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Transcatheter Aortic Valve Replacement in Bicuspid Aortic Valve Stenosis

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Abstract

After 15 years of successive randomized, controlled trials, indications for transcatheter aortic valve replacement (TAVR) are rapidly expanding. In the coming years, this procedure could become the first line treatment for patients with a symptomatic severe aortic stenosis and a tricuspid aortic valve anatomy. However, randomized, controlled trials have excluded bicuspid aortic valve (BAV), which is the most frequent congenital heart disease occurring in 1% to 2% of the total population and representing at least 25% of patients 80 years of age or older referred for aortic valve replacement. The use of a less invasive transcatheter therapy in this elderly population became rapidly attractive, and approximately 10% of patients currently undergoing TAVR have a BAV. The U.S. Food and Drug Administration and the “European Conformity” have approved TAVR for low-risk patients regardless of the aortic valve anatomy whereas international guidelines recommend surgical replacement in BAV populations. Given this progressive expansion of TAVR toward younger and lower-risk patients, heart teams are encountering BAV patients more frequently, while the ability of this

therapy to treat such a challenging anatomy remains uncertain. This review will address the singularity of BAV anatomy and associated technical challenges for the TAVR procedure. We will examine and summarize available clinical evidence and highlight critical knowledge gaps regarding TAVR utilization in BAV patients. We will provide a comprehensive overview of the role of computed tomography scans in the diagnosis, and classification of BAV and TAVR procedure planning. Overall, we will offer an integrated framework for understanding the current role of TAVR in the treatment of bicuspid aortic stenosis and for guiding physicians in clinical decision-making.

Initially designed as a new therapeutic option for inoperable patients with symptomatic severe aortic stenosis (AS),¹ the effectiveness of transcatheter aortic valve (AV) replacement (TAVR) has been confirmed through 15 years of successive randomized, controlled trials (RCTs). Transfemoral TAVR has demonstrated similar results or superiority over surgical AV replacement (SAVR) in low- to high-surgical risk elderly patients with tricuspid AV (TAV) stenosis.²⁻⁵ Thus, TAVR is now the gold standard for patients at high surgical risk or deemed inoperable,⁶ and is favored in patients at intermediate risk suitable for a transfemoral approach.⁷ Conversely, the European Society of Cardiology guidelines recommend surgery (IIa/C) as the first line therapy for patients with severe AS and a bicuspid AV (BAV) anatomy⁶ because these patients were excluded from previous RCTs. Thus, the efficacy and safety of TAVR are not well established in this population, while it is already frequently used. The balloon-expandable (BE) valve (SAPIEN-3) and self-expanding (SE) transcatheter heart valves (THVs) (Evolut-R/Pro) have received U.S. Food and Drug Administration and “European Conformity” approval for all surgical risk regardless of the valve anatomy and precaution regarding BAV, have recently been removed from commercial labeling.^{8,9} Before being discontinued, the mechanical-expandable (ME) valve (Lotus Edge) was approved for high-risk patients regardless of the anatomy but with a precaution concerning the lack of data in BAV.¹⁰

This review aims to: (1) examine and summarize the currently available evidence for TAVR efficacy and identify the critical knowledge gaps; (2) address technical challenges of TAVR in BAV anatomy; (3) emphasize the role of computed tomography (CT) for BAV evaluation and TAVR procedure planning; and (5) offer an integrated framework for understanding the current role of TAVR in the treatment of bicuspid AS.

BAV Burden in Patients Referred for TAVR

BAV is the most frequent congenital heart disease, occurring in 1% to 2% of the population,¹¹ and represents half of the patients referred for AVR. Before the TAVR era, BAV patients 80 years of age or older represented 22% to 28% of the patients referred for SAVR.^{12,13} In this elderly population, the utilization of a less invasive therapy is frequently preferred and approximately 10% of patients currently treated by TAVR have a BAV.¹⁴ Thus, a substantial number of patients are referred for TAVR in contemporary practice.

Diagnosis and classification of BAV anatomy in TAVR patients

BAV has several morphological types and the identification of these phenotypes is challenging in degenerative and heavily calcified AS.¹⁵ Diagnosis should be made using a CT scan, preferably with acquisition throughout the entire cardiac cycle.¹⁶ Echocardiography (mainly transthoracic) has lower sensitivity and may miss up to 88.5% of BAV in elderly patients referred for TAVR.¹⁴ There are various classifications of BAV but the classification proposed by Sievers is the most widespread. BAV phenotypes are categorized according to the number of raphe (0, 1, 2), and subcategorized according to the spatial position of the cusps or raphe and the functional status of the valve (Figure 1A).¹⁷ Based on the Sievers classification, BAV type 1 is the most common phenotype (90%) and results in a fusion of the left and right coronary cusp in 70% of patients, the right coronary cusp with the noncoronary cusp in 10% to 20% of patients, and the left coronary cusp with the noncoronary cusp in 5%

to 10% of patients.¹⁷ Although widely used, this classification may not be the most appropriate for TAVR. A new classification designed for TAVR has been proposed based on the number of commissures and the presence of a raphe. This takes into account the interaction between the THV frame and the AV complex which may have important implications with regards to the THV expansion and orientation, as well as the postprocedural outcomes¹⁸ (Figure 1B): bicommissural with raphe corresponding to a fusion of 2 cusps by a complete raphe; bicommissural with a fusion of 2 cusps but with neither raphe nor third commissure; and tricommisural corresponding to 3 cusps with an incomplete raphe or an acquired fusion of 2 cusps near the commissure (ie, type 1 Sievers with partial raphe; Figure 2). The latter subtype can be easily misclassified as TAV by echocardiography.

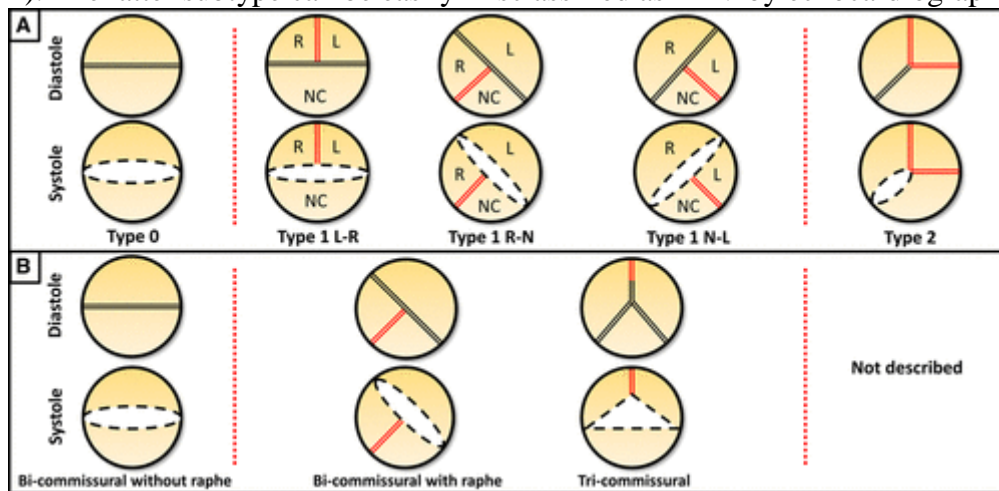


Figure 1. Classification of bicuspid aortic valve anatomy. Classification is made according to the Sievers¹⁷ (A) or Jilaihawi¹⁸ (B) classification systems. L indicates left coronary cusp; N, noncoronary cusp; and R, right coronary cusp.

