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Review Article

Bicuspid Aortic Valve Disease: Classifications, Treatments, and Emerging Transcatheter Paradigms

Ankur Kalra, MD [a,1], Rajiv Das, MB ChB, MD [b,1], Mohammad Alkhalil, MD, DPhil [b,1], Iryna Dykun, MD [c], Alessandro Candreva, MD [d], Omar Jarral, MBBS, PhD [e], Syed M. Rehman, MBBS [f], Monil Majmundar, MD [g], Kunal N. Patel, MD, MPH [h], Josep Rodes-Cabau, MD, PhD [i], Michael J. Reardon, MD [j], Rishi Puri, MBBS, PhD [c,*]

[a] Department of Cardiology, Franciscan Health, Lafayette, Indiana, USA
[b] Department of Cardiothoracic Services, Freeman Hospital, Newcastle-upon-Tyne, UK
[c] Department of Cardiovascular Medicine, Heart, Vascular and Thoracic Institute, Cleveland Clinic, Cleveland, Ohio, USA
[d] Department of Cardiology, University Heart Centre, University Hospital Zurich, Zurich, Switzerland
[e] Department of Cardiothoracic Surgery, St. Thomas Hospital, London, UK
[f] Department of Cardiothoracic Surgery, OLV Hospital, Aalst, Belgium
[g] Department of Cardiology, University of Kansas Medical Center, Kansas City, Kansas, USA
[h] Department of Cardiology, West Virginia University Hospital, Morgantown, West Virginia, USA
[i] Department of Interventional Cardiology, Quebec Heart & Lung Institute, Quebec City, Canada
[j] Department of Cardiothoracic Surgery, Houston Methodist Hospital, Houston, Texas, USA

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ABSTRACT

Bicuspid aortic valve (BAV) is a common congenital valvular malformation, which may lead to early aortic valve disease and bicuspid-associated aortopathy. A novel BAV classification system was recently proposed to coincide with transcatheter aortic valve replacement being increasingly considered in younger patients with symptomatic BAV, with good clinical results, yet without randomized trial evidence. Procedural technique, along with clinical outcomes, have considerably improved in BAV patients compared with tricuspid aortic stenosis patients undergoing transcatheter aortic valve replacement. The present review summarizes the novel BAV classification systems and examines contemporary surgical and transcatheter approaches.

ABBREVIATIONS

ACC, American College of Cardiology; AR, aortic regurgitation; AS, aortic stenosis; BAV, bicuspid aortic valve; CI, confidence interval; CT, computerized tomography; ICD, intercommissural distance; PVL, paravalvular leak; SAVR, surgical aortic valve replacement; STS, Society of Thoracic Surgeons; TAV, tricuspid aortic valve; TAVR, transcatheter aortic valve replacement; TVT, transcatheter valve therapies.

Introduction

Described over 400 years ago by Leonardo da Vinci in his anatomical sketches, bicuspid aortic valve (BAV) disease is the most common congenital cardiac defect with an estimated prevalence between 0.5% and 0.77%.[1,2] As a clinical consequence, the vast majority of patients with BAV will require intervention during their lives not necessary only for aortic stenosis (BAV-AS), aortic regurgitation (BAV-AR), and infective endocarditis but also for associated aortic pathology, including thoracic aortic aneurysm, coarctation, and dissection.[3] An early valvular degenerative process is well described in BAV, with rapidly progressive fibrosis in the second decade leading to irreversible calcification within the

[1] Equal contributions.
* Address correspondence to: Rishi Puri, MBBS, PhD, Department of Cardiovascular Medicine, Cleveland Clinic, Mail Code J2-3, 9500 Euclid Ave, Cleveland, OH 44195.

E-mail address: purir@ccf.org (R. Puri).

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fourth decade.[4,5] This explains why, for BAV-AS, the mean age of patients requiring surgical aortic valve replacement (SAVR) is at least 5 years lower than those with tricuspid aortic valves (TAV) and why BAV is the major cause of AS in patients in the relatively younger age group of 60 to 75 years.[6,7] This supports the even greater relevance of surgery compared with transcatheter aortic valve replacement (TAVR) in these patients. This review will cover the recent updates on BAV classifications and discusses various surgical and transcatheter options to treat BAV.

Morphology and Classification

Although the Sievers and Schmidtke BAV morphological classification has to-date been the most widely adopted (based on the number of raphe; Figure 1A), a novel international consensus BAV classification has been recently proposed, based upon the type and phenotype of the BAV along with valve function, the presence/characteristics of the raphe, cusp shape/size and BAV symmetry, and the presence/absence of aortopathy/coarctation.[8,9]

Another BAV classification system, proposed by Jilaihawi et al,[10] describes 3 types of valves (tricommissural, bicommisural raphe type, and bicommisural nonraphe type) in an attempt to enable a greater understanding of the interaction of the implanted valves with the valvular complex at both the basal leaflet plane (presence or absence of raphe) and the commissural level (presence of 2 or 3 commissures) (Figure 1B). Tricommissural BAV was not associated with aortopathy and, as such, was termed “functional” or “acquired” BAV disease, arising from either rheumatic or degenerative processes. It was also noted that a significant proportion of bicommissural valves in Asia were nonraphe type (61.9%) compared with just 11.9% in America or 9.4% in Europe.

Michelena et al have proposed 3 types of BAV with sub-phenotypes for each one. The fused BAV is the predominant type, with 3 aortic sinuses, 2 cusps, 2 commissures, and a single raphe. The cusps are, commonly, of different sizes with various commissural angles of the nonfused cusp and are labeled as symmetrical if the angle is 160° to 180° and asymmetrical if less than that. Figure 2 summarizes this novel International Consensus classification. The International Consensus has the following advantages over the Sievers classification: a) it is able to define all BAV phenotypes such as fused, 2-sinus and partial fusion (forme fruste) phenotypes; b) it is able to recognize fused BAV without raphe, which is different from 2-sinus BAV; c) it gives a symmetry assessment required for surgical repair planning of fused BAV; d) it includes aorta phenotypes (root, ascending, and extended); and e) it uses more simplistic and descriptive intuitive language. The international classification supports decision-making for BAV repair by highlighting the following important technical factors[11]: a) presence of raphe: presence of raphe (especially if calcified) on the conjoined leaflet impacts the mobility of this leaflet, which has a subsequent impact on effective orifice area, the eccentricity of blood flow out of the ventricle, and most likely longevity of the repair; b) symmetry: asymmetric valves pose a significantly greater challenge when it comes to repair. This challenge is more pronounced when there is limited geometric height of the conjoined leaflet. There is significant debate in the community as to whether very asymmetric valves should be repaired. In such cases, the decision should be made by an experienced valve surgeon, as it may be that other procedures should be considered (e.g., SAVR or a Ross procedure).

