

Bicuspid aortic valves and TAVI: is it still an exclusion criterion? State of the art and open issues

Bicuspid aortic valve (BAV) is the most common congenital valvular disease, and is found in approximately 22% of all patients presenting with symptomatic severe aortic stenosis who are deemed high-risk for surgery. While BAV has historically been considered a relative contraindication to transcatheter aortic valve implantation, technical improvements in addition to greater operator confidence and experience has resulted in an increased number of percutaneous valve implantations in this patient group. Areas of uncertainty remain, but data from the literature suggests that the procedure can be safely performed in the setting of BAV, with results comparable to tricuspid aortic valve patients, at the expense of higher rates of short-term complications and postprocedural aortic regurgitation.

Keywords: aortic stenosis • bicuspid aortic valve • TAVI
• transcatheter aortic valve implantation

Bicuspid aortic valve (BAV) is the most common congenital valvular disease, occurring in 0.5–2% of the general population and its prevalence is substantially greater in patients undergoing surgical aortic valve replacement. Aortopathy often coexists with the presence of BAV and is frequently associated with aneurysmal dilatation of the ascending aorta, aortic dissection and aortic coarctation. The abnormal anatomy of both the valve and the aortic annulus in the setting of BAV is associated with increased mechanical stress over the valve leaflets, and a predisposition to increased rates of calcification and resultant aortic stenosis (AS) or aortic regurgitation (AR). In spite of the complications associated with BAV, two large contemporary series have demonstrated that life expectancy in adults with BAV disease is comparable to that of the general population [1–3]. Thus the incidence of BAV in the elderly population is significant, accounting for 22% in octogenarians and 18% in nonagenarians, as diagnosed from surgically excised valves [4] in symptomatic elderly patients presenting with severe AS.

Considerations in BAV

Concerns with regard to the suitability of TAVI for the treatment of BAV due to marked anatomical variations in valve morphology and commonly associated aortopathy has resulted in a tendency to not offer this therapeutic strategy to this patient group, due to the higher likelihood of a suboptimal result, including the greater risk of residual AR [5]. In BAV, several anatomical abnormalities can determine the final result of transcatheter treatment. The bicuspid valve is typically made of two unequal-sized leaflets. The asymmetry of the valve and annular ring can result in an extreme elliptical shape of the annulus with associated extensive and eccentric calcium distribution [6,7]. This may preclude the full expansion of the prosthesis and can lead to an increased rate of prosthesis misplacement [8], and consequently of valve dislocation, coronary artery obstruction, uneven expansion, paravalvular regurgitation, prosthesis dysfunction and early degeneration of the prosthesis [9–11].

Additionally, nonvalvular abnormalities are encountered in up to 50% of adults with

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BAV, the most common of which is dilation of the ascending aorta, possibly due to concomitant connective tissue disorders [3]. This is associated with a higher risk of intraprocedural complications, principally aortic dissection and annulus rupture and thus postimplantation optimization including postdilatation of the valve is not recommended to reduce the risk of these complications (albeit with a higher chance of achieving a suboptimal final result). Furthermore, the high frequency of large aortic annular diameters in patients with BAV has precluded many patients from TAVI in the absence of suitable prostheses.

Current recommendations

As a result of these concerns, TAVI is currently regarded as a relative contraindication for the treatment of BAV. BAV was excluded from the large prospective, randomized PARTNER (Placement of Aortic Transcatheter Valves) trial with the Edwards-Sapien valve system [12] and from the randomized controlled CoreValve US Pivotal Trial High-Risk Study, which compared the CoreValve prosthesis to surgical aortic valve replacement [13]. Thus, there is currently a paucity of data with regard to procedural success and outcomes in this patient group. Consequently, BAV is not among the inclusion criteria in the 2012 ACCF/AATS/SCAI/STS Expert Consensus Document on Transcatheter Aortic Valve Replacement [14] and the ESC/EACTS Guidelines on the management of valvular heart disease (version 2012) [15]. These recommendations appear to have been generally adopted into current clinical practice with published data from a large cohort from the German TAVI Registry reporting that only 3% of all patients undergoing TAVI between January 2009 and June 2010 were found to have BAV [16], and from a recent registry from five academic centers in Poland, where only 6.7% of five patients treated with TAVI were identified as BAV [17]. Consequently, a significant number of patients with symptomatic severe AS and BAV continue to be declined this intervention.

