Journal of Cardiothoracic and Vascular Anesthesia 37 (2023) 3–5

Contents lists available at ScienceDirect

Journal of Cardiothoracic and Vascular Anesthesia

journal homepage: www.jcvaonline.com

Editorial

Trends and Outcomes of Bicuspid Aortic Valve Stenosis in the TAVI Era

BICUSPID AORTIC VALVE (BAV) anatomy occurs in approximately 1.3% of live births, both predisposing patients to develop aortic stenosis (AS) and accelerating the progression of valve calcification.[1,2] Although perceived as a disease of younger individuals, 25% of patients >80 years old whom are referred for aortic valve replacement (AVR) have BAV disease.[3] Although the management of AS has evolved rapidly in the transcatheter aortic valve implantation (TAVI) era, BAV was initially considered a contraindication.[4] The BAV anatomy was the criterion for exclusion from many noteworthy multicenter TAVI studies, and although data have increased modestly in recent years, TAVI for BAV disease has not been studied independently in randomized clinical trials.[5] Largely due to this lack of evidence, society guidelines favor surgical AVR (SAVR) over TAVI in patients with BAV anatomy.[6,7]

Nonetheless, there is a growing body of scientific literature that provides insight into appropriate patient selection and outcomes of TAVI with BAV disease.[8,9] The recently published "Transcatheter and Surgical Aortic Valve Replacement in Patients With Bicuspid Aortic Valve Stenosis" by Sanaiha et al. is a recent addition to our knowledge base.[10] In this editorial review, we define what was already known regarding the use of TAVI for BAV, and outline what has been learned from the Sanaiha et al's report before discussing the direction of management going forward.

The Challenges of TAVI With BAV

There are numerous reasons that led to the historical preference of SAVR for BAV stenosis.

Unlike degenerative calcified disease of a trileaflet AV (TAV) that frequently presents in isolation, BAV disease results from a genetic disorder of cardiac and vascular development. Nonvalvular pathology occurs in ≤50% of patients, most commonly an aortopathy occurring in 20% to 40%.[2,11] The associated medial degeneration is a risk factor for both aneurysm and dissection of the ascending aorta.[12] For patients with BAV with an indication for AVR, the elective replacement of the ascending aorta is recommended when the aortic diameter grows to ≥4.5 cm.[6] Therefore, when concurrent disease exists, open surgery is the treatment of choice.

When isolated valvular disease exists, there remain significant challenges. First, the dimensions of all aortic valve components (ie, annulus, sinuses, and ascending aorta) are significantly larger with BAV disease, which increases the likelihood that BAV annular size would fall outside of the range that is covered by the commercially available TAVI devices.[13] Second, the shape of the annulus is more elliptical in BAV, which poses a challenge for devices that have been designed for more circular anatomy.[14] Placing these circular implants in elliptical anatomy comes with an increased risk of inadequate seal, resulting in paravalvular regurgitation.[15] Third, BAVs tend to have greater overall calcification that is bulky in nature. This is clearly demonstrated by the difference in valve weights that are excised after SAVR in men (3.61 g *v* 2.31 g) and women, (2.62 g *v* 1.64 g).[16] These bulky calcifications are hypothesized to further impair annular sealing.

The BAV anatomy can be classified into phenotypes based on the number of raphes, with a single fused raphe (type 1) occurring in 90% of patients.[17] The raphe phenotype alone has not been shown to predict outcomes after TAVI.[3] One study evaluated 927 patients with type-1 anatomy, and found 26.0% had both excessive leaflet calcium and a calcified raphe. When both of these findings were present, patients were more likely to have worse paravalvular regurgitation, higher 30-day mortality, and higher 2-year all-cause mortality.[18] The remainder of patients, including those who had only one of these findings (either excessive leaflet calcium or a calcified raphe), had favorable outcomes, suggesting calcium burden and valve morphology may play a larger role in patient selection. During SAVR, valve leaflets are completely excised, so one would not expect worse outcomes when this morphology is treated with open surgery; however, this should be confirmed with further study.