Recommendations for Intervention from the ACC/AHA and European Society of Cardiology Guidelines

According to European and US guidelines, indications for aortic valve intervention in patients with lone BAV (i.e., without aortopathy) follow the same recommendations for TAV-associated AS and/or AR (Table 1).[12,13] Therefore, valvular intervention is performed in accordance with symptoms, cardiac remodeling, and concomitant indication for other cardiac interventions (such as coronary artery bypass or other valve surgery). This approach is shared across the European and US guidelines in BAV patients without aortopathy. In the case of BAV-associated aortopathy, specific recommendations exist, addressing both the aortic root and valve, but with some differences between the 2 guidelines. Firstly, a maximal ascending aortic diameter of ≥55 mm (confirmed by electrocardiogram-gated CT measurement) should be surgically referred (IIaC, European Society of Cardiology) in all patients (BAV included). On the other hand, in the US guidelines, surgery is recommended with class I indication in BAV patients with aortic measurements >55 mm. In case of “*additional risk factors*” (see Table 1), the accepted operative cut-off is 50 to 55 mm in the US guidelines and ≥50 mm in European guidelines (class IIa for both). Both the United States and European guidelines consider that concomitant aortic surgery is a

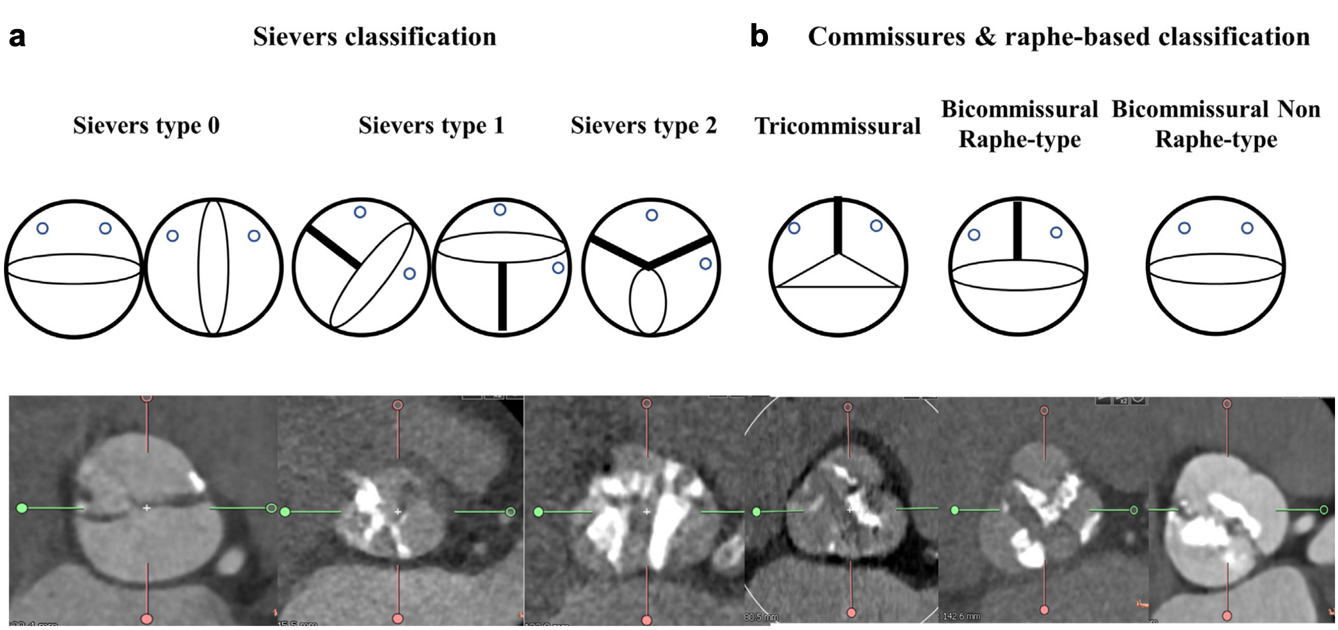


Figure 1. Classification systems for BAV. (a) Schematic (top panel) and computed tomography images (bottom panel) of each type of Sievers classification. (b) This more novel proposed system is based on number of commissures (2 or 3), and in the presence of 2 commissures, the presence or absence of a raphe. Abbreviation: BAV, bicuspid aortic valve.

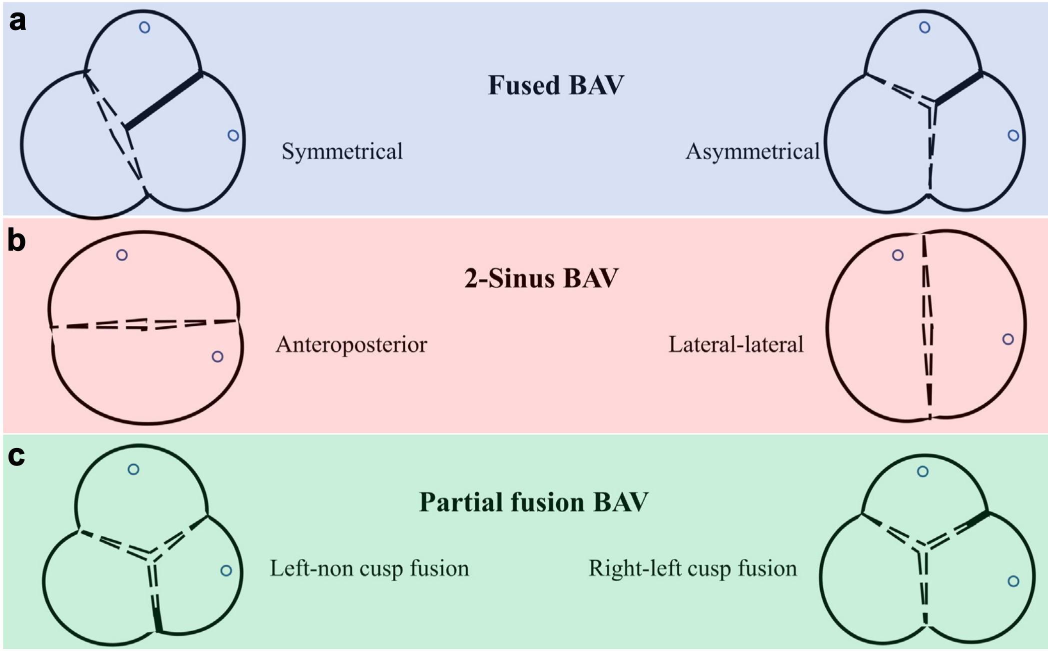


Figure 2. A new international consensus classification of bicuspid aortic valve. (a) represents the fused BAV type with symmetrical phenotype based on the wide angle of the nonfused non coronary cusp or asymmetrical phenotype with angulation of less than 160°. (b) represents the 2-Sinus BAV with its 2 phenotypes, anteroposterior, and lateral-lateral. (c) represents partial fusion BAV whereby 2 commissures are fused by <50%.
Abbreviation: BAV, bicuspid aortic valve.

reasonable approach (class IIa) in BAV patients undergoing surgery for severe AS or regurgitation with dilated aortic root/ascending aorta of ≥45 mm.