Current status

With greater operator experience and improvements in the design of transcatheter prostheses, TAVI is increasingly being used for other 'off-label' indications including the treatment of BAV. Whilst long-term data with regard to safety, efficacy and outcomes are still awaited, there are a number of reports with regard to the feasibility of TAVI in BAV, in single case studies or small cohorts of patients [18–21].

The results of the largest cohorts enrolling BAV patients for TAVI procedures are summarized in Table 1.

At the present time, the majority of the available data are based upon experiences with two devices – the Edwards Sapien valve (Edwards Life Sciences, Inc., CA, USA) and the CoreValve (Medtronic, Inc., MN, USA). The CoreValve bioprosthesis in BAV has been shown to be associated with good procedural and clinical outcomes over a mean follow-up period of 8 ± 7 months in a cohort of 15 patients, with nonsignificant differences in comparison to the TAVI control group [7]. Implantation of the Edwards Sapien bioprosthesis in a cohort of 11 patients was also associated with acceptable results in terms of reduction of the aortic gradient and postprocedural AR. Two noncardiac deaths and one late valve migration requiring surgery were observed over a 30-day follow-up period [9].

More recently, larger multicenter trials based upon national Registries compared the results of TAVI in BAV and patients with tricuspid valves (TAV) [16,17]. Within the large German TAVI Registry, 38 BAV patients (3%) were compared with the remaining 1357 TAV patients (97%) [16]. There was a higher rate of relevant AR (≥ 2) after TAVI among patients with BAV (25 vs 15%; $p = 0.05$), whereas pacemakers were more often implanted in patients with TAV (17 vs 35%; $p = 0.02$). Thirty-day mortality rates were similar in both cohorts (11 vs 11%). In a Cox proportional regression analysis, BAV was not associated with higher 1-year mortality rate (hazard ratio 0.64; 95% CI: 0.29–1.41), although the occurrence of more-than-mild AR was greater in patients with BAV but this did not result in an elevated 30-day and 1-year mortality rate in comparison to the control group. Similarly, in the Poland National Registry, which investigated the outcomes of 28 patients with BAV who underwent TAVI [17]. In comparison to patients with TAV there were no significant differences between groups with regard to device success, annular rupture or conversion to open cardiac surgery. The postprocedural mean pressure gradient, presence of AR grade ≥ 2 , 30-day mortality and 1-year all-cause mortality were also similar between groups.

Two recent systematic reviews have summarized all currently available data [20,21] and included a total of 92 patients from selected case series and case reports. The self-expanding CoreValve was implanted in 56% of patients with the remainder receiving the balloon expandable Edwards valve. The 30-day mortality rate was 8.6%. Half of these events occurred in the periprocedural period – two following emergency surgery for aortic dissection and severe AR and two due to hypovolemic shock after a transapical approach. Complications included: pacemaker implantation in 21%, major bleeding in 14% and vascular access complications 23.6%. No strokes were reported. There were no cases of device embolization and only a single report of coronary

Table 1. Summary of registries of transcatheter aortic valve implantation in bicuspid aortic valve.