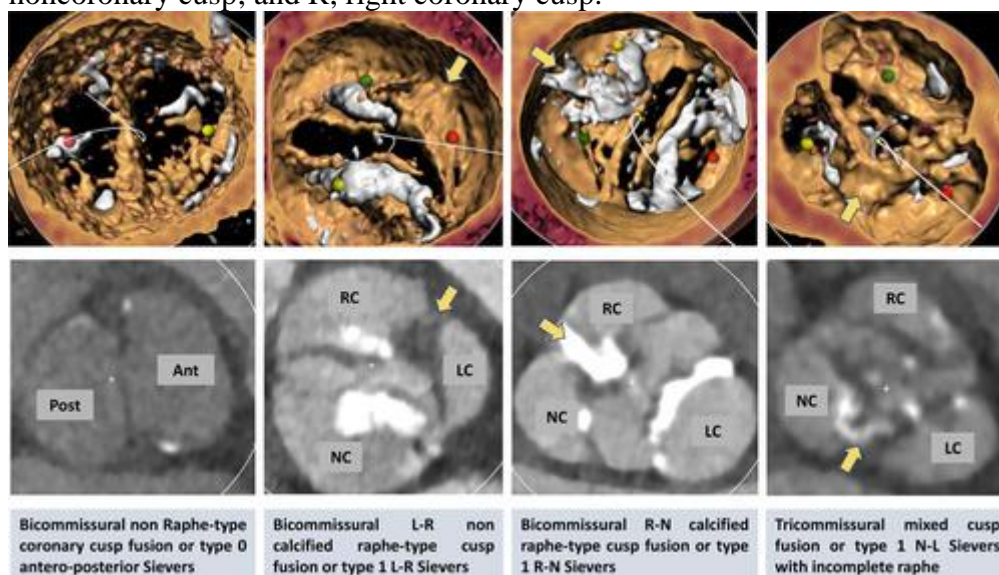


Figure 2. Computed tomography scan of bicuspid aortic valve anatomy and classified according to the Sievers¹⁷ or Jilaihawi¹⁸ classification systems. Top, Volume-rendered computed tomography; Bottom, Two-dimensional computed tomography. Yellow arrow indicates raphe. Ant indicates anterior; LC, left coronary cusp; NC, noncoronary cusp; Post, posterior; and RC, right coronary cusp.

This classification included neither aortopathy, calcification burden, nor the type 2 Sievers classification because of its low prevalence in the TAVR series (Table 1). To date, there are no clear correlation of the BAV phenotypes with clinical outcomes after TAVR, regardless of the classification used. Lei et al did not observe differences in the outcomes of spatial position using Sievers classification¹⁹ between type 0 BAV with lateral and anteroposterior cusps. Kim et al used the new classification in a cohort of 144 BAV patients referred for TAVR. The majority (54.1%) of patients had tricommissural valves, 41.6% had bicommissural BAV with raphe, and 4.1% had bicommissural BAV without raphe. No difference in clinical outcomes was observed between the different BAV types.¹⁹ Conversely, Yoon et al were the first to identify the type 1 BAV with calcified raphe and excess leaflet calcification as associated with all-cause mortality and periprocedural complications.²⁰

Table 1. Characteristics and 30-Day Main Outcomes of Observational Studies of Transcatheter Aortic Valve Replacement in Patients With BAV

Author, year	Number of patients (n)	Male	Mean age (y)	Mean STS score	Mean EuroSCORE	BAV subtype	Prediction	THV	BE valve	SE valve	ME valve	Equal or greater than moderate PVR	PPI	Stroke	30-day mortality
Wijesinghe et al, 2010 ⁹²	11	55%	73	4.4%	NR	NR	100%	SAPIEN	100%	0%	0%	27%	NR	NR	18%
Himbert et al, 2012 ⁴²	15	80%	80	8%	17% (I)	Type 0: 13% Type I: 67% UD: 20%	100%	CoreValve	0%	100%	0%	13.3% ($\geq 2+$)	43%	0%	7%
Hayashida et al, 2013 ¹²¹	21	57%	82	NR	19.9% (I)	Type I: 86% Type II: 14%	NR	SAPIEN CoreValve	52%	48%	0%	19% ($\geq 2/4$)	14%	0%	5%
Bauer et al, 2014 ¹²²	38	45%	81	NR	18% (I)	NR	NR	SAPIEN CoreValve	32%	68%	0%	25% ($\geq 2/4$)	17%	0%	11%
Costopoulos et al, 2014 ¹²³	21	57%	77	7.6%	23.9% (I)	NR	NR	SAPIEN CoreValve	38%	62%	0%	24%	14%	0%	14%
Kochman et al, 2014 ¹²⁴	28	46%	78	NR	19.2% (I)	NR	100%	SAPIEN CoreValve	15%	85%	0%	32% ($\geq 2/4$)	29%	0%	4%
Mylotte et al, 2014 ⁹³	139	56%	78	4.9%	14.8% 4.6% (II)	(I) Type 0: 27% Type I: 68% Type II: 5%	99%	SAPIEN CoreValve	34.5%	65.5%	0%	34% ($\geq 2/4$)	23%	2.2%	5%
Yousef et al, 2015 ¹²⁵	108	64%	75	NR	17.2%	Type 0: 12% Type I: 53% Type II: 7% UD: 28%	96%	SAPIEN CoreValve	56%	44%	0%	31% ($\geq 2/4$)	19%	2.8%	8.3%
Liu et al, 2015 ¹²⁶	15	60%	75	5.6%	16.1%	Type 0: 73% Type I: 27% Type II: 0%	NR	VENUS A CoreValve	0%	100%	0%	0%	13%	6.7%	6.7%
Kosek et al, 2015 ¹²⁷	7	43%	78	NR	19.8%	NR	NR	SAPIEN SAPIEN-	29%	71%	0%	28%	29%	0%	14%

Table 1. Characteristics and 30-Day Main Outcomes of Observational Studies of Transcatheter Aortic Valve Replacement in Patients With BAV

Author, year	Number of patients (n)	Male	Mean age (y)	Mean STS score	Mean EuroSCORE	BAV subtype	Prediction	THV	BE valve	SE valve	ME valve	Equal or greater than moderate PVR	PPI	Stroke	30-day mortality
Perlman et al, 2016 ⁹⁴	51	47%	76	5.2%	NR	Type 0: 11.8% Type I: 74.4% Type II: 1.9% UD: 11.6%	53%	XT CoreValve SAPIEN-3	100%	0%	0%	0%	23%	1.9%	3.9%
Yoon et al, 2016 ⁹⁵	301	57%	77	4.7%	14.9%	Type 0: 10.3% Type I: 74.4% Type II: 1.7% UD: 13.6%	NR	SAPIEN-XT SAPIEN-3 CoreValve LOTUS	59%	37%	4%	6%	14%	2.3%	4.3%
Jilaihawi et al, 2016 ¹⁸	130	61%	77	4.7%	NR	Type 0: 20.9% Type I: 54.9% Type II: 0% UD: 24.2%	91%	SAPIEN SAPIEN-XT SAPIEN-3 CoreValve	54%	46%	0%	18%	21%	3.3%	4%
Chan et al, 2017 ¹²⁸	3	67%	78	6.2%	NR	Type I: 100%	67%	LOTUS	0%	0%	100%	0%	33%	0%	0%
Yoon et al, 2017 ⁴³	546	63%	77	4.6%	16.1%	Type 0: 11% Type I: 75% Type II: 1% UD: 13%	NR	SAPIEN-XT SAPIEN-3 CoreValve Evolut-R LOTUS	58%	34%	8%	10%	15%	2.9%	3.7%
Yoon et al, 2017 ¹²⁹	108	71%	74	5.2%	13.8%	Type 0: 6% Type I: 94%	NR	SAPIEN-XT	100%	0%	0%	6%	12%	4.6%	0.9%

Table 1. Characteristics and 30-Day Main Outcomes of Observational Studies of Transcatheter Aortic Valve Replacement in Patients With BAV