Indexed aortic diameter measurement should be preferred in short-statured patients with Turner syndrome (karyotype 45X0) and BAV since absolute measurements may not predict the risk of aortic dissection. An aortic diameter index ≥25 mm/m^2 is the generally accepted operative cut-off value in these cases,[14,15] or an aortic cross-sectional area--to-height ratio of >10.[16] Notably, in patients with BAV requiring aortic root replacement, valve-sparing surgery may be considered if the surgery is performed at a Comprehensive Valve Centre.[13]

Recent studies have highlighted that aortopathy associated with BAV-associated AR was more malignant than with BAV-associated AS.[17] Faster aneurysmal growth and aortic dissection were more common with AR compared with AS following SAVR for BAV patients.[18,19] In fact, periodic imaging should be considered lifelong in patients with BAV and previous AVR if the aortic diameter is ≥ 40 mm.[13] For patients with BAVs, it is appropriate to have an echocardiographic screening of first-degree relatives.[12,13]

Surgical Strategies for BAV

Surgical intervention remains the default strategy for patients with symptomatic BAV. Nonetheless, TAVR may be considered an alternative to surgery after considering patient-specific factors, including patient preference.[13] BAV was excluded from all the pivotal randomized trials

Table 1
Guideline recommendations for interventions on patients with severe aortic stenosis with focus on BAV

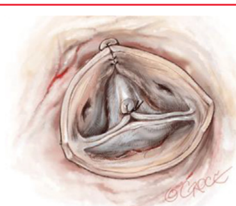
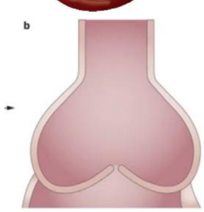
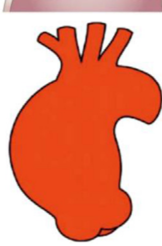
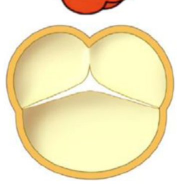
Bicuspid aortic valve	AHA/ACC guidelines	ESC guidelines
Without aortopathy	Follow same recommendations for tricuspid-associated stenosis and/or regurgitation. TAVR may be considered as an alternative to SAVR after consideration of patient and procedural characteristics	Follow same recommendations for tricuspid-associated stenosis and/or regurgitation. TAVR is not specified as potential treatment option for BAV patients.
With aortopathy	Replacement of the ascending aorta is reasonable in patients with BAV undergoing AVR because of severe aortic stenosis or aortic regurgitation when the diameter of the ascending aorta is 4.5 cm or greater if the surgery is performed at Comprehensive Valve Centre (class IIa, level of evidence C-EO) Surgery is indicated in asymptomatic or symptomatic patients with BAV if the diameter of the aortic root or ascending aorta is greater than 5.5 cm (class I, level of evidence B-NR) Surgery is reasonable in asymptomatic patients with BAV if the diameter of the aortic root or ascending aorta is 5.0 to 5.5 cm and an additional risk factor for dissection is present (family history of aortic dissection or aortic growth rate ≥0.5 cm per year) if the surgery is performed at Comprehensive Valve Centre (class IIa, level of evidence B-NR) Surgery may be considered in asymptomatic patients with BAV if the diameter of the aortic root or ascending aorta is 5.0 to 5.5 cm and have no additional risk factors and the patient is at low surgical risk and the surgery is performed at Comprehensive Valve Centre (class IIb, level of evidence B-NR)	*Indication is primarily aortic valve disease:* Replacement of aortic root or tubular ascending aorta, alongside the aortic valve, should be considered when diameter ≥45mm (class IIa, level of evidence C) *Indication is primarily aortic root disease:* Surgery should be performed in patients with BAV, who have a maximal aortic diameter ≥55 mm (class IIa, level of evidence C) Replacement of the root or tubular ascending aorta should be considered if diameter ≥50mm in the presence of bicuspid aortic valve with additional risk factors (family history of aortic dissection [or personal history of spontaneous vascular dissection], severe aortic regurgitation or mitral regurgitation, desire for pregnancy, systemic hypertension, and/or aortic size increase >3 mm/year) (class IIa, level of evidence C)

Abbreviations: ACC, American College of Cardiology; AHA, American Heart Association; AVR, aortic valve replacement; BAV, bicuspid aortic valve; ESC, European Society of Cardiology; SAVR, surgical aortic valve replacement; TAVR, transcatheter aortic valve replacement.

comparing TAVR with SAVR for severe AS; thus, SAVR remains the standard of care in most BAV-associated aortic valve interventions, both stenotic and regurgitant pathologies. Isolated SAVR can be accomplished via a sternotomy, mini sternotomy, small right anterior thoracotomy, and robotically. SAVR also allows for concomitant procedures such as multivalve procedures, coronary artery bypass, maze procedure, and ascending aortic replacement.

Notably, surgical outcomes of aortic valve replacement were not influenced by the morphology of the valve with no difference in pacemaker rate, for example, between BAV and tricuspid valves in patients undergoing SAVR.[20] On the other hand, anatomical features in BAV had a significant impact on time to reoperation in patients undergoing BAV repair.[21] Reconstructing regurgitant BAVs were reported 25 years ago with good early results; nonetheless, durability was not maintained after 5 years.[22,23] A better understanding of the failure mode in BAV repair allowed identification of certain anatomical features that were associated with valve failure, namely annular size and circumferential orientation of the commissures of the nonfused cusp.[11] Additionally, technical factors included use of autologous pericardium as partial cusp replacement was associated with a high rate of BAV repair failure.[11,24] A selective approach to identify suitable patients for BAV repair coupled with systemic modifications based on anatomic concepts led to a significant reduction in the incidence of reoperation compared with the historical approach.[21] The anatomic repair concept included suture annuloplasty to tackle annular dilatation alongside modification of circumferential orientation to a mirror-symmetric configuration in BAV.[25-27] The current guidelines include aortic valve repair as a possible strategy in selected AR patients with "*pliable noncalcified bicuspid valves who have type I (enlargement of the aortic root with normal cusp motion) or type II (cusp prolapse) valve morphology.*"[14] Major concerns against aortic valve repair are (i) the higher level of expertise required, (ii) the lack of evidence at the general community level, and (iii) the yet-to-be-defined durability of the repair, although recent data reported durable outcomes following BAV repair after 15-year follow-up.[21] Because of the aforementioned reasons, BAV repair should be performed only in centers with proven expertise in the procedure, and candidates' feasibility is to be approved by an experienced heart team.[12,13] Table 2 summarizes surgical repair techniques that are used in patients with BAV. The choice of prosthetic valve type in BAV is similar to that of the tri-leaflet valve.[13] Additionally, an estimated life expectancy longer than 10 years is suggested for a

Table 2
Bicuspid aortic valve repair table: summary of repair techniques

Lesion		Repair techniques	Repair durability
Isolated prolapse of the fused cusp		Leaflet plication with interrupted sutures Triangular resection Figure-of-eight stitch in the pericommissural area	Good mid-term results provided adequate cusp tissue/ geometric height and coaptation
Isolated cusp restriction		Decalcification Resection and pericardial patch reconstruction[11,24]	Questionable short and mid-term results
Annular dilatation[11]		Gore-Tex suture or external ring/band annuloplasty around the root externally Reimplantation of the root (David procedure)[25-27] Aortic annuloplasty ring at the level of the functional annulus Sinotubular junction stabilisation with a band	Annular dilatation is an independent risk factor for recurrence of regurgitation
Aortic aneurysm		Concomitant root or ascending aorta replacement	
Asymmetric position of the commissures		Reposition commissures inside a root replacement (e.g., David) Plication of the aortic sinuses to alter commissural position	Commissural angle of <160° has poor durability
Leaflet perforation or significant fenestration		Leaflet free edge reinforcement with a Gore-Tex suture Pericardial patch reconstruction	Use of pericardium is an independent risk factor for early failure

mechanical prosthesis.[12] Prosthesis-related risks in pregnancy and teratogenicity of warfarin should be carefully explained in cases of young women contemplating pregnancy and bioprostheses should be favored (IIaC).[12] Exceptionally, young patients (<50 years of age) with contraindicated or undesirable anticoagulation are good candidates for replacement of the aortic valve by a pulmonary autograft (Ross procedure) if they have appropriate anatomy when performed by an experienced surgeon.[13] In these cases, and in cases where the international normalized ratio >2 is not clinically bearable, the novel Food and Drug Administration-approved On-X valve (On-X Life Technologies, Austin, Texas) was reported to provide superior hemodynamics and greater thromboresistance, therefore allowing for a lower anticoagulation level (i.e., international normalized ratio 1.5-2).[28] Data from observational and propensity-matched studies, randomized controlled trials, and meta-analyses have provided evidence of survival advantage of mechanical aortic valves over bioprosthetic valves, especially in patients younger than 65 years of age as bioprosthetic valves lack durability.[29]