Name of registry – description of study	Canadian multicenter registry [9]	Single-center observational [7]	Single-center observational [19]	Italian multicenter [22]	German TAVI Registry [16]	Poland multicenter registry [11]	TAV in-BAV registry [27]
Period of the study	May 2006–April 2010	Jan 2009–Jan 2012	Oct 2006–Jan 2012	Nov 2007–Dec 2012	Jan 2009–June 2010	Jan 2009–Sept 2012	April 2005–Jan 2014
Bicuspid patients (n; %)	11	15 (5%)	21 (10%)	21 (4.7%)	38 (2.7%)	28	139
Tricuspid patients (n; %)	–	301	208	447	1357	84 (control)	–
Balloon expandable device implanted (n; %)	11 (100%) Edwards Sapien	0	11 (52.4%) Edwards Sapien	8 (38%) Edwards Sapien	12 (32%) Edwards Sapien	5 (18%) Edwards Sapien	48 (34.5%) Edwards Sapien
Self-expandable device implanted (n; %)	0	15 (100%) CoreValve	10 (46.7%) CoreValve	13 (62%) CoreValve	26 (68%) CoreValve	23 (82%) CoreValve	91 (65.5%) CoreValve
Primary end points (n; %)	–	–	–	–	–	–	–
In-hospital mortality	2 (18%)	1 (7%)	1 (4.8%)	3 (14%)	4 (11%)	1 (4%)	5 (3.6%)
Conversion to open surgery	1 (9%)	1 (7%)	0	1 (5%)	1 (3%)	1 (4%)	3 (2.2%)
Bleeding (any cause)	na	na	3 (14.3%)	5 (24%)	10 (26%)	9 (32%)	37 (26.6%)
Life-threatening bleeding	na	na	2 (9.5%)	1 (5%)	na	3 (11%)	10 (7.2%)
Major vascular complications	na	na	1 (4.8%)	2 (10%)	9 (25%)	3 (11%)	9 (6.5%)
PPM implantation	na	6 (40%)	3 (14.3%)	3 (14%)	7 (17%)	8 (29%)	–
Coronary occlusion	0	0	1 (4.8%)	0	0	0	0
Procedural results (n; %)	–	–	–	–	–	–	–
Successful implantation	10 (90%)	14 (93%)	21 (100%)	18 (86%)	38 (100%)	27 (96%)	137 (98.6%)
Device embolization	1 (9%)	0	0	1 (5%)	0	1 (4%)	3 (2.2%)
Second device implantation	na	na	na	2 (9.5%)	na	0	5 (3.6%)
Postimplantation AR ≥ 2	3 (27%)	0	4 (19%)	5 (24%)	9 (25%)	9 (32%)	39 (28.4%)
Follow-up (n; %)	–	–	–	–	–	–	–
30 days mortality	2 (18%)	1 (7%)	1 (4.8%)	3 (14%)	4 (11%)	1 (4%)	7 (5%)
30 days myocardial infarction	0	0	1 (4.8%)	0	0	0	3 (2.2%)
30 days stroke	0	0	0	0	0	0	3 (2.2%)
6 months mortality	na	na	na	na	na	na	13 (9.6%)
12 months mortality	4 (36%)	2 (13%)	na	6 (32%)	5 (13%)	5 (18%)	21 (17.5%)
End points (n; %)	–	–	–	–	–	–	–
Device success	9 (82%)	14 (93%)	21 (100%)	18 (86%)		26 (93%)	125 (89.9%)
Safety	–	14 (93%)	–	15 (71%)	–	–	110 (79.1%)
Combined efficacy end point	9 (82%)	14 (93%)	18 (85.7%)	–	–	–	118 (84.9%)

AR: Aortic regurgitation; BAV: Bicuspid aortic valve; n: Number; na: Not applicable; PPM: Permanent pacemaker implantation; TAVI: Transcatheter aortic valve implantation.

occlusion. Paravalvular leak (PVL) was present in 68.5% of patients, with the majority (80%) reported as mild. At follow-up, 61% of the patients were in NYHA class I–II symptoms, with good improvement in symptoms and quality of life. The reported post-discharge mortality (average range 7–12 months) was 15%. Of these, six deaths occurred after 30 days: two patients due to device failure, two due to aortic dissection and two due to non-cardiac etiologies. In another recent case series of 21 consecutive BAV patients treated with the Edwards or CoreValve prosthesis [22], device success (85.7 vs 94.4%; $p = 0.10$) was lower in patients with BAV. Although the 30-day composite safety end point (23.8 vs 21.0%; $p = 0.76$) was similar between the two groups. The mortality rate at 30-days was higher (14.2 vs 3.6%; $p = 0.02$) in the BAV group. Cardiovascular mortality at 1-year did not differ significantly between the two groups (10.5 vs 7.4%; $p = 0.62$).

PVL even when mild has been shown to be associated with poor outcomes [23]. In the setting of BAV, PVL rates have been reported in as many as 80% of patients treated with TAVI, with 31% reported to be of greater than mild severity [20]. These rates are higher than the reported rate of 11.2% in the non-BAV treated patient populations. Importantly, in BAV patients treated with TAVI, the observed 1-year mortality rate was significantly lower than those patients treated with medical therapy alone (49.7%).

The exact etiology of the higher rates of PVL in patients with BAV is likely multifactorial and little is known about the biomechanical features of currently available devices in the setting of BAV disease. In an intraoperative model [24], an experimental transcatheter valve was temporarily implanted in patients with both bicuspid and tricuspid AS before conventional aortic valve replacement. Asymmetric, noncircular stent expansion was observed in BAV – which may result in the higher observed incidence of PVL in BAV patients. However, predilatation of the native valve and postdilatation following valve deployment was not performed. The mechanical characteristics of the self-expanding stent used might not be comparable to clinically available transcatheter valves [25]. In a clinical series that evaluated self-expanding valves, valve expansion appeared relatively circular on TEE in all 11 cases evaluated [9], presumably related to the mechanical properties of nitinol [25,26], which include an increase in maximal radial force with the passage of time, following an initial overexpansion. Moreover, BAV does not necessarily preclude symmetric expansion of a balloon-expandable valve with sufficient radial strength. In contrast, eight others authors [7,13] reported an elliptical deployment in 36 patients with BAV treated with the CoreValve system.