Author, year	Number of patients (n)	Male	Mean age (y)	Mean STS score	Mean EuroSCORE	BAV subtype	Prediction	THV	BE valve	SE valve	ME valve	Equal or greater than moderate PVR	PPI	Stroke	30-day mortality
Arai et al, 2017 ¹³⁰	10	43%	81	NR	19.0%	Type I: 90% Type II: 10%	NR	SAPIEN-3	100%	0%	0%	0%	0%	0%	0%
Sannino et al, 2017 ¹³¹	88	60%	80	7.4%	NR	Type 0: 14% Type I: 85% Type II: 1%	NR	SAPIEN-XT SAPIEN-3 CoreValve Evolut-R	52%	48%	0%	5%	23%	2.3%	3.4%
Song et al, 2018 ¹³²	44	57%	74	5.0%	NR	Type 0: 50% Type I complete raphe: 45% Type I partial raphe: 5%	98%	Venus A-Valve	100%	0%	0%	11.4%	20.5%	2.3%	6.8%
Aalaei-Andabili et al, 2018 ¹³³	32	56%	69	6.0%	NR	Type 0: 75% Type I: 12.5% Type II: 6.25% UD: 6.25%	66%	SAPIEN-XT SAPIEN-3 CoreValve	78%	22%	0%	3%	12%	6.2%	6.2%
Liao et al, 2018 ¹³⁴	87	57%	73	7.9%	NR	Type 0: 56% Type I: 44%	93%	CoreValve VENUS A	0%	100%	0%	14%	24%	1.1%	9.2%
Liu et al, 2018 ¹¹⁴	12	67%	76	6.9%	NR	Type 0: 67% Type I: 33%	NR	VENUS A VitaFlow	0%	100%	0%	0%	0%	8%	0%
Kim et al, 2018 ¹³⁵	140	NR	NR	NR	NR	Type 0: 4.2% Type I complete raphe: 41.7% Type I partial raphe: 54.1%	NR	SAPIEN-XT SAPIEN-3 CoreValve Evolut-R	63%	32%	5%	11.1 (≥2)	NR	NR	4.9%

Table 1. Characteristics and 30-Day Main Outcomes of Observational Studies of Transcatheter Aortic Valve Replacement in Patients With BAV

Author, year	Number of patients (n)	Male	Mean age (y)	Mean STS score	Mean EuroSCORE	BAV subtype	Prediction	THV	BE valve	SE valve	ME valve	Equal or greater than moderate PVR	PPI	Stroke	30-day mortality
Mangieri et al, 2018 ¹¹⁵	54	49%	80	NR	17.7%	Type 0: 3.7% Type I: 90.7% Type II: 1.8% UD: 1.8%	94%	Portico Acurate Neo	0%	100%	0%	7.4	9.2%	7.4%	3.7%
Attinger-Toler et al, 2019 ¹⁰⁰	70	56%	76	3.8%	NR	Type 0: 6% Type I: 81% Type II: 5% UD: 8%	56%	SAPIEN-3	100%	0%	0%	0%	18%	1.3%	1.3%
Lei et al, 2019 ¹⁹	71	45%	72	7.0%	NR	Type 0: 100%	93%	CoreValve VENUS A LOTUS VitaFlow	0%	78%	22%	4.3	20%	4.2%	7.0%
Nagaraja et al, 2019 ¹³⁶	407	66%	67	NR	NR	NR	NR	NR	NR	NR	NR	NR	9.9%	2.5%	4.9%
Tchetche et al, 2019 ¹¹	101	65%	78	11.3%	NR	Type 0: 12.9% Type I: 86.1% Type II: 1%	28%	SAPIEN-3 Evolut-R LOTUS	65%	20%	10%	21% (mild or moderate)	13%	2%	0%
Elbadawi et al, 2019 ²⁵	1055	61%	68	NR	NR	NR	NR	NR	NR	NR	NR	NR	14%	1.9%	2.9%
Makkar et al, 2019 ⁹⁶	2726	60%	73	4.9%	NR	NR	NR	SAPIEN-3	100%	0%	0%	2.0%	9%	2.5%	2.6%
Weir-	44	59%	75	4.3%	NR	Type 0: 5%	NR	SAPIEN-3	100%	0%	0%	0%	9%	NR	12%

Table 1. Characteristics and 30-Day Main Outcomes of Observational Studies of Transcatheter Aortic Valve Replacement in Patients With BAV

Author, year	Number of patients (n)	Male	Mean age (y)	Mean STS score	Mean EuroSCORE	BAV subtype	Predil- THV	BE valve	SE valve	ME valve	Equal or greater than moderate PVR	PPI	Stroke	30-day mortality	
McCall et al, 2019 ³⁷						Type I: 95% Type II: 0%									
Waksman et al, 2020 ⁹⁷	61	43%	69	1.5%	NR	Type 0: 13.3% Type I: 78.3% Type II: 3.3%	NR	SAPIEN-3 Evolut- R/Pro	74%	26%	0%	1.6%	13%	1.6%	0%
Halim et al, 2020 ⁵²	5412	59%	74	3.8%	NR	NR	NR	SAPIEN- XT SAPIEN-3 CoreValve	81%	19%	0%	4%	NR	2.2%	2%
Forrest et al, 2020 ⁵³	932	55%	73	5.3%	NR	NR	NR	Evolut- R/Pro	0%	100%	0%	6%	15%	3.4%	2.6%
Mangieri et al, 2020 ¹¹⁵	353	65%	78	4.4%	NR	Type 0: 10.3% Type I: 61.8% Type II: 0.9% Undeterminate/NR: 29.8	43%	SAPIEN-3 Evolut- R/Pro	69%	31%	0%	4%	16%	1.6%	4.3%
Yoon et al, 2020 ²⁰	1034	59%	75	3.7	NR	Type 0: 7.1% Type I: 89.7% Type 1 with calcified raphe: 44.6%	NR	SAPIEN-3 Evolut- R/pro Lotus/edge Portico Acurate Neo	72%	24%	4%	3.4%	12.2%	2.7%	2%
Forrest et al, 2020 ⁹⁸	150	52%	70	1.4%	NR	Type 0: 9.3% Type I: 90.7%	91.3%	Evolut- R/Pro	0	100%	0%	0%	15.1%	4.0%	0.7%

BAV indicates bicuspid aortic valve; BE, balloon-expandable; EuroSCORE, European System for Cardiac Operative Risk Evaluation; ME, mechanical-expandable; NR, not reported; PPI, permanent pacemaker implantation; PVR, paravalvular regurgitation; SE, self-expandable; STS, Society of Thoracic Surgeons; THV, transcatheter heart valve; and UD, undetermined.

Overall, large-scale observational prospective studies with a core laboratory CT scan analysis are needed to delineate the value of existing classification systems and develop other dedicated risk stratifications tools that can predict procedural and long-term outcomes with TAVR. It should focus not only on the type of BAV, but also on the AV complex including the AV morphology, commissures and sinus numbers, presence or absence of raphe, degree and distribution of the calcifications of the raphe, leaflets, and left ventricle outflow track, and pattern and degree of aortopathy.

To address this, a roster of international experts is developing a consensus document aimed at establishing a uniform nomenclature and classification scheme for BAV and its associated aortopathy for universal use in surgery, interventional cardiology, and clinical research.²¹

What are the results of surgery?

The outcomes of surgery are excellent in BAV patients, with very low hospital mortality ranging from 0.9% to 2.4%^{22,23}; however, studies have mainly reported outcomes in young patients at very low operative risk treated with biological or mechanical valves for different types of AV diseases, and with or without concomitant aortic intervention.²³⁻²⁷

Contrary to TAVR, long-term data are available for SAVR. Borger and David reported an excellent 88% survival rate at 10 years in a series of 231 patients with an average age of 52 years and treated by AVR with concomitant ascending aorta replacement.²² Other studies reported a 15-year survival rate ranging between 40% and 78% after SAVR with or without aortic replacement.^{23,28-30} However, there is a paucity of data on the outcomes of SAVR in BAV patients at increased surgical risk. Elbadawi et al reported a 44.6% bleeding rate, 27.2% blood transfusion, and 3.1% in-hospital death²⁵ after SAVR in a cohort of patients matched with high-risk TAVR. Overall, SAVR is a well-known and standardized procedure that provides excellent procedural and long-term results in young BAV patients with few comorbidities.

