

RHYTHMOS



July 2017 • Volume 12 • No 3 (47)

ISSN: 1792-7919

e-ISSN: 1792-7927

URL: www.rhythmos.gr / <http://rhythmos.info.tm>

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EDITORIAL

TAVI in Bicuspid Aortic Valve Stenosis: Cautiously Feasible

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Abstract

Bicuspid aortic valve (BAV) disease is the most common congenital cardiac malformation with a prevalence of 0.4% to 2%. For a long time, a BAV has not been considered an indication for transcatheter aortic valve implantation (TAVI) due to insufficient technology and poor procedural results conferred by a challenging valvular anatomy leading to poor stability of the prosthetic valve and/or paravalvular regurgitation due to distorted native valve leaflets. Large randomized controlled TAVI trials typically excluded bicuspid aortic stenosis (AS) because of its unique anatomic features. However, current technological advancements are apparently changing this landscape, and over the last few years, TAVI appears technically feasible, albeit a demanding procedure, and has been used to treat severe bicuspid AoV stenosis with promising results, as shown, apart from earlier case reports and patient series, in several recent observational studies and comparative trials between patients with tricuspid and patients with BAV. Thus, current literature cautiously supports a role of TAVI in selected BAV AS patients; however, the final role of this technique in this challenging group of patients will need to be determined

from randomized controlled trials comparing TAVI with surgical replacement and studies comparing TAVI in bicuspid and tricuspid aortic valves. Technological advancements appear to play a significant and crucial role in