The results of all these studies suggest that TAVI in high-risk symptomatic patients with BAV may be performed, at higher risk in the short-term with regard to procedural complications but with mid-term outcomes comparable to patients with tricuspid valves.

Patient work-up

Patient selection and the implantation of the appropriate prosthesis is critical in further improving outcomes in patients with BAV treated with TAVI, and thus a thorough work-up of patients with BAV before TAVI consideration is imperative.

Diagnosis of bicuspid anatomy with 2D echocardiography can be challenging. 3D imaging modalities are superior to 2D techniques to assess the elliptical geometry and to accurately measure the dimensions of the aortic annulus. Multidetector row computed tomography (MDCT) (Figure 1) is invaluable, complementing echocardiography, providing further anatomical information with regard to the valve, aortic annulus, location of the coronary ostia, appearance of the aorta and for the assessment of the peripheral vasculature.

Practical considerations

The secure seating of the prosthesis within the native annulus in BAV is more challenging and thus accurate sizing is important. It is noteworthy that the selection of the most suitable device for the native aortic annulus is paramount to final procedural success with undersizing resulting in a higher risk of paravalvular leak and oversizing increasing the risk of aortic dissection or annular rupture. The extent and distribution of valvular calcification may also affect the success of deployment of transcatheter valves. Other important anatomical considerations in ascertaining the suitability of TAVI and selection of device include the presence or absence of a concomitant aortopathy, and the location and dominance of the coronary arteries, which are more likely to have anatomic variations in patients with BAV and thus be associated with a higher rate of coronary occlusion following TAVI.

With regard to device selection, the majority of the experience to date is with two devices: the Edwards Sapien valve and the Medtronic CoreValve with greater use of the latter likely due to the larger mean CT-measured annulus diameters in BAV and operator preference due to concerns of the risk of aortic dissection with balloon expandable valves. However, there does not appear to be a difference with regard to patient outcome between devices [7,9,12,13,16,17,19–22].

More recently, there have been rapid developments in valve and delivery system design. They have been designed to reduce the incidence of PVL, vascular

complications, the risk of atrioventricular block and stroke. New self-expandable devices that are now available include the Portico valve (St. Jude Medical, MN, USA), the JenaValve (Jena-Valve, Munich, Germany) and the Medtronic Engager (Medtronic, Inc., MN, USA). Fully retrievable prostheses are also now available including the Direct Flow valve (Direct Flow Medical, Inc., CA, USA) and the Lotus valve (Boston Scientific Corporation, MA, USA) and may represent new strategies in the treatment of BAV, although currently no data exist as to their efficacy in this patient group.

Technically, the appreciation of the higher likelihood of short-term risks may result in a more prudent approach periprocedurally (e.g., pre- and postdilatation), and to accept mild or higher degrees of residual leak with the knowledge that medium-term outcomes are comparable. Longer term follow-up data with regard to patient outcomes, quality of life and symptoms are awaited with both current and next-generation devices in this patient group to determine their optimal strategy.

Conclusion

In conclusion, with greater operator experience and improvements in devices and delivery systems, TAVI is increasingly being used in the treatment of high-risk patients presenting with symptomatic severe BAV. Whilst the short-term risks appear to be higher in patients with BAV, medium term outcome data appear to be comparable to patients treated for more

conventional indications. With better patient and device selection and greater appreciation of the periprocedural risks, TAVI may well become an established therapeutic strategy in this patient group in the future.

Future perspective

The last few years has seen rapid advances in the development of TAVI devices and delivery systems with the requirement of smaller vascular sheaths, a reduction in periprocedural complications, shorter procedure times and the development of repositionable and completely retrievable devices that have increased the rates of procedural success. With greater operator and center experience, in conjunction with these technological advances, TAVI is increasingly being used to treat pathology beyond established indications.

The treatment of patients with degenerative BAVs disease with TAVI deemed to be of high surgical risk or inoperable has been shown to be safe and efficacious with a significant improvement in mortality compared to medical therapy alone.