TAVR challenges in BAV anatomy

Aortic Valve Anatomy

BAV patients were generally excluded from RCTs evaluating TAVR because of several anatomic features that could increase the risk of TAVR procedural complications or failure. There remain some distinct differences between bicuspid and tricuspid AS. First, the dimensions of all components of the AV complex are generally larger in BAV than in TAV, increasing the likelihood of having an annulus size outside of the range covered by currently available THV (annulus area, $521 \pm 21 \text{ mm}^2$ versus $463 \pm 20 \text{ mm}^2$; ascending aorta, $36.7 \pm 5.4 \text{ mm}$ versus $30.4 \pm 3.4 \text{ mm}$; $P < 0.01$).^{11,31,32} Second, several studies on CT or transesophageal echocardiography for BAV have described a similar circular geometry of the aortic annulus as that found in TAV.^{31,33-35} However, the supra-annular geometry, especially at the level of the sinus of Valsalva, is more elliptical in BAV patients.³³

The AV complex shape (from the annulus to the leaflet tips) is nontubular (flared or tapered) in two-thirds of BAV patients^{11,36} (Figure 3). It has been suggested that in this latter configuration (14%–40.1% of patients^{11,36,37}) the narrowest dimensions and point of highest resistance of the AV complex may be located above the annulus, at the commissural level,^{11,38,39} especially in those with a tricommissural raphe-type anatomy³⁶ (Figure 3), which may contribute to a less circular deployment,⁴⁰ THV oversizing, and subsequent risk of THV underexpansion or annulus injury if sized according to the annulus dimensions.

Figure 3. Computed tomography scan sizing strategy and transcatheter heart valve design choice in bicuspid aortic valve. Top, A, Aortic valve sizing at different level of a tapered bicuspid aortic valve type 1 left/right bicuspid aortic valve (A) annulus level, (B) 4 mm above annulus, (C) 8 mm above annulus, (D) simulated Evolut-R/Pro 26 mm (dashed blue and pink circle). Bottom, B, Aortic valve sizing at different level of a flared bicuspid

aortic valve type 1 left/right bicuspid aortic valve (A) annulus level, (B) 4 mm above annulus, (C) 8 mm above annulus, (D) simulated SAPIEN 3 26 mm (blue circle). BE indicates balloon-expandable; and SE, self-expandable.

Third, BAVs are more heavily calcified than TAVs, as demonstrated by the higher weight in excised BAVs than in TAVs (men, 3.61 g versus 2.31 g; women, 2.62 g versus 1.64 g),¹³ and higher calcium score (5143 ± 4730 AU versus 3038 ± 3671 AU; $P=0.02$).¹¹ The BAV's calcification burden is also more eccentric and asymmetrical. Fourth, the presence of a calcified raphe, cumulated with the heterogeneous distribution of the calcium load and asymmetrical morphology of the AV complex, might prevent the optimal expansion of the THV stent frame.^{31,41,42} When localized between the right coronary cusp and left coronary cusp, the raphe may also indirectly induce conduction disturbances through an increase of the compression forces applied on the contralateral stent frame toward the noncoronary cusp area, which is very close to the His bundle.⁴³ Fifth, coronary anomaly may be more frequent in BAV than in TAV,^{32,44} particularly a left dominance and separate ostia for the left main and circumflex artery. Moreover, 1 or both of the coronary ostia may lie more frequently in close proximity to the commissure, unlike in TAV in which both ostia are in the middle of the sinuses. This, along with a longer and heavier calcified leaflet particularly at the tip, could potentially increase the risk of coronary obstruction. However, the height of the coronary ostia has been reported to be similar or higher for BAV than for TAV, which is reassuring about this risk.^{31,34,45} Sixth, the aorta also has a more horizontal orientation exposing it to difficulties in accurate positioning of the THV within a vertical annulus.^{35,46} Lastly, aortopathy frequently coexists with BAV and cannot be addressed by TAVR.

BAV Patients With Pure Aortic Regurgitation or Mixed Aortic Regurgitation/AS Disease

BAV patients, especially the type 1 R-N of the Sievers classification, have faster hemodynamic valve deterioration compared with TAV patients.^{47,48} Moderate-to-severe calcific AS is the most common presentation between the fifth and sixth decades of life, while pure isolated aortic regurgitation (AR) accounts for only 10% to 15% of young BAV patients.⁴⁹ Some degree of AR is frequently associated with AS (mixed AV disease) and may worsen the hemodynamic burden imposed on the left ventricle. Indeed, it was previously demonstrated that patients with moderate mixed AV disease had similar outcomes as patients with isolated severe AS,⁵⁰ while AVR was associated with better outcomes.⁵¹ Hence, both BAV and TAV patients with mixed AV disease may be considered for TAVR. However, there is a paucity of data on this subset of patients because the prevalence of mixed AV disease is rarely reported.^{4,5} In the recent Society of Thoracic Surgeons (STS)/American College of Cardiology (ACC) transcatheter valve therapy (TVT) studies focusing on BAV patients, moderate-to-severe AR was observed in 3% to 15% of patients treated by TAVR.^{52,53} Unfortunately, none of these studies reported subgroup analysis in patients with mixed AV disease. However, it can be assumed that for those with a predominant stenotic lesion, TAVR can be considered, as is performed for BAV patients with pure AS. BAV patients with isolated pure AR are typically young with a low calcification burden and frequently present root aortopathy. These patients should be treated with surgical replacement or repair, as the results are excellent.^{54,55} TAVR may be considered for very high-risk patients with pure AR, but this is associated with a low device success (81%)⁵⁶ and data on BAV anatomy are scarce.

BAV Aortopathy and Evolution After AVR

BAV patients have a dilated ascending aorta compared with healthy subjects or TAV patients with a similar degree of AS severity.⁵⁷ The prevalence of BAV aortopathy is difficult to estimate but ranges between 20% and 84% depending on the evaluation technique and aortic size thresholds used to define aortic dilatation.^{58,59} However, most BAV patients undergoing

AVR do not require aortic root replacement surgery as prophylactic replacement of the ascending aorta is performed in approximately 25% of BAV patients.^{60,61} All segments from the aortic root to the proximal descending aorta can be dilated, but we commonly distinguish 3 different patterns according to the segment predominantly involved: isolated dilation of the tubular ascending aorta (the most common; $\approx 70\%$), isolated dilation of the aortic root ($\approx 20\%$), or dilation of the entire ascending aorta.⁵⁸ All BAV phenotypes can be associated with each aortopathy pattern, but some associations are more frequent,⁶² even though numerous inconsistencies exist between studies.⁶³ This association may be explained by different embryological entities and/or different distributions of the aorta wall shear stress related to the type of AV dysfunction (aortopathy is more preponderant in AS than in AR),⁶⁴ and the eccentric transvalvular systolic flow pattern according to the BAV phenotype.⁶⁵⁻⁶⁷ Patients with BAV type 1 left-right coronary cusp fusion present mainly aortic root dilation.⁶⁸ Patients with BAV type 1 right-noncoronary cusp fusion are associated with a larger diameter of the tubular ascending aorta and aortic arch while sparing relatively the aortic root.⁶⁹ Patients with type 1 noncoronary-right coronary cusp fusion have mainly aortic root dilation. Data for BAV type 0 are scarce but isolated dilation of the tubular ascending aorta is frequently associated with AS, whereas isolated aortic root dilation is frequently associated with AR.^{70,71} BAV type 2 is rare but frequently associated with diffuse aortopathy in almost 50% of patients. The BAV phenotype and severity of the valve dysfunction may also influence the progression of the aortopathy, but published data are inconsistent.^{64,72-74} The risk conveyed by the aortopathy is also difficult to determine. Patients with BAV have an 8-fold increased relative risk of aortic events compared with the general population,⁶⁰ but the absolute risk remains low and considerably lower than in patients with Marfan syndrome.⁷⁵ Although the aortic dimension is associated with the risk of aortic dissection, it remains a poor predictor of this complication.^{76,77} In a recent investigation, the mean diameter at dissection in BAV patients was 10 mm greater than that in TAV patients (66 ± 15 mm versus 56 ± 11 mm; $P=0.0004$).⁷⁸ The flow pattern generated by a BAV and assessed by 4-dimensional flow MRI is abnormal (higher wall shear stress level than control) and could participate in aortopathy progression.^{79,80} To reduce the need for late reoperation, the European Society of Cardiology, American Heart Association, and American Association for Thoracic Surgery guidelines,^{6,81-83} recommend performing a combined AVR and aortic surgery when the diameter is ≥ 45 mm regardless of the aortopathy pattern or the underlying BAV phenotypes (with respectively IIa/C, I/C, and IIa/B levels of recommendation and evidence). These recommendations are mainly based on single-center observational studies^{30,84} that mixed up AS and AR with diverse aortopathy patterns. This aggressive surgical treatment strategy for all BAV-associated aortopathy remains debated.⁷⁶ A previous study comparing SAVR alone or associated with aortic root surgery in BAV patients with aortic dilation (including AR) failed to delineate any prognostic cut-off.⁸⁵ The abnormal flow pattern induced by BAV^{79,80} can remain abnormal after AVR and could impact postoperative progression of the aortopathy.⁸⁶ Yasuda et al observed progressive aortic dilatation after isolated SAVR in BAV patients, but not in TAV patients, and Kim et al found a similar annual aortic dilatation rate after SAVR in both BAV and TAV patients.⁸⁷ Other studies found that BAV patients with mild-to-moderate (40–50 mm) ascending aorta dilation undergoing isolated SAVR for AS were at very low risk of adverse aortic events at long-term (15 years) follow-up,⁸⁸ which is comparable to patients with TAV stenosis.²⁸ Concerning TAVR, only 2 small studies described the postoperative evolution of aortopathy. A cohort of 67 patients with aortopathy showed a stabilization of aortic dilatation after a short follow-up of 12 months.⁸⁹ A CT scan study comparing 86 BAV patients with 122 TAV patients demonstrated a similar rate of progression of the aortic dilatation (0.2 ± 0.8 mm/year versus 0.3 ± 0.8 mm/year; $P=0.59$, respectively), but very few (3.5%) patients completed the 5-year follow-up.⁹⁰ Overall,