Transcatheter Treatment Paradigms

Our current understanding of the safety and efficacy of TAVR in patients with BAV has been based on outcomes from registries and observational studies. More contemporary evidence of TAVR feasibility in BAV using newer/current generation devices is now available. The Society of Thoracic Surgeons (STS)/American College of Cardiology (ACC) Transcatheter Valve Therapies (TVT) Registry published their results on 2691 propensity-score matched pairs of bicuspid and tricuspid AS patients undergoing TAVR with a balloon-expandable valve.[30] This was a prospective cohort study of patients undergoing TAVR at 552 US centers. Successful implantation was recorded in 99% of cases in both groups, with no difference in device success between the bicuspid and the tricuspid group (96.5 vs. 96.6%, $p = 0.87$). There was no significant difference in 30-day or 1-year mortality between the groups, but bicuspid patients had a significantly higher incidence of stroke (2.5 vs. 1.6%, $p = 0.02$) and pacemaker implantation rate (9.1 vs. 7.5%, $p = 0.03$) at 30 days.[30] Valve hemodynamics were similar between the bicuspid and tricuspid groups, along with moderate or severe paravalvular leak rates at 1-year follow-up. A recent Chinese registry with longer follow-up showed similar survival (87.1 vs. 79.5%, $p = 0.13$), adverse clinical outcomes, and valve hemodynamics between bicuspid and tricuspid groups at 3 years, but lower pacemaker implantation in the bicuspid group.[31]

An updated report from the US STS/ACC/TVT Registry was recently published using data from 5412 BAV patients undergoing TAVR, including 3705 patients who underwent procedures with current-generation devices.[32] Notably, this updated report included both balloon-expandable and self-expanding valves. The use of newer generation valves was associated with a significant reduction in paravalvular leak when compared with old generation valves. However, residual moderate to severe AR incidence remained marginally higher in bicuspid compared with trileaflet valves undergoing TAVR (2.7 vs. 2.1%, $p < 0.001$). There was a lower adjusted mortality risk with BAV compared with tricuspid valves (hazard ratio 0.88, 95% CI 0.78 to 0.99) with no difference in 1-year stroke risk between the 2 groups (hazard ratio 1.14, 95% CI 0.94 to 1.39).

The performance of new generation self-expanding vs. balloon-expandable valves in BAV-AS was compared in the BEAT International Collaborative Registry.[33] This study included 242 patients treated with the balloon-expandable Sapien 3 valve compared with 111 patients treated with the self-expanding Evolut (41 patients with Evolut PRO and 70 patients with Evolut R) valve. Device success was similar between the groups in both the unmatched cohort and following propensity-score matching. Despite having similar annular sizing (both area and perimeter) in the matched cohort, patients in the balloon-expandable valves received smaller size prostheses compared with the self-expanding group (23 mm: 23.4 vs. 3.9%; 26 mm: 41.6 vs. 23.4%, $p < 0.001$). There were no differences in 30-day clinical outcomes, including death, cardiovascular death, stroke, and cardiac hospitalizations between the 2 groups in the matched and unmatched cohorts. Hemodynamic parameters favored the self-expanding group, although a greater proportion of patients had moderate to severe AR (9.3 vs. 0%, $p = 0.043$). There was a relatively high (1.7%) rate of annular rupture in the balloon-expandable group. Similar results were seen in a meta-analysis of 7 studies (706 patients) comparing balloon-expandable ($n = 367$) with self-expanding valves ($n = 339$) in BAV. It showed similar mortality at 1 year, stroke, and moderate-severe paravalvular leak. Balloon-expandable valves were associated with lower rate of second valve implantation (2.8 vs. 9.1%, $p = 0.05$), new pacemaker implantation (15 vs. 22.1%, $p = 0.05$), but carried a higher risk of annular rupture (3.5 vs. 0%).[34]

To assess the relationship between the morphology of bicuspid valve and outcomes following TAVR, Yoon et al reported the data of 1034 patients from the International BAV Stenosis Registry.[35] This study included consecutive BAV patients who underwent TAVR from 24 centers across 8 countries. Seventy-two percent of included patients were treated with the Sapien 3 valve with a 2-year mortality rate of 12.5%. Calcified raphe and excess leaflet calcification were demonstrated to be independently associated with 2-year all-cause mortality. Notably, the combination of both features was common (26%) and was associated with significantly higher 2-year all-cause mortality compared with patients with 1 or none of these features (25.7, 9.5, and 5.9%, respectively, $p < 0.001$). The combination group had similar effective orifice area and aortic valve gradients post-TAVR; nonetheless, the incidence of at least moderate paravalvular regurgitation was significantly higher when compared with the other 2 groups (6.5%, 2.5%, and 1.6% respectively, $p = 0.002$). Table 3 summarizes studies assessing outcomes of TAVR in BAV.[10,35-46] More recently, and perhaps pertinent to transcatheter therapies with respect to treatment strategy and procedural technique, Yoon et al described a BAV classification by raphe number and degree of calcification (no raphe [type 0], noncalcified raphe [type 1], and calcified raphe [type 1]), and their association with all-cause mortality following TAVI with newer generation valves.[35] Calcified raphe were associated with the highest mortality, lower mortality in noncalcified raphe, and the lowest mortality in nonraphe BAV.

Recently, the US Food and Drug Administration approved revised commercial labeling that expands the indication for the Evolut platform to include low-risk BAV patients. This modified the previous precaution in BAV patients and now allows heart teams to consider TAVR according to the clinical and anatomical characteristics. The revised labeling was supported by data from the Low-Risk Bicuspid Study, which was a prospective single-arm study that recruited 150 BAV patients from 25 high-volume centers in the United States.[41] The device success rate was 95.3%, with no major or severe paravalvular regurgitation incidence. The primary endpoint of all-cause mortality or disabling stroke at 30 days was remarkably low (1.3%), with low major vascular complication rates (1.3%) and low mean transthoracic gradients (7.6 ± 3.7 mmHg) post TAVR. Similar results were reported in the low-risk TAVR study, an investigator-initiated, prospective, multicenter study.[47] There was zero mortality and no disabling stroke at 30 days among 61 low-risk BAV patients who underwent TAVR with either balloon-expandable or self-expanding valves. As such, several factors need to be considered in TAVR device selection, including valvular, outflow and root calcifications, vascular access, pre-existing conduction abnormalities, and coronary reaccess. No data support using a particular valve type in BAV patients, and procedural success is feasible using different valve types.[48]

Challenges of TAVR for BAV

Initial experience using TAVR in BAV did result in a relatively high incidence of paravalvular leak. This seems to have been overcome with the improvement in valve design and sealing skirts.[32]

Table 3
Major studies of transcatheter aortic valve replacement in bicuspid aortic valve

