCT-based sizing were considered and was similar between balloon- and self-expanding prostheses (16.7% vs. 17.6%, respectively; $p = 0.99$). Consistent with prior studies (37,38), MSCT-based TAV sizing was associated with reduced paravalvular regurgitation and should be considered a mandatory element of patient screening for TAV-in- BAV. Nevertheless, MSCT-based TAV sizing is unlikely to represent a panacea for post-implantation AR in BAV because the unique anatomic features of BAV pathology appear to present a challenge for first-generation TAVI systems. The TAV frame may be unable to expand completely and appose to the native annulus in the presence of pronounced annular ellipticity (mean ellipticity ratio: 1.25 ± 0.12), heavy calcification, and calcified raphe. The latter may have contributed to the increased rate of post-implantation AR observed in patients with BAV type 1 compared with those with type 0 (34.2 vs. 13.3%, respectively; $p = 0.03$). Aortic root dilation and/or angulation, as well as concomitant native aortic valve incompetence, may further impede accurate TAV positioning and contribute to the risk of paravalvular regurgitation. Given the strong association between post-procedural AR and both short- and long-term mortality (22,35), the high incidence of AR observed in BAV patients is disconcerting, and the suboptimal echocardiographic outcomes mandate further longer term follow-up to ascertain the clinical implications of aortic incompetence in BAV cohorts.

Comparison with SAVR

Comparisons between current study outcomes and those of historical surgical series of patients undergoing isolated SAVR for BAV disease are challenging. Most surgical series included younger and lower-risk patients who do not reflect the complexities of the current cohort (39,40). Furthermore, such comparisons are also likely to be confounded by considerable selection bias, whereas in our study, each case was discussed by a dedicated heart team whose members recommended TAV-in-BAV rather than SAVR. Surgery, however, should remain

the treatment of choice for BAV disease, especially in low-risk patients or in the presence of aortic root dilation. Ultimately, a randomized comparison between TAV-in-BAV and SAVR will be required to prove equivalent safety and long-term efficacy.

Choice of prosthesis

BAV morphology presents potential advantages and disadvantages for balloon-and self-expanding TAV systems. The balloon-expandable valve exerts greater radial force and may circularize the native annulus, obliterating potential sites of paravalvular AR. Calcified nodules or raphe, however, may impair complete prosthesis expansion, thereby necessitating post-implantation balloon dilation or, potentially, resulting in residual paravalvular leakage. The self-expanding THV could have greater propensity to such paravalvular regurgitation given the reduced radial strength relative to balloon-expandable systems. The greater compliance of self-expanding prostheses and the supra-annular position of the leaflets could, however, mitigate the unequal circular stress at the level of the annulus and potentially improve long-term hemodynamic outcomes. In our study, clinical outcomes among patients treated with balloon expandable TAV were similar to those observed in patients treated with the self-expanding prostheses. We observed a trend toward increased rates of post-implantation AR grade ≥2 with the self-expandable THV; however, the considerably lower use of MSCT-based TAV sizing in the self-expandable THV cohort might have accounted for this difference. Subgroup analysis of patients undergoing MSCT-based TAV sizing demonstrated no significant between-group differences in the rates of post-implantation AR. Further study is required to evaluate the comparative effectiveness of the balloon-expandable and self-expandable valve systems in patients with BAV disease.

Currently unproven emerging TAV technology with dedicated sealing cuffs (Sapien 3 [Edwards Lifesciences]), repositionable systems (CoreValve Evolut R [Medtronic], Portico [St. Jude Medical, Minneapolis, Minnesota], or Lotus [Boston Scientific, Natick, Massachusetts]) may have the potential to reduce post-implantation AR (41–44).

Study limitations

The study findings should be interpreted in light of the study design. This predominantly retrospective voluntary registry of TAV-in-BAV cases necessitates cautious interpretation, and definitive conclusions should be avoided. The exact indication for proceeding with TAV-in-BAV rather than SAVR was not available for each patient, although all cases were reviewed by the institutional heart team. Adverse events and post-implantation AR, which may be operator and laboratory dependent, were adjudicated by the participating centers rather than by a core laboratory. Information about the depth of implantation and invasive hemodynamic data, such as the AR index, were not available in this study. The cover index and annular ellipticity were not entered into the multivariate regression because MSCT data were only available in 64% of patients.

CONCLUSIONS

TAV-in-BAV is feasible, with encouraging short-and intermediate-term clinical outcomes. A high incidence of post-implantation aortic regurgitation is observed following TAV-in-BAV. The incidence of post-implantation paravalvular leak is moderated by MSCT-based TAV sizing, which should be considered mandatory for TAV-in-BAV. Longer-term follow-up of a larger cohort of patients is required to more completely assess the efficacy and durability of TAV implantation in patients with bicuspid disease.

PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE 1: TAVR of bicuspid aortic valves is associated with high rates of grade ≥2 post-implantation aortic regurgitation.

COMPETENCY IN MEDICAL KNOWLEDGE 2: Sizing of the prosthesis based on measurements obtained by multislice computed tomography can reduce the likelihood of developing post-implantation aortic regurgitation in patients with bicuspid aortic valves undergoing TAVR.

TRANSLATIONAL OUTLOOK: Further studies are needed to determine whether later generation TAVR devices reduce the risk of aortic regurgitation after TAVR in patients with bicuspid aortic valves.

ABBREVIATIONS AND ACRONYMS

BAV = bicuspid aortic valve
CI = confidence interval
MSCT = multislice computed tomography
NYHA = New York Heart Association
OR = odds ratio
SAVR = surgical aortic valve replacement
STS PROM = Society of Thoracic Surgeons predicted risk of mortality
TAV-in-BAV = transcatheter aortic valve in bicuspid aortic valve
TAVR = transcatheter aortic valve replacement
TEE = transesophageal echocardiography
THV = transcatheter heart valve
VARC = Valve Academic Research Consortium

APPENDIX

For a supplemental table, please see the online version of this article.

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