aortopathy and BAV phenotypes are intertwined between genetic and mechanical hemodynamic factors.⁹¹ These features should probably be considered when determining the need for concomitant aortic surgery. However, to date, no classification encompassing the aortopathy pattern, BAV phenotype, and type of AV dysfunction has demonstrated its prognostic significance. Furthermore, other factors should be considered such as age, concomitant hypertension, progression rate, diameter indexed to body surface area, and family history of acute aortic events. Given the uncertainties on the need and optimal timing for aortic replacement, TAVR could represent the best option in selected patients without severe dilatation of the proximal aorta.

Outcomes of TAVR in BAV patients

Early Experience of TAVR in BAV

The first TAVR series in BAV patients came out in 2010 with the first generation of BE valve (n=11),⁹² followed by a series with the second generation of SE and BE valves in 2014 (n=139).⁹³ In these earlier series, the rate of periprocedural complications was high with 13% to 34% equal or greater than moderate PVR, 13% to 43% of permanent pacemaker implantation (PPI), and a 1-year mortality between 4% and 18% (Table 1). In 2017, Yoon et al compared the outcomes of propensity score–matched cohorts of 561 BAV patients and 4546 TAV patients treated by old and new generations of THV.⁴³ The 2-year mortality was similar in the 2 groups (17.2% versus 19.4%; $P=0.28$), but procedural success was lower in the BAV cohorts because of more surgical conversion (2% versus 0.2%; $P=0.006$), fewer implantation successes (85.3% versus 91.4%; $P=0.002$), and higher rates of equal or greater than moderate PVR (10.4% versus 6.8%; $P=0.04$). There was no difference in the rate of PPI (14.7% versus 13.7%; $P=0.72$).⁴³ A recent large observational study from the STS/ACC TVT registry including all types and generations of valves compared 5412 BAV patients to 165 547 TAV patients and reported that STS was relatively low at 3.8% (2.3–6.1) and patients were younger in the BAV group than in the TAV group (74.0 years [65.0–81.0] versus 82.0 years [76.0–87.0]; $P<0.001$). The 1-year unadjusted risk of mortality was slightly lower in BAV patients (hazard ratio [HR], 0.88 [0.78–0.99]).⁵² The risk of conversion to open heart surgery was similar in both groups but a slightly lower procedural success (96.0% versus 96.7%; $P=0.004$) and higher incidence of equal or greater than moderate PVR (4.7% versus 3.5%; $P<0.001$) were observed in BAV patients. There was no difference in the adjusted 1-year hazard of stroke (HR, 1.14 [95% CI, 0.94–1.39]).

Impact of Refining TAVR Technology

Major improvements of the third generation THV combined a smaller delivery sheath and an outer sealing skirt for SAPIEN-3, or a pericardial outer wrap and recapturable capabilities for Evolut-R/Pro. The systematic use of CT scan for aortic annulus and root sizing also contributed to an increase in procedural success and dramatically decreased the rate of significant PVR (Table 1). Perlman et al first described a cohort of 51 BAV SAPIEN 3 recipients without any equal or greater than moderate PVR.⁹⁴ A study comparing 102 BAV patients treated with older generation THV versus 199 BAV patients treated with third generation THV demonstrated a sharp decrease in the rate of equal or greater than moderate PVR (8.5% versus 0%; $P=0.002$), and an increase in device success implantation rate (80.9% versus 92.2%; $P=0.01$).⁹⁵ While low and decreasing compared with the first valve generation, Yoon et al observed that the rate of conversion to surgery in BAV patients remained numerically higher with the third generation valve (1.3% versus 0.0%; $P=0.25$) than in TAV patients.⁴³ In the STS/ACC TVT registry (n=3714; 73.4% SAPIEN-3), the change for the third generation valve was associated with a global decrease in the rate of adverse events in BAV patients while remaining slightly higher than in TAV patients with a higher rate of equal or greater than moderate PVR (2.7% versus 2.1%; $P=0.006$) and a lower rate of device success (96.3% versus 97.4%; $P<0.001$).⁵² The study by Makkar et al, also based on the

STS/ACC TVT registry, compared 2691 BAV patients only treated with SAPIEN 3 with the same number of propensity score–matched TAV patients (Table 1). There was no difference in the 30-day (2.6% versus 2.5%; $P=0.82$) or in the 1-year mortality (12.9% versus 14.1%; $P=0.74$). However, a greater risk of stroke (2.5% versus 1.6%; $P=0.02$), PPI (9.1% versus 7.5%; $P=0.03$), and conversion to open chest surgery (0.9% versus 0.4%; $P=0.03$) at 30 days were observed in BAV patients than in TAV patients. At 1 year, the rate of stroke (3.4 versus 3.1%; $P=0.16$), equal or greater than moderate PVR (3.2% versus 2.5%; $P=0.47$), and AV reintervention was similar in the 2 groups.⁹⁶ Forrest et al reported the outcomes of 929 BAV patients propensity score–matched with 929 TAV patients in the STS/ACC TVT registry study with Evolut-R/Pro. There was no difference between the 2 groups in the 30-day or 1-year mortality (10.4% versus 12.4%; $P=0.63$), or for device success (96.5% versus 96.4%; $P=0.88$), conversion to open chest surgery (0.6 versus 0.2%; $P=0.29$), or PPI rate (15.4% versus 13.7%; $P=0.30$). The rate of stroke at 1 year was similar in both groups (3.9% versus 4.4%; $P=0.63$), but the need for AV reintervention at 1 year was greater in BAV patients than in TAV patients (1.7% versus 0.3%; $P=0.01$). AR was more prevalent in BAV than in TAV (5.6% versus 2.1%; $P<0.001$) at 30 days but was similar at 1 year. In a multicentric registry of 301 patients, the need for PPI was high but similar between BAV and TAV patients (13.1% versus 16.7%; $P=0.40$).⁹⁵ Recently, Elbadawi et al compared, after propensity score matching, the in-hospital outcomes of TAVR in BAV versus TAV patients ($n=1035$ in each arm). Mortality (2.9% versus 3.4%; $P=0.76$) and other procedural-related complications were similar between the 2 groups, including the rate of stroke (1.9% in both groups) and PPI (14% in BAV versus 12.1% in TAV; $P=0.51$). However, the study had several limitations related to the methodology (data obtained from the National Inpatient Sample database, which is administrative and does not have detailed information about the procedures) and did not provide granularity on THV design and BAV subtypes.²⁵ Overall, the short-term outcomes improved dramatically with the newest generation of THV and approximated the excellent outcomes achieved in TAV patients.