Author, year	Bugani 2021[39]	Guo 2021[40]	Forrest 2020[41]	Zhao 2020[42]	Yoon 2020[35]	Toller 2019[43]
Study characteristic						
Type of study	Retrospective	Retrospective	Prospective	Prospective	Retrospective	Retrospective
Follow-up	1 y	1 mo	30 d	30 d	1 y	390 d
Number of patients	353	209	150	75	1034	79
Baseline characteristics						
Mean age (Years)	77.8 ± 8.3	75.12 ± 6.79	70.3 ± 5.5	73.8 ± 5.8	74.7 ± 9.3	76 ± 9
Male (%)	229 (64.9%)	128 (61.2%)	78 (52%)	44 (58.7%)	610 (59.0%)	44 (56%)
Society of Thoracic Surgeons score %	4.4 ± 3.3	5.5 (3.6–9.1)	1.4 ± 0.6	7.3 ± 4.2	3.7 ± 3.3	3.8 (2.3–5.5)
Logistic EuroSCORE %	NA	NA	NA	NA	NA	NA
Left ventricular ejection fraction (%)	52 ± 14	57.0 (46.0–63.4)	63.4 ± 8.3	52.0 ± 16.1	53.5 ± 15.3	50 ± 15
Bicuspid valve subtypes (%)						
Type 0	25 (7.1%)	99 (47.4%)	14 (9.3%)	46 (61.3%)	107 (10.3%)	5 (6%)
Type I	218 (61.8%)	79 (37.8%)	136 (90.7%)	NA	927 (89.7%)	64 (81%)
Type II	3 (0.9%)	NA	0	NA	NA	4 (5%)
UD	106 (30.1%)	NA	NA	NA	NA	6 (8%)
Echocardiographic findings						
Aortic valve area (cm^2)	0.68 ± 0.01	NA	0.8 ± 0.2	NA	0.7 ± 0.2	0.65 ± 0.16
Mean gradient (mmHg)	48.3 ± 16.6	56.0 (43.0–70.5)	49.9 ± 15.5	67.6 ± 19.7	47.5 ± 16.5	50.2 ± 16.2
Transcatheter valve subtypes (%)						
New generation	353 (100%)	NA	64 (42.7%)	75 (100%)	975 (94.3%)	79 (100%)
Sapien 3	242 (68.6%)	NA	NA	NA	740 (71.6%)	79 (100%)
Lotus	NA	NA	NA	NA	47 (4.5%)	NA
Venus A	NA	NA	NA	75 (100%)	NA	NA
Vita flow	NA	NA	NA	NA	NA	NA
Evolut R	111 (31.4%)	NA	64 (42.7%)	NA	188 (18.2%)	NA
Old generation	NA	NA	NA	NA	NA	NA
Sapien	NA	NA	NA	NA	NA	NA
Sapien XT	NA	NA	NA	NA	NA	NA
Core valve	NA	NA	NA	NA	NA	NA
Access route						
Transfemoral	317 (89.8%)	205 (98.1%)	147 (98.7%)	75 (100%)	975 (94.3%)	75 (95%)
Transapical	NA	NA	NA	NA	0	3 (4%)
Transaxillary	NA	NA	NA	NA	0	NA
Transubclavian	30 (8.5%)	NA	NA	NA	0	1 (1%)
Transcarotid	NA	4 (1.9%)	NA	NA	0	NA
Transaortic	6 (1.7%)	NA	NA	NA	0	NA
Procedural clinical outcomes						
Conversion to surgery	3 (0.8%)	NA	1 (0.7%)	0	9 (0.9%)	1 (1.3%)
Device success	306 (86.7%)	176 (84.5%)	141 (95.3%)	63 (84.0%)	NA	75 (95%)
New pacemaker implantation	51 (16.1%)	16 (7.7%)	22 (15.1%)	14 (18.7%)	118 (12.2%)	14 (18%)
Annular rupture	4 (1.2%)	NA	NA	0	NA	0
Second valve implantation	17 (4.8%)	17 (8.1%)	5 (3.3%)	9 (12.0%)	14 (1.4%)	1 (1.3%)
Procedure related death	4 (1.1%)	1 (0.5%)	NA	NA	NA	NA
Postprocedural echocardiographic outcomes						
Mean gradient (mmHg)	NA	12.5 ± 6.8	9.9	13.0 ± 5.7	10.6 ± 5.0	NA
Paravalvular leakage						
Mild	NA	NA	60 (40%)	18 (24.0%)	291 (28.6%)	NA
≥ Moderate	14 (4.0%)	13 (8.1%)	0	8 (10.7%)	33 (3.2%)	NA
Clinical outcomes at 30 d						
All-cause mortality	0	1 (0.5%)	1 (0.7%)	2 (2.7%)	21 (2.0%)	3 (3.8%)
Cardiovascular mortality	NA	NA	NA	NA	17 (1.6%)	1 (1.3%)
Stroke	NA	2 (1%)	6 (4%)	0	28 (2.7%)	1 (1.3%)
Major vascular complications	11 (3.1%)	NA	2 (1.3%)	2 (2.7%)	34 (3.3%)	1 (1%)
Major or life-threatening bleeding	22 (6.2%)	NA	6 (4%)	7 (9.3%)	37 (3.6%)	1 (1.3%)
Acute kidney injury stage 2 or 3	NA	NA	0	NA	20 (1.9%)	NA
Clinical Outcomes - medium/long-term						
1-y mortality	NA	NA	NA	NA	55 (6.7%)	6 (7.7%)
2-y mortality	NA	NA	NA	NA	74 (12.5%)	NA

Author, year	Lei 2019[44]	Yoon 2017[45]	Yoon 2016[46]	Perlman 2016[36]	Jilaihawi 2016[10]	Yousef 2015[37]	Mylotte 2014[38]
Study characteristic							
Type of study	Retrospective	Retrospective	Retrospective	Retrospective, Prospective	Prospective	Retrospective	Retrospective
Follow-up	1.5 y	1 y	1 y	30 d	6 mo	1 y	1 y
Number of patients	71	108	301	51	130	108	139
Baseline characteristics							
Mean age (Years)	71.9 ± 5.8	74.4 ± 10.6	77 ± 9.2	76.2 ± 9.3	76.6 ± 10.4	75.5 ± 14.4	78 ± 8.9
Male (%)	32 (45.1%)	77 (71.3%)	173 (57.5%)	24 (47.06%)	80 (61.5%)	69 (63.9%)	78 (56.1%)
Society of Thoracic Surgeons score %	7.0 ± 3.6	5.2 ± 3.4	4.7 ± 5.2	5.2 ± 3.7	4.7 (3-7.3)	NA	4.9 ± 3.4
Logistic EuroSCORE %	NA	13.8 ± 12.5	14.9 ± 11.7	NA	NA	17.2 ± 12.2	14.8 ± 10.6
Left ventricular ejection fraction (%)	NA	53 ± 18	51.1 ± 15.1	NA	NA	50 ± 15.6	50.4 ± 14.6
Bicuspid valve subtypes (%)							

(continued on next page)

Table 3 (*continued*)