Looking forward, further refinements in technology, greater operator experience and a greater understanding of the anatomy will all enable better patient and device selection to further reduce complications and improve patient outcomes. With the emergence of longer term data with regard to valve durability and clinical outcomes in this patient group, TAVI may well become an established treatment for patients presenting with severe symptoms secondary to degeneration of a bicuspid valve.

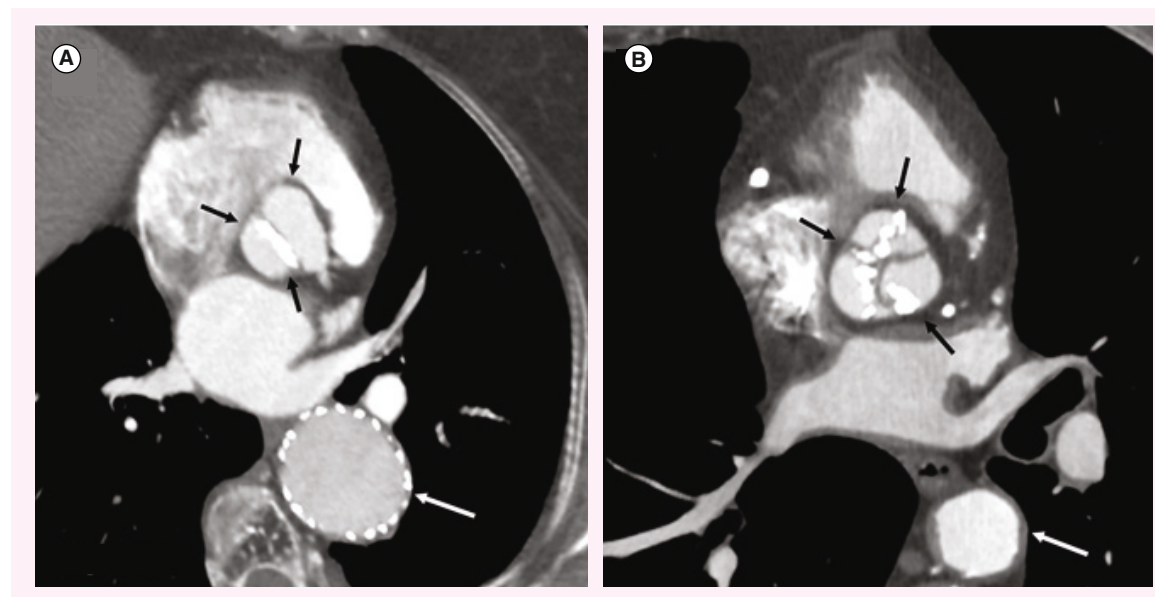


Figure 1. Computed tomography appearances of bicuspid aortic valve. Bicuspid aortic valve illustrated in (A). Note elliptical root appearance and eccentric calcification (black arrows), and also concomitant aortopathy with previous aortic stenting (white arrow). For comparison, appearance of tricuspid valve (B). Note less eccentricity of calcium and a more circular shape (black arrows). Normal caliber aorta (white arrows).

Executive summary

Considerations in bicuspid aortic valve

- Most common congenital valvular disease.
- Commonly associated with anatomical abnormalities including: elliptical shape of aortic annulus, extensive and eccentric calcification, location of the coronary ostia and concomitant aortopathy which are important in assessing patient suitability for transcatheter aortic valve implantation (TAVI) and device selection.

Current recommendations

- Regarded as a relative contraindication for TAVI in current guidelines.

Current status

- TAVI is increasingly being used for the treatment of bicuspid aortic valve.
- Higher postprocedural aortic regurgitation noted in registries, in association with a higher rate of vascular complications.
- Similar 1-year mortality following TAVI when compared with tricuspid valves and significantly lower when compared to medical therapy alone.

Patient work-up

- Importance of using 2D and 3D echocardiography in conjunction with multislice computed tomography to accurately define the anatomy to aid selection of patients with suitable anatomy and the most appropriate device.

Conclusion

- While short-term complication rates are higher in patients with bicuspid valves in comparison to patients with tricuspid valve, medium term outcomes are comparable.
- With better patient and device selection and greater appreciation of periprocedural risks, TAVI may well become an established therapeutic strategy for bicuspid aortic valve stenosis in the future.

Financial & competing interests disclosure

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