Toward TAVR for Low-Risk BAV Patients

Waksman et al conducted a small (61 patients) multicenter prospective trial in low-risk patients and reported excellent 30-day outcomes (no death and no disabling stroke) in a highly selected BAV population mainly treated with SAPIEN 3 (74%).⁹⁷ The rate of PPI was at 13% and that of equal or greater than moderate or equal or greater than mild PVR was at 1.6% and 35.3%, respectively. The Low Risk Bicuspid Study was a prospective single-arm study evaluating Evolut-R/Pro in 150 BAV low-risk patients with neither aortopathy nor prohibitive calcification in the left ventricle outflow track. STS score was $1.4\pm 0.6\%$, and 90.7% of patients had type 1 BAV (Sievers), while the remaining had type 0. The early results at 30 days showed a high device success rate of 95.3%, 1 case of coronary obstruction, and no annulus rupture. The number of deaths or disabling stroke was low (1 event for each). The rate of PPI was 15.1%, which was high but comparable to the 17.4% rate observed in low-risk TAV patients.⁵ No patient had moderate or worse AR, whereas 40.4% had mild AR.⁹⁸ Preliminary data ($n=75$) from another prospective cohort (BIVOLUT-X [Bicuspid Aortic Stenosis with Evolut Platform International Experience]; NCT03495050) with Evolut-R/Pro confirmed promising early results with no equal or greater than moderate PVR and excellent hemodynamic outcomes. However, an unusually high risk of disabling stroke was observed (5.3%) that could be attributable to a high calcium burden, frequent predilation maneuvers, and valve repositioning required during implantation.³⁴ The PARTNER 3 trial (Placement of Aortic Transcatheter Valves 3) bicuspid registry with SAPIEN 3 that enrolled 75 low-risk patients will be presented this year. We can anticipate that these single-arm registries will confirm the feasibility and safety of the TAVR procedure on low-risk patients for both THV design. However, their limited sample size (75–150 patients) and the

enrollment of highly selected patients without bulky eccentric calcification, left ventricle outflow track significant calcifications, or anomalous coronary arteries (selected both by clinical sites investigators and then by eligibility committee of the trials) limit the incremental clinical value of these cohorts. The anatomy of patients not included in these registries would be very informative. Overall, results of TAVR in low-risk BAV patients are encouraging but larger cohorts and long-term data are needed to determine the impact of PPI and mild PVR as it could contribute to a late superiority (beyond 2 years) of SAVR over TAVR similar to the one observed in intermediate-risk TAV patients with second generation valve.⁹⁹

THV Durability in BAV Patients

Data on THV durability in BAV versus TAV are scarce and limited to valve hemodynamic performance. In the BAVARD (Bicuspid Aortic Valve Anatomy and Relationship with Devices) registry, 30-day post-TAVR mean gradient (9.4 ± 4.9 mm Hg versus 10.7 ± 4.9 mm Hg; $P=0.15$) and effective orifice area (2.1 ± 0.5 cm² versus 1.9 ± 0.6 cm²; $P=0.07$) were comparable between BAV and TAV patients. The indexed effective orifice area was smaller (1.17 ± 0.4 cm²/m² versus 1.33 ± 0.37 cm²/m²; $P<0.01$) in BAV patients than in TAV patients, but the incidence of severe prosthesis–patient mismatch was similar in both groups.¹¹ In the STS/ACC TVT registry, 1-year mean gradient (13.1 ± 8.1 mm Hg versus 13.0 ± 6.2 mm Hg; $P=0.86$) and equal or greater than moderate PVR (3.2% versus 2.5%; $P=0.47$) were similar between BAV and TAV patients treated with SAPIEN-3.⁹⁶ The longer follow-up by echocardiography reported stable mean transvalvular gradients of 14.5 ± 9.6 mm Hg at 15 months after TAVR in a cohort of 79 BAV patients.¹⁰⁰ The BAVARD registry was also reassuring on the overall THV stent circularity after TAVR with BE, SE, or ME valves between BAV ($n=101$) and TAV ($n=88$) patients (ellipticity index at the annulus level, 1.18 ± 0.14 versus 1.18 ± 0.11 ; $P=0.5$). However, BE valves, having a higher radial force than SE valves,¹⁰¹ achieved a lower ellipticity index. All THVs were also more constrained and underexpanded in BAV patients compared with TAV patients.¹¹ As prosthesis expansion could impact the THV durability and promote leaflet thrombosis, these findings raised concerns of a potential accelerated structural valve degeneration process in BAV patients.¹⁰² In a recent study, a 30-day CT scan was systematically performed after TAVR in 60 BAV patients and found hypoattenuated leaflet thickening⁹⁷ in 10% of patients, which is comparable to the findings of previous studies in TAV.¹⁰³ Thus, the short-term durability of THV seems acceptable although long-term data are required.¹⁰³

Outcomes of SAVR for THV Explant

The increasing rate of THV implantation in BAV patients, especially in a young population, may also lead to an increased need for surgical intervention for structural valve degeneration or aortopathy during a patient's lifetime. Recent data suggest that TAVR explant could be challenging. A study of 17 patients undergoing TAVR explantation reported neoendothelialization of the THV into the aortic wall (both BE and SE valves), requiring intense aortic endarterectomy in all 5 THVs older than 1 year and 2 required unplanned aortic root repair.¹⁰⁴ A recent registry on 123 patients implanted with an early generation of THV requiring SAVR for early valve dysfunction (median time, 2.5 months; interquartile range, 0.7–13) reported worse outcomes than expected by the STS risk model for redo-SAVR (in-hospital mortality of 17.1%).¹⁰⁵ Further research is needed to optimize surgical techniques, evaluate the risk of these operations, and understand the difference between SE and BE valve explant. These gaps of knowledge are of paramount importance as successive TAVR and SAVR could be considered in the lifetime management of BAV patients.

Outcomes of TAVR versus SAVR: Do We Need a Randomized Trial?

To date, studies comparing TAVR and SAVR have been only observational. The propensity score matching study by Elbadawi et al is the largest study ($n=975$ patients in each arm) and compared periprocedural outcomes between TAVR versus SAVR in BAV patients.²⁵ In-

hospital mortality (3.1%) and serious adverse events were similar between the 2 groups, while TAVR was associated with a higher rate of PPI (13.8% versus 4.6%; $P<0.01$) but a lower rate of bleeding and transfusion. Length of hospital stay was also shorter after TAVR versus SAVR (4 days versus 7 days; $P<0.01$). This result is promising for TAVR, but should be interpreted with caution because major information was lacking (eg, type of THV, rate of equal or greater than moderate PVR, and absence of long-term follow-up), data were retrospectively obtained from codes of large healthcare databases (National Inpatient Sample), and residual confounding factors could not be eliminated. While only a direct head-to-head comparison study of TAVR versus SAVR will confirm the efficacy and safety of TAVR in BAV patients (Figure 4), it is reasonable to question whether a randomized trial could be practically conducted. Given that TAVR is well-established in the high- and intermediate-risk population, we can anticipate that some physicians and the majority of patients may be reluctant to participate. Conversely, SAVR remains the first-line therapeutic option in lower risk and younger BAV patients. Thus, the targeted population for an RCT should be those who are at low risk for surgery (STS score $<4\%$), or at intermediate risk but are <75 years of age, eligible for a bioprosthetic valve (≥ 55 years of age), and with aorta dilation <50 mm. AV and aortic root anatomy should be evaluated by a CT core laboratory to determine the BAV type and TAVR feasibility. A potential approach for such RCT could be a randomized noninferiority trial stratified on surgical risk and severity of aortopathy with a primary composite end point of all-cause death, stroke, equal or greater than moderate PVR and rehospitalization at a minimum of 2 year follow-up. The follow-up should be annual for 10 years to detect valve and aorta-related events such as leaflet thrombosis, structural valve degeneration and aortic dissection, aneurysm, or aorta intervention. Based on an expected event rate comparable to that previously observed in TAV patients, we can estimate that the sample size would be between 1000 and 1500 patients depending on the noninferiority margin. Patients excluded for AV anatomic considerations but who underwent SAVR or TAVR should also be included in a registry and followed up to assess clinical outcomes in this population with unfavorable anatomy.

Figure 4. Established and missing evidence for TAVR for patients with BAV. BAV indicates bicuspid aortic valve; BE, balloon expandable; CT, computed tomography; PVR, paravalvular regurgitation; TAV, tricuspid aortic valve; TAVR, transcatheter aortic valve replacement; and THV, transcatheter heart valve.

Management of TAVR in BAV patients

Patient Selection

Surgery remains the preferred option for BAV patients, especially in young patients or patients at low risk for surgery. TAVR may be an alternative in elderly patients (≥ 75 years of age) with a favorable AV complex anatomy but without significant aortic dilatation (<45 mm or <50 mm in high surgical-risk patients). According to the majority of published studies, the referral of BAV patients to TAVR should be considered at intermediate or greater risk for SAVR based on clinical assessments by a multidisciplinary heart team or an STS score $>4\%$ (Table 1). When TAVR is considered, a comprehensive CT scan assessment of BAV anatomic features is mandatory to identify suitable patients and to select the THV design and size based on patients' characteristics (Figure 5).

Figure 5. Key screening steps when considering transcatheter aortic valve replacement in a patient with bicuspid aortic valve. * <50 mm for high-surgical risk patients; ** <683 mm² according to instructions for use of SAPIEN 3 29 mm and <94.2 mm according to instructions for use of Evolut-R/Pro 34 mm; however, successful implantation with additional

balloon volume until 904 mm² has been reported with SAPIEN-3.¹⁰⁶ CT indicates computed tomography; STS, Society of Thoracic Surgeons; and THV, transcatheter heart valve.

Which BAV Anatomy Is Favorable for TAVR?

Procedural and clinical outcomes reported in observational studies can be applied only to patients with a BAV anatomy considered favorable by operators, and therefore, to a highly selected population. Data are lacking to clearly identify BAV patients who are the most favorable for TAVR, but we can delineate some markers of procedural complexity and potentially worse outcomes (Table 2). The major challenge is to predict the behavior of the AV complex (particularly the raphe) during and after THV deployment. Sievers type 1 BAV is preponderant and most patients implanted with TAVR had this anatomy. The characteristics of the raphe are critical, and a heavily calcified raphe is generally considered hostile to the proper expansion of the THV. In the study of 561 patients, all cases of annulus rupture (1.6%) occurred in type 1 BAV with a calcified raphe and treated with BE valve.⁴³ Yoon and Makkar reported the largest CT-based BAV cohort with core laboratory analysis of 1034 patients (89.7% type 1, 10.3% type 0) mainly treated with SAPIEN 3 (71.6%). They identified the presence of calcified raphe and excess leaflet calcifications (defined as more than median calcium volume of 382 mm³) as an independent morphological features associated with all-cause mortality.²⁰ Both calcified raphe plus excess leaflet calcification were found in 26.0% of patients and they had higher rates of procedural complications compared with those with either or none of these features (aortic root injury, 4.5% versus 0.7% versus 0.9%; $P<0.001$; equal or greater than moderate PVR, 6.5% versus 2.5% versus 1.6%; $P=0.002$) and higher 2-year mortality (25.7% versus 9.5% versus 5.9%; log-rank $P<0.001$).

Table 2. Anatomic Aspects to Be Considered by the Heart Team for the Decision Between Surgical Aortic Valve Replacement and Transcatheter Aortic Valve Replacement for Bicuspid Aortic Valve Patients

Favorable for transcatheter aortic valve replacement

Tricommissural bicuspid aortic valve with incomplete raphe (Incomplete or acquired Type 1 Sievers)
 Sievers type 1 with noncalcified raphe or incomplete raphe
 Sievers type 0 (if circularity preserved)
 Annulus dimensions within transcatheter heart valve sizing range
 Homogenous and moderate calcified leaflets
 Absence of aortopathy or aorta dimension <45 mm (50 mm in high-risk patients)

Favorable for surgical aortic valve replacement

Sievers type 1 with heavily calcified raphe and excess leaflet calcification
 Sievers type 2
 Extreme elliptic shape
 highly calcified leaflet
 Circumferential calcifications
 Highly calcified left ventricular outflow tract
 Low calcium burden and large annulus (mixed aortic regurgitation and aortic stenosis)
 Shallow/effaced sinus and long calcified leaflet or low coronary takeoff
 Anomaly of coronary implantation

Type 0 Sievers BAV has been associated with a favorable outcome, especially a low rate of PVR, but its prevalence is low in TAVR series ($\approx 10\%$).^{20,93} Type 2 is rare in the general population and could be associated with very poor expansion of the stent frame. Tricommissural BAV with incomplete and noncalcified raphe (ie, incomplete type 1 of Sievers) could be the most favorable to achieve a circular orifice and proper sealing of the THV. Beyond the BAV type, an extreme elliptic shape of the AV complex or a large discrepancy between annulus and sinus morphology may complicate the sizing and THV selection. Even if THV can be safely overexpanded, dimensions of the landing zone should fit with the available THV size¹⁰⁶ (Figure 5). Importantly, the burden and topography of the calcification should be carefully evaluated through the entire AV complex. The presence of bulky, heavy, and asymmetrical calcification patterns extending toward the left ventricle outflow track could be associated with a higher risk of PPI, PVR, and annulus rupture via direct damage of the calcified tissue or via a contrecoup mechanism.¹⁰⁷ Calcified leaflet tips could also be associated with a higher risk of coronary occlusion or embolization. Conversely, a low calcium burden, as observed in BAV-related AR or mixed AV disease, may increase the risk of THV migration and embolization. The presence of abnormal coronary artery implantation could also be considered because THV may further increase the difficulties of coronary access. Overall, new tools are clearly needed to stratify TAVR feasibility in BAV patients.

Role of the Preoperative CT Scan

Beyond conventional measures (annulus size measurements with modification for bicommissural phenotype, sinus of Valsalva width, and height of coronary ostia), a thorough assessment of the number of cusps, presence of a raphe, extension and topography of calcifications, and dimensions of the aortic root is essential, as defined per guidelines.¹⁰⁸ This helps to plan the procedure, anticipate the THV expansion, and avoid potential complications such as PVR or annulus injury^{109,110} (Figure 3). Yoon et al illustrated in detail how a CT scan before TAVR can improve the procedural results in BAV patients. A CT scan was performed in 100% of patients treated with the third generation THV (versus 78.9% with the second generation), and its use was associated with a greater procedural success rate (92.2% versus 80.9%; $P=0.01$) and lower rates of annulus rupture (2.0% versus 1.0%; $P=0.01$) and equal or greater than moderate PVR (0% versus 8.5%; $P=0.002$).⁹⁵

THV sizing should be primarily based on the annulus size which has been shown to be a reliable and safe approach in BAV patients.^{36,37} For the minority of patients with tapered or funnel anatomy, a supra-annular sizing³⁸ has been suggested to be of incremental value¹¹ to select a smaller THV than suggested by annulus dimensions and avoid the oversizing-related risks³⁹ (Figure 3); however, supra-annular techniques of measurements are not standardized, have inferior reproducibility than annulus measurements,³⁷ and would result in a beneficial modification of THV size in a minority of cases. Hence, the clinical evidence supporting this approach are scarce.