Author, year	Lei 2019[44]	Yoon 2017[45]	Yoon 2016[46]	Perlman 2016[36]	Jilaihawi 2016[10]	Yousef 2015[37]	Mylotte 2014[38]
Type 0	71 (100%)	6	31 (11.9%)	6 (11.8%)	NA	13/78 (16.67%)	32/120 (26.7%)
Type I	NA	102	224 (86.2%)	38 (74.51%)	NA	57/78 (73.08%)	82/120 (68.3%)
Type II	NA	0	5 (1.9%)	1 (1.96%)	NA	8/78 (10.26%)	6/120 (5%)
UD	NA	0	41 (13.6%)	6 (11.8%)	NA	30/78 (38.46%)	0
Echocardiographic findings							
Aortic valve area (cm^2)	NA	0.6 ± 0.2	0.7 ± 0.2	0.66 ± 0.18	0.64 (0.52-0.80)	0.7 (0.5-0.8)	0.6 ± 0.2
Mean gradient (mmHg)	NA	45.3 ± 14.4	52.1 ± 18.5	49.4 ± 16	49.5 (41-60)	48.4 ± 17	48.7 ± 16.5
Transcatheter valve subtypes (%)							
New Generation	55 (77.5%)	74 (68.5%)	102 (33.9%)	51 (100%)	8 (6.2%)	0	0
Sapien 3	NA	74	91 (30.23%)	51	8 (6.2%)	0	0
Lotus	16 (22.5%)	0	11 (3.65%)	0	0	0	0
Venus A	33 (46.5%)	0	0	0	0	0	0
Vita flow	6 (8.5%)	0	0	0	0	0	0
Evolut R	NA	0	0	0	0	0	0
Old generation	16 (22.5%)	34 (31.5%)	199 (66.1%)	0	122 (93.9%)	108	139
Sapien	NA	0	0	0	17 (13.1%)	61 (56.5%)	48
Sapien XT	NA	34	87 (28.9%)	0	45 (34.6%)	0	0
Core valve	16 (22.5%)	0	112 (37.21%)	0	60 (46.2%)	47 (43.52)	91
Access route							
Transfemoral	71 (100%)	102 (94.4%)	253 (84.1%)	49 (96.1%)	114 (87.7%)	90 (83.3%)	109 (78.5%)
Transapical	0	NA	19 (6.31%)	0	NA	8 (8.7%)	12 (8.6%)
Transaxillary	0	NA	0	0	NA	0	0
Transubclavian	0	NA	10 (3.32%)	0	NA	5 (5.6%)	5 (3.6%)
Transcarotid	0	NA	2 (0.66%)	2 (3.9%)	NA	0	1 (0.7%)
Transaortic	0	NA	17 (5.65%)	0	NA	5 (5.6%)	12 (8.6%)
Procedural clinical outcomes							
Conversion to surgery	NA	1 (0.93%)	8 (2.9%)	0	4 (3.1%)	4	3 (2.2%)
Device success	NA	100 (92.6%)	255 (84.7%)	50 (98%)	NA	92 (85.2%)	125 (89.9%)
New pacemaker implantation	14 (19.7%)	13 (12%)	43 (14.3%)	12 (23.5%)	28 (26.2%)	21	32 (23.2%)
Annular rupture	0	1 (0.9%)	5 (1.7%)	0	NA	1	NA
Second valve implantation	11 (15.5%)	2 (1.9%)	14 (4.7%)	0	4 (3.1%)	11	5 (3.6%)
Procedure related death	NA	4 (1.3%)	0	0	2 (1.5%)	1	5 (3.6%)
Postprocedural echocardiographic outcomes							
Mean gradient (mmHg)	15.6 ± 6.7	11.2 ± 4.2	10.8 ± 5.5	11.2 ± 4.7	NA	10.5	11.4 ± 9.9
Paravalvular Leakage							
Mild	23 (33.3%)	NA	NA	19 (37.2%)	61 (48%)	NA	NA
≥ Moderate	0	7 (6.5%)	17 (5.6%)	0	23 (2.36%)	32 (30.8%)	38 (28.4%)
Clinical outcomes at 30 d							
All-cause mortality	5 (7.0%)	1 (0.9%)	13 (4.3%)	2 (3.9%)	5 (3.8%)	9 (8.3%)	7 (5%)
Cardiovascular mortality	NA	NA	11 (3.7%)	NA	NA	7 (7.6%)	NA
stroke	3 (4.2%)	5 (4.6%)	7 (2.3%)	1 (1.9%)	4 (3.2%)	3 (2.8%)	3 (2.2%)
Major vascular complications	5 (7.0%)	6 (5.6%)	12 (4%)	2 (3.9%)	NA	7 (6.5%)	9 (6.5%)
Major or life-threatening bleeding	8 (11.3%)	1 (0.9%)	24 (7.97%)	5 (9.81%)	NA	7 (6.5%)	19 (13.67%)
Acute kidney injury stage 2 or 3	NA	2 (1.9%)	8 (2.7%)	1 (1.9%)	1 (0.9%)	7 (6.5%)	3 (2.2%)
Clinical outcomes - medium/long-term							
1-y mortality	6 (8.5%)	7 (6.9%)	NA	NA	NA	15/89 (16.9%)	21 (17.5%)
2-y mortality	NA	NA	NA	NA	NA	NA	NA

Abbreviation: NA, not reported.

BAV anatomy is associated with greater calcium burden requiring more frequent balloon predilatation during TAVR. These factors may account for the increased stroke risk associated with TAVR, reflected by a significantly higher incidence of stroke in BAV compared with TAV patients during in-hospital stay (2.1 vs. 1.2%) and at 30 days (2.5 vs. 1.6%).[30] Similarly, BAV patients demonstrated a greater number and larger brain lesion size than TAV patients undergoing TAVR.[49] Notably, the stroke risk did not differ between the 2 groups at 1 year (3.4 vs. 3.1%). Larger data from the US STS/ACC/TVT registry, including a broader cohort of self-expanding and balloon-expandable valves, showed that the 1-year adjusted risk of stroke was comparable between BAV and TAV patients (hazard ratio 1.14; 95% CI, 0.94–1.39).[32] This stroke risk may be modifiable using embolic protection devices, and whether a subset of TAVR patients, for example, patients with BAV, may sustain a larger reduction in procedure-related stroke warrants further evaluation.

BAV predisposes to a variety of coronary anomalies, which need to be taken into account when selecting patients for TAVR.[50] For example, type 0 BAV patients with a vertically orientated orifice (lateral type with left and right coronary cusps) may have a narrow separation distance between the right and left main coronary ostia. Coronary occlusion is rare but potentially life-threatening. Studies have shown a coronary occlusion rate of 0.1% to 1.2%.[51-54] Bicuspid TAVR registry data report a similar