TAVI Versus SAVR With BAV

Previous research involving BAV TAVI abstracted data from the National Inpatient Sample database, part of the

https://doi.org/10.1053/j.jvca.2022.09.081

Healthcare Cost and Utilization Project of the United States Department of Health and Human Services' Agency for Healthcare Research and Quality. Results showed that between 2011 and 2014, only 1% of patients undergoing TAVI had BAV anatomy.[15] Despite being a younger population with fewer comorbidities, patients undergoing BAV TAVI had similar rates of in-hospital mortality and major complications when compared to patients undergoing TAV. A follow-up study querying this database for the years 2012 to 2016 reported that patients with BAV represented 3.3% of patients undergoing TAVI.[19] When comparing TAVI to SAVR for BAV stenosis, results showed a similar in-hospital mortality, with mixed results regarding a variety of individually reported complications.

In their manuscript, Sanaiha et al. used a related Agency for Healthcare Research and Quality tool, the Nationwide Readmissions Database (NRD). This specific instrument allowed the authors to expand upon the previous clinical outcomes research by including readmissions, reinterventions, and overall financial outcomes in a more contemporary era. The NRD captures data from 35 million hospital discharges annually from 30 geographically diverse states, representing approximately 61.8% of the United States population. The data are collected from all types of payers.[20]

The authors hypothesized that patients undergoing AVR (SAVR or TAVI) for BAV AS would have similar index hospitalization outcomes consistent with previous research, but those undergoing TAVI would have higher rates of readmission. Their reasoning for this supposition was not well-explained; although TAVI is frequently reserved for patients with BAV and greater comorbid disease that may ultimately result in higher readmission, we believe a risk-adjusted analysis would be expected to account for this.[19] The primary study endpoint was mortality during index hospitalization. Additional endpoints included a composite of common complications, nonhome discharge, 30-day all-cause readmission, 90-day readmission, and reintervention at first readmission. Hospitalization costs and length of stay data were analyzed. The authors performed multiple adjusted analyses, including both NRD-provided weighting and inverse probability of treatment weighting to account for these differences in baseline patient characteristics.

The records of 623,721 patients with AS undergoing isolated AVR between 2012 and 2019 were reviewed, of whom 56,331 (9.0%) had BAV anatomy. Overall, the use of TAVI represented 6.8% of isolated AVR for BAV stenosis. This figure increased 21-fold over the course of the study period, and in 2019, >20% of patients undergoing TAVI had BAV anatomy (Fig 1). The number of centers performing TAVI for BAV increased from 25 to 221. The absolute number of patients with BAV anatomy treated with either therapy declined after a peak in 2015, but again increased in 2018 and 2019. We believe this may have resulted from an increased reluctance to undergo SAVR that temporarily outpaced the increasing use of TAVI.

Not surprisingly, patients who underwent TAVI were older and with more comorbidities compared with those undergoing

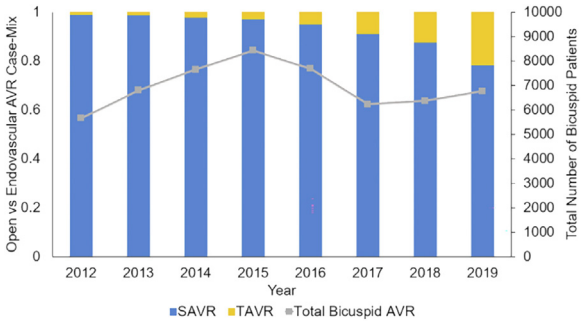

Fig 1. Annual trends in aortic valve replacement with bicuspid aortic valve anatomy. Adapted with permission from Sanaiha et al.[10]

SAVR, consistent with prior research.[19] In an unadjusted analysis, the primary endpoint of mortality during index hospitalization was higher with TAVI (1.6% *v* 0.8%; p = 0.001); however, composite complications were greater with SAVR (33.6% *v* 22.2%; p < 0.001). This was primarily driven by hemorrhage, as seen in the PARTNER 1 trial.[21] When risk-adjustment analysis was used, these differences were no longer observed. Unadjusted nonhome discharge was higher in TAVI compared to SAVR (8.5% *v* 6.6%; p = 0.007), and this difference persisted with risk-adjusted analyses using NRD weighting, but not with the inverse probability of treatment weighting.

All-cause readmission rates were higher at 90 days with TAVI compared with SAVR in unadjusted analysis; however, the differences resolved when only one weighted analysis method was used. Regardless of statistical analysis performed, there were no differences in 30-day readmission. Although these factors contribute to a higher total cost observed with TAVI, the cost of the index hospitalization also was higher with TAVI despite a shorter length of stay, indicating the cost of the valve is the primary driver of this difference. Note that previous randomized clinical trial data evaluating only patients undergoing TAV found that rehospitalization for a procedural or cardiac-related cause was lower in TAVI (7.3% *v* 11%; hazard ratio 0.65, 95% CI 0.42-1.00).[22]

Data reported by the authors regarding reintervention require additional consideration. Defined as angioplasty, valvuloplasty, or TAVI at first readmission, the reintervention variable is not limited strictly to valve reintervention; hence, it cannot be appropriately adjudicated. This definition also does not include repeat SAVR or SAVR after TAVI. In unadjusted outcomes, the rates of reintervention were significantly higher after TAVI (5.4%) than SAVR (0.3%), and remained significantly higher after both methods of statistical adjustment. With a 90-day readmission rate of 15.5%, this translates to a remarkable 1 in 3 readmitted patients requiring a return trip to the hybrid room. We found this to be exceptionally high and without obvious explanation.

Typically, only valvular reinterventions on readmission have been previously studied, and most frequently only repeat SAVR or TAVI, but not valvuloplasty. Therefore, most published data report significantly lower incidences over longer study periods.[23,24] Evaluating the supplemental data from Sanaiha et al., we found that BAV TAVI was associated with

higher rates of reintervention when compared to BAV SAVR, and also when compared to TAV TAVI (5.9% *v* 4.1%; p = 0.001). Further insight into the cause or specific type of intervention is not available but would be informative.

Strategies Going Forward

Previous long-held fears of treating BAV AS with TAVI are dissipating as this therapeutic option grows in popularity. This increase in comfort appears to be well-founded, supported by the authors' conclusion that the risk of in-hospital morbidity and mortality were comparable for TAVI and SAVR in this population. This aligns with the United States Food and Drug Administration's decision to remove language from device labeling that cautioned use with BAV anatomy.[3]

However, some caution is still advised. Not all bicuspid disease is equivalent, and we must learn to better identify positive prognostic indicators with TAVI. For younger patients, we must have data at 10 years and beyond that are comparable to SAVR. Finally, we must better understand the implications of previously unthinkable practices, including SAVR after TAVI, valve-in-valve TAVI, or even "valve-in-valve-in-valve-in-valve." Just as TAVI for BAV has become commonplace after previously being contraindicated, these scenarios may soon become encountered frequently by cardiac anesthesiologists.

Conflict of Interest

None.

Peter J. Neuburger, MD, FASE*
Leslie James, MD†
Homam Ibrahim, MD†
*Department of Anesthesiology, Perioperative Care and Pain Medicine, NYU Grossman School of Medicine, New York, NY
†Department of Cardiothoracic Surgery, NYU Grossman School of Medicine New York, NY

References

1 Hoffman JI, Kaplan S. The incidence of congenital heart disease. J Am Coll Cardiol 2002;39:1890–900.
2 Siu SC, Silversides CK. Bicuspid aortic valve disease. J Am Coll Cardiol 2010;55:2789–800.
3 Vincent F, Ternacle J, Denimal T, et al. Transcatheter aortic valve replacement in bicuspid aortic valve stenosis. Circulation 2021;143:1043–61.
4 Wijesinghe N, Ye J, Rodés-Cabau J, et al. Transcatheter aortic valve implantation in patients with bicuspid aortic valve stenosis. JACC Cardiovasc Interv 2010;3:1122–5.
5 Cormican DS. The puzzle of TAVR for bicuspid AS: Still missing a piece? J Cardiothorac Vasc Anesth 2022;36:1225–7.
6 Otto CM, Nishimura RA, Bonow RO, et al. 2020 ACC/AHA guideline for the management of patients with valvular heart disease: A report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. Circulation 2021;143:e72–227.
7 Vahanian A, Beyersdorf F, Praz F, et al. 2021 ESC/EACTS Guidelines for the management of valvular heart disease. Eur Heart J 2022;43:561–632.
8 Waksman R, Craig PE, Torguson R, et al. Transcatheter aortic valve replacement in low-risk patients with symptomatic severe bicuspid aortic valve stenosis. JACC Cardiovasc Interv 2020;13:1019–27.
9 Halim SA, Edwards FH, Dai D, et al. Outcomes of transcatheter aortic valve replacement in patients with bicuspid aortic valve disease: A report From the Society of Thoracic Surgeons/American College of Cardiology Transcatheter Valve Therapy Registry. Circulation 2020;141:1071–9.
10 Sanaiha Y, Hadaya JE, Tran Z, et al. Transcatheter and surgical aortic valve replacement in patients with bicuspid aortic valve stenosis. [e-pub ahead of print]. Ann Thorac Surg 2022. https://doi.org/10.1016/j.athoracsur.2022.06.030. Accessed September 10, 2022.
11 Masri A, Svensson LG, Griffin BP, et al. Contemporary natural history of bicuspid aortic valve disease: A systematic review. Heart 2017;103:1323–30.
12 Augoustides JG, Wolfe Y, Walsh EK, et al. Recent advances in aortic valve disease: Highlights from a bicuspid aortic valve to transcatheter aortic valve replacement. J Cardiothorac Vasc Anesth 2009;23:569–76.
13 Tchetche D, de Biase C, van Gils L, et al. Bicuspid aortic valve anatomy and relationship with devices: The BAVARD Multicenter Registry. Circ Cardiovasc Interv 2019;12:e007107.
14 Philip F, Faza NN, Schoenhagen P, et al. Aortic annulus and root characteristics in severe aortic stenosis due to bicuspid aortic valve and tricuspid aortic valves: Implications for transcatheter aortic valve therapies. Catheter Cardiovasc Interv 2015;86:E88–98.
15 Nagaraja V, Suh W, Fischman DL, et al. Transcatheter aortic valve replacement outcomes in bicuspid compared to trileaflet aortic valves. Cardiovasc Revasc Med 2019;20:50–6.
16 Roberts WC, Janning KG, Ko JM, et al. Frequency of congenitally bicuspid aortic valves in patients ≥80 years of age undergoing aortic valve replacement for aortic stenosis (with or without aortic regurgitation) and implications for transcatheter aortic valve implantation. Am J Cardiol 2012;109:1632–6.
17 Sievers HH, Schmidtke C. A classification system for the bicuspid aortic valve from 304 surgical specimens. J Thorac Cardiovasc Surg 2007;133:1226–33.
18 Yoon SH, Kim WK, Dhoble A, et al. Bicuspid aortic valve morphology and outcomes after transcatheter aortic valve replacement. J Am Coll Cardiol 2020;76:1018–30.
19 Elbadawi A, Saad M, Elgendy IY, et al. Temporal trends and outcomes of transcatheter versus surgical aortic valve replacement for bicuspid aortic valve stenosis. JACC Cardiovasc Interv 2019;12:1811–22.
20 Healthcare Cost and Utilization Project. Overview of the Nationwide Readmissions Database (NRD). Available at: https://www.hcup-us.ahrq.gov/nrdoverview.jsp. Accessed August 27, 2022.
21 Smith CR, Leon MB, Mack MJ, et al. Transcatheter versus surgical aortic-valve replacement in high-risk patients. N Engl J Med 2011;364:2187–98.
22 Mack MJ, Leon MB, Thourani VH, et al. Transcatheter aortic-valve replacement with a balloon-expandable valve in low-risk patients. N Engl J Med 2019;380:1695–705.
23 Fukuhara S, Tanaka D, Brescia AA, et al. Aortic valve reintervention in patients with failing transcatheter aortic bioprostheses: A statewide experience [e-pub ahead of print]. J Thorac Cardiovasc Surg 2021. https://doi.org/10.1016/j.jtcvs.2021.08.057. Accessed September 10, 2022.
24 Makkar RR, Thourani VH, Mack MJ, et al. Five-year outcomes of transcatheter or surgical aortic-valve replacement. N Engl J Med 2020;382:799–809.