Overall, BAV sizing should rely on a multilevel (from the annulus to the aortic root) and multiparameter (area, perimeter, supra-annular or intercommissural distance/area, and median/minimum/maximum diameter) integrative approach to determine the optimal THV size and implant position (Figures 3 and 5). A CT scan is also useful to localize and quantify the calcification burden through Agatston or calcium volume scoring.^{41,107} New tools such as patient-specific computer simulation have been recently developed to better identify patients who are suitable for TAVR and optimize sizing and procedural planification.¹¹¹

Procedural Characteristics

TAVR procedure may be more challenging in BAV anatomy. The asymmetrical and heavily calcified valve orifice, presence of the raphe, and horizontal aorta may lead to guidewire crossing difficulties and lateralization of the stiff guidewire path through the valve. The risk

of coronary obstruction should also be carefully evaluated beforehand. Innovative strategies of leaflet laceration by electrified guidewire have been proposed to prevent coronary obstruction or to create tricuspidization and allow better prosthesis expansion, but further validation studies are required.^{112,113} Predilation of the valve is more frequently performed in BAV than in TAV to facilitate the crossing of the delivery system and ensure appropriate expansion of the THV, as well as to assess the response of the supra-annular anatomy.¹¹⁴ Balloon valvuloplasty should be sized according to the minor axis of the AV complex, and the appearance of a waist may indicate a calcified or resistant raphe and a risk of THV underexpansion or annulus injury, thus influencing the THV type (SE valve preferred) and size selection. In cases of BE valve implantation, a low degree of oversizing is recommended (<10%) with respect to the risk of annulus rupture. In combination with contrast injection, balloon valvuloplasty may also be valuable to judge the leaflets behavior in relation to coronary ostia. In some instances, there may be a higher-than-normal AR after predilation and the implanting team should be facile in moving forward quickly with the TAVR if necessary. In a tapered anatomy, a supra-annular positioning of the THV may be considered to achieve optimal sealing while minimizing the risk of PPI. Recapturable features of SE and ME valves may be advantageous for deploying the THV at the optimal landing zone. Postdilation should also be more frequently considered in BAV than in TAV because raphe and calcifications burden may lead to valve underexpansion and insufficient sealing in the pericommissural zones, particularly with SE valves that have a lower radial force.¹¹⁵ All of these technical and anatomic parameters might explain the potential higher risk of stroke and of new ischemic lesions^{115a} noted in some observational exploratory studies. The benefit of using a cerebral embolic protection device remains unclear in TAVR. However, a recent pooled analysis suggested that the use of dual-filter protection decreases the rate of periprocedural stroke.¹¹⁶ This benefit may be greater in populations at high risk of stroke such as BAV patients (Figure 5), but there are no data to support this hypothesis.

Which THV Design Is Suitable for BAV Anatomy?

No head-to-head randomized comparison has ever been conducted in BAV patients, which precludes inferences being drawn on the superiority of 1 valve over another. The large majority of studies separately reported the results of each THV design, and the few studies reporting post-TAVR outcomes according to the THV design did not observe significant difference in outcomes on hard clinical endpoints such as mortality or stroke.^{18,95} In a large STS/ACC registry, Halim et al reported the same device success rate between SE and BE valves ($P=0.19$) but observed a higher incidence of PVR after SE valve than after BE valve (odds ratio, 2.97, [1.93–5.59]; $P<0.001$) in the third generation THVs, as previously observed in TAV populations.^{52,117} Conversely, a meta-analysis of 758 patients reported a comparable rate of equal or greater than moderate PVR (3.4% versus 3.4%; $P=0.80$) and postprocedural PPI (13.3% versus 11.7%; $P=0.43$) between BE (SAPIEN-3) and SE valves (Evolur-R).¹¹⁸ Waksman et al, in the prospective, single-arm, low-risk trial including BAV patients mostly treated with SAPIEN 3 (74%), reported a higher rate of PPI in patients treated with SE valve (31.3%) than in those treated with BE valve (6.7%),⁹⁷ but in a very limited sample size of 61 patients. Yoon et al reported that SAPIEN XT recipients with BAV had more frequent aortic root injury than TAV patients (4.5% versus 0.0%; $P=0.015$), whereas no root injury was observed with Corevalve recipients.⁴³ Interestingly, the same team also reported that all cases of annulus rupture in type 1 BAV patients with calcified raphe occurred with BE valve (SAPIEN XT or SAPIEN-3).⁹⁵ Similarly, Makkar et al observed a low, but higher, risk of annulus rupture with SAPIEN 3 in BAV patients than in TAV patients (0.3% versus 0.0%; $P=0.02$) in an STS/ACC TVT registry.⁹⁵ A meta-analysis reported a similar 30-day and 1-year mortality, rate of stroke, equal or greater than moderate PVR, coronary obstruction, and acute kidney injury in BAV patients treated with a BE versus SE valve, while

the use of a SE valve was associated with a higher rate of second device and PPI but a lower rate of annulus rupture.¹¹⁹ A first multicenter registry comparing the third generation THV design ([SAPIEN-3] n=242 versus [Evolut-R/Pro] n=111) observed similar device success but BE valve recipients experienced higher annular ruptures (1.7% versus 0%; $P=0.173$) and higher transvalvular gradient (11.5 ± 4.3 9.7 ± 4.9 ; $P=0.026$) and had less equal or greater than moderate PVR (0.8% versus 10.8%; $P<0.001$) than SE valve recipients. Only the PVR rate and mean gradient remained significantly different between the 2 designs after propensity score matching.¹¹⁵ These findings suggest that a rapid balloon inflation at high pressure against a highly and asymmetrical calcified area could produce a contrecoup injury and annulus damages on the opposite and less-calcified side of the AV complex.

In the most hostile anatomy, such as a calcified raphe, a SE or ME valve could be preferred to mitigate the risk of annulus injury. THV with repositionability features (SE valve or ME valve) allows the operator to test different depths of implantation, which could be advantageous in tapered-shape anatomy. The ME valve had a high radial strength that could help in achieving optimal sealing in heavily calcified BAV patients.¹²⁰ A postmarket registry with ME valve on a very small sample size (n=31) reported excellent procedural success and no equal or greater than moderate PVR, but a very high rate of PPI in BAV patients compared with that in TAV patients (37.4% versus 22.2%; $P=0.14$). Overall, large multicentric prospective cohorts including all commercially available THVs with core laboratory CT and echocardiographic analysis and an independent adjudication committee are eagerly needed to define precisely the BAV anatomies and THV designs that are the most favorable for TAVR.

Shared Decision-Making for BAV Treatment in a TAVR Era: A Lifetime Plan

Shared decision-making in AS management is an increasingly complex process given the pros and cons of both AVR modalities. Risk and benefits of these 2 techniques should be explained to the patients as well as the uncertainties of using a treatment not as well evaluated as in TAV anatomy. SAVR is an open-chest intervention but offers the option of a combined surgery (coronary and/or aorta), whereas TAVR can only treat AS but without sternotomy nor cardiopulmonary bypass. Hence, a lifetime plan of care should be discussed with the patient to put in perspective that both techniques are complementary and could be required during the patient's lifespan. The presence and severity of aortopathy will be at the center of the discussion in many situations. Some may speculate that a patient in their mid-60s with favorable BAV anatomy and mild or moderate aortopathy (<45 mm) could benefit from a TAVR followed by a low-risk SAVR combined—or not—with aorta intervention at the time of THV deterioration during their 70s. Then, a TAVR valve-in-valve could be safely performed when the patient is 80 years of age or older. If an aorta surgery is required during the patient's 70s, before THV deterioration, a TAV-in-TAV may be considered at a later time when the THV will be deteriorated.

This strategy could offer 3 AVRs using a bioprosthetic valve for only 1 sternotomy. However, given the many uncertainties on TAVR durability, aortopathy evolution, and surgical outcomes of SAVR after TAVR, it seems too early to suggest such a standardized plan for lifetime management. Overall, heart teams may be more important now than ever before to individualize and optimize the therapeutic strategy according to a patient's risk, age, anatomy, preference, life expectancy, and functional status.

Conclusions

We have seen from large RCTs that short- and long-term outcomes of TAVR were similar or superior to those of surgery in TAV patients. Despite the absence of controlled studies comparing surgery with TAVR in BAV patients, there are several observational studies showing comparable outcomes of TAVR in BAV and TAV AS. However, we should avoid invalid syllogistic reasoning and conclude that TAVR is similar to SAVR in BAV AS patients. Many uncertainties remain in the indications of TAVR in the absence of RCTs or

longer-term follow-up. Further trials are needed to define the anatomic features of BAV that are the most suitable for TAVR as well as the optimal sizing technique and best implantation techniques. Surgery remains the first-line treatment for the vast majority of BAV patients. Nevertheless, TAVR using the latest THV prostheses may be a safe and reasonable alternative in patients with increased risk for surgery after a meticulous imaging evaluation of the AV anatomy.

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Footnotes

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