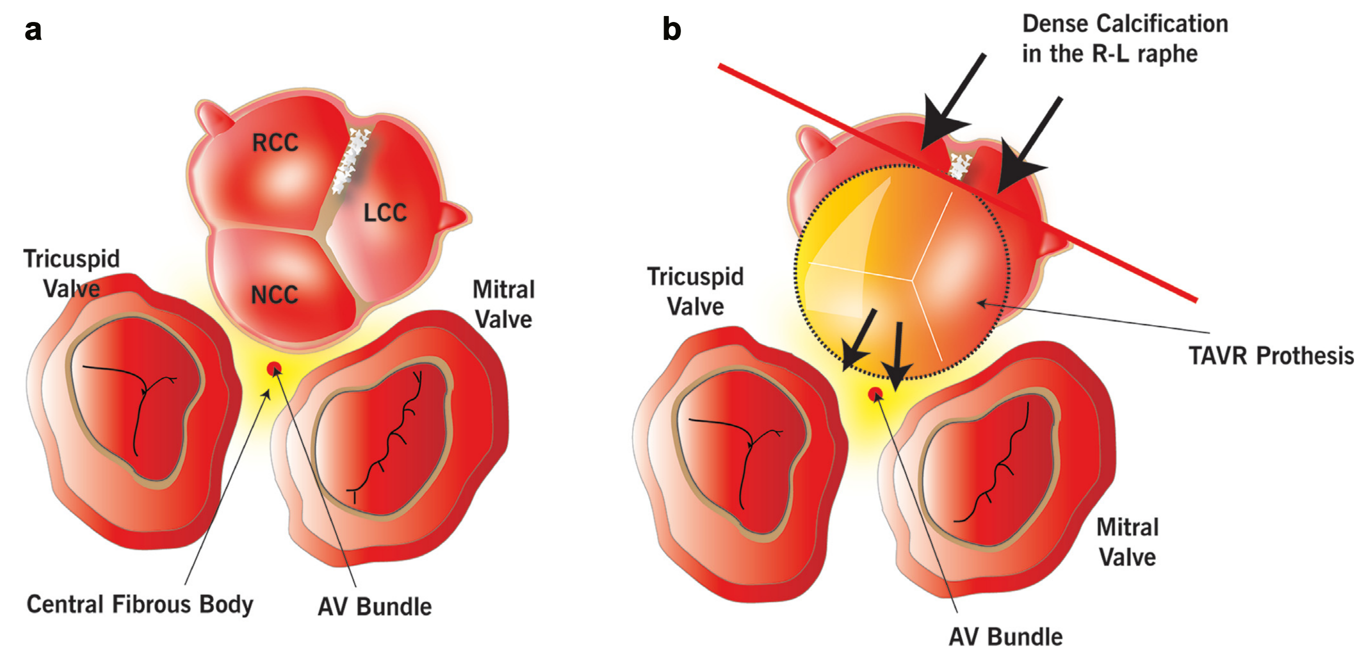


Figure 3. Potential mechanism of higher rate of pacemaker in BAV. (a) Aortic valve complex in a BAV Sievers 1 configuration with R-L fusion with calcium. (b) The asymmetrical TAVR expansion resulting from resistant calcific raphe and leaflet fusion may compress the non-coronary cusp toward the conduction fiber pathway along the central fibrous body.
Abbreviations: BAV, bicuspid aortic valve, TAVR, transcatheter aortic valve replacement.

incidence of 0% to 1.5%.[10,36,38,46,55] Whilst these studies initially reported that BAV patients, when compared with TAV patients with AS remained at increased procedural risk, including conversion to open-heart surgery, the recent update from US STS/ACC Registry showed that device success was marginally higher in tricuspid compared with BAV (96.7 vs. 96%, $p = 0.004$) with comparable rates of conversion to open-heart surgery.[32] There were no differences in procedural complications in BAV patients between self-expanding and balloon-expandable valves.[30,32,33]

Pacemaker rates during TAVR in tricuspid AS tend to reflect a combination of valve choice (more common with self-expanding valves), greater implant depth, native annular anatomy with respect to membranous septal length and calcium burden as well as local decision-making algorithms regarding pacemaker insertion.[56] In BAV patients, pacemaker implantation rates were higher than would be expected for TAV patients.[35,38] The higher rate of pacemaker implantation in BAV patients may relate to the asymmetric TAVR expansion that results from the resistant calcific raphe and leaflet fusion that make up Sievers type 1 and 2 BAVs (Figure 3). This may result in preferential expansion toward the noncoronary cusp, which is situated near the conduction pathway, whilst tricuspid valves or Sievers type 0 BAVs may allow for more symmetrical expansion of TAVR prostheses, diverting tissue away from the AV node. Sievers L-R Type 1 BAV, in particular, may have bulky calcification that may protrude through the membranous part of the interventricular septum, leading to atrioventricular and interventricular conduction block.[57]

Technical Considerations for TAVR in BAV

Patients with BAV present a variety of technical challenges for TAVR operators and require careful planning for valve deployment and minimizing procedural complications.[58] A study using multi-slice computed tomography to compare bicuspid with tricuspid aortic valves showed generally larger annular areas in BAV patients (5.21 vs. 4.63 cm^2).[59] Anatomical challenges commonly encountered with BAV (severe annular calcification, large annular size, dilated, and horizontal aorta) can pose numerous challenges for TAVR operators.[60,61] The BAVARD multicentre registry provided a unique insight on sizing using multi-slice computed tomography. The registry confirmed that an annular sizing approach could be used in the majority of bicuspid patients (86%) with minimal (3% to 4%) oversizing. In gray-zone cases, the intercommissural distance (ICD), 4-mm above the annulus, was found to be useful, particularly when the ICD was smaller and "tapered, " compared with the annulus perimeter-diameter area. Selecting a device based on the annulus size in these "tapered" cases could increase the risk of aortic root rupture or device underexpansion (Figure 4),[62] and in these instances valve sizing derived off the diameter of the intercommissural distance (around 4 mm above the true annulus) may be recommended.

Reports from large series of BAV patients indicate that current commercial prostheses of appropriate sizes are adequate.[36,38,63] However, oversizing of the prosthesis can lead to distortion and poor expansion leading to paravalvular leaks, whilst intraprocedural postdilatation is a risk factor for annular rupture, aortic root hematoma, and heart block. Whilst self-expanding prostheses reduce the risk of aortic trauma, they may increase the risk of paravalvular leak and heart block in BAV patients.[46,64] Tchetche et al reported that in a series of 101 BAV and 88 tricuspid aortic valve patients, oversizing (defined as the mean prosthesis:annulus ratio) was applied in both groups, but to a lesser degree in BAV patients. Design improvement of second-generation valves with high radial force was translated into more stable prosthesis diameter and ellipticity.[62] However, patients with BAV tend to have slightly more elliptical prostheses, but overall retain cylindrical configuration with stable diameters from the distal edge to 12-mm above it. Notably, prostheses in BAV patients were observed to be underexpanded, which was highlighted by mean diameters being constantly smaller than the mean aortic annulus and ICD. Whether this may impact valve durability or leaflet thrombosis is yet to be determined.

SAVR vs. TAVR for BAV

Patients with BAV have been excluded from pivotal randomized trials comparing SAVR vs. TAVR.[65,66] Contemporary data highlight the feasibility of TAVR in treating BAV patients with a relatively low complication

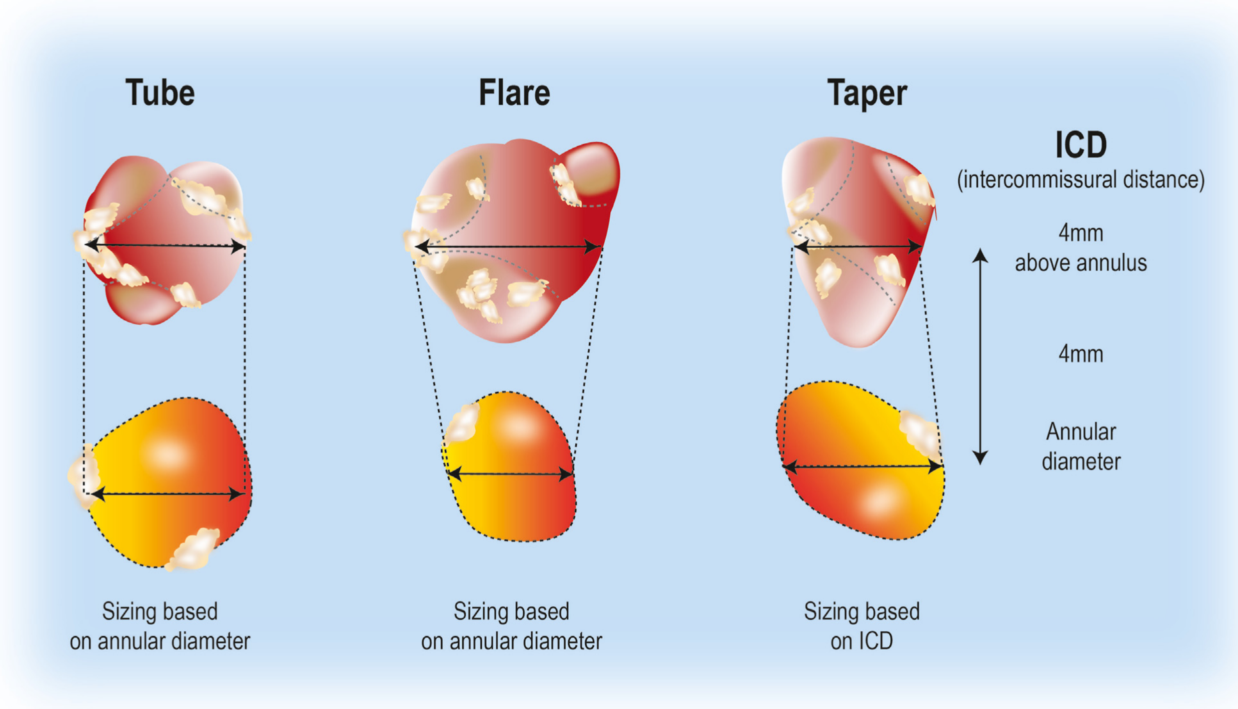


Figure 4. Transcatheter heart valve sizing based on aortic root anatomy. In bicuspid annuli that have diameters similar (tubed) or less (flared) than the intercommissural distance (ICD), valve sizing can be based simply off the annular dimensions as in tricuspid aortic valve stenosis. When the ICD is smaller than the annular diameter (tapered), valve sizing based off the ICD should be considered.

rate. A recent meta-analysis assessing the outcomes of TAVR in BAV vs. conventional tricuspid anatomy in 181,433 patients demonstrated that TAVR was a feasible option in certain BAV anatomies. However, higher rates of moderate to severe paravalvular leak (PVL), annular rupture, and cerebrovascular events were observed in the BAV group.[67,68] Nonetheless, whether outcomes following TAVR are comparable with SAVR in BAV is yet to be determined in a dedicated, prospective randomized trial. One of the challenges in conducting such a trial is the close association of BAV with aortopathy, typically rendering SAVR a more appropriate treatment option. Similarly, concomitant coronary artery disease also favors SAVR, particularly in young patients according to the current guidelines. Therefore, a head-to-head comparison between SAVR and TAVR will require careful planning to identify BAV patients that are potentially amenable to both therapeutic options. Additionally, a better understanding of valve sizing and standardizing deployment techniques are needed to ensure optimal outcomes for TAVR in this group. Furthermore, the comparative role of transcatheter valve types should be better defined to assess if there is equipoise when evaluating TAVR vs. SAVR. Prospective registries will add important insights into procedural success and long-term outcomes when using balloon-expandable or self-expanding valves in BAV patients.

Few observational studies have compared early- and mid-term outcomes of BAV patients who underwent TAVR or SAVR using national registries.[69-72] Data from a large US database retrospectively identified 975 pairs of BAV patients who underwent TAVR and SAVR between 2012 and 2016.[70] TAVR and SAVR recipients had similar in-hospital mortality (3.1 vs. 3.1%), aortic root injury, and acute stroke rates (2.1 vs. 2.6%). TAVR is associated with lower rates of acute myocardial infarction, vascular complications, postoperative bleeding, and shorter length of stay; however, this came at the expense of higher permanent pacemaker implantation rates than SAVR.[70] Using Medicare data, similar results were reported in 699 propensity-matched pairs of patients who underwent TAVR and SAVR.[69] In-hospital mortality rates were similar between the 2 groups, and this remained evident for a median follow-up of 631 days (adjusted hazard ratio 1.08; 95% CI 0.93 to 1.26; $p = 0.30$).[69] In a relatively smaller study of 75 well-matched pairs from the FinnValve registry, the mortality rate was numerically lower in TAVR than SAVR patients (9.7 vs. 18.7%, $p = 0.27$).[71] Moderate to severe PVL was similar between SAVR and TAVR using new generation devices (0 vs. 0.7%, $p = 1.0$).[71] Another study using large national database from United States identified 1393 pairs of BAV patients who underwent TAVR vs. SAVR from 2016 to 2018. It showed that TAVR was associated with lower in-hospital mortality (0.7 vs. 1.8%, odds ratio 0.35, 95% CI 0.13-0.93, $p = 0.035$), similar post-procedure stroke (2.9 vs. 3.2%, $p = 0.72$) and MACE at 30 days and 6 months compared with SAVR. TAVR was associated with lower post-procedure major bleeding, vascular complication, and acute kidney injury. TAVR was associated with similar paravalvular leak (0.9 vs. 0.6%, $p = 0.58$) but higher risk of pacemaker implantation (11.8 vs. 8.6%, $p = 0.033$) compared with SAVR.[72] These results collectively provided indirect evidence of the suitability of TAVR in BAV patients. However, these results could also be due to the differences in the centers where TAVR and SAVR were performed for BAV patients: TAVR may have been performed at experienced high-volume centers, while SAVR may have been performed at a variety of centers. Moreover, these results cannot substitute for a prospective randomized trial comparing TAVR with SAVR in BAV patients. Such a trial will ultimately need to take into consideration technical suitability and indications for intervention for aortopathy. Based on above data, we believe that following factors should be taken into consideration while deciding between SAVR and TAVR: patient's age (mechanical AVR or Ross procedure with pulmonary autograft replacement for patients <65 years of age,[73] comorbidities, life expectancy, patient's preference of surgery, and lifetime management strategy such as willingness of reintervention if they choose to have TAVR at a young age and risk of bleeding while on anticoagulation.

Authors believe that young and active patients should be offered mechanical aortic valve replacement or Ross procedure with pulmonary autograft, patients with high anatomical risk should be offered SAVR, and old and frail patients should be offered TAVR. If the patient is neither old nor young, we should give them a choice and shared-decision making should be taken into consideration.

Conclusions

Indications for surgical intervention in patients with BAV mirror the same for patients with TAV with additional considerations related to anatomic challenges and patient characteristics for transcatheter-based interventions. The data for TAVR in patients with BAV, especially using newer generation prostheses, are nevertheless encouraging. However, patients with BAV are typically younger with lower operative risk (and longer life expectancy), suggesting caution needs to be exercised with strict evaluation on a case-by-case basis with anatomical considerations guiding treatment choice. Newer prostheses have improved sealing skirt designs reducing PVL rates, and the ability to reposition and retrieve devices have further enhanced procedural success, with short-term survival rates equivalent to those undergoing TAVR for tricuspid valve AS. As the evidence supporting TAVR in younger and lower risk patients accumulates, the proportion of patients with BAV being considered for TAVR will rise. Prospective studies specifically addressing TAVR in these populations may be required to assess durability and long-term outcomes as well as determining anatomical criteria for suitability before it becomes a viable option for patients across the board with BAV.

ORCIDs

Ankur Kalra https://orcid.org/0000-0003-0080-1660
Mohammad Alkhalil https://orcid.org/0000-0002-3088-8878
Alessandro Candreva https://orcid.org/0000-0002-6676-7541
Monil Majmundar https://orcid.org/0000-0002-5389-5878
Kunal N. Patel https://orcid.org/0000-0003-2712-0670
Michael J. Reardon https://orcid.org/0000-0002-2880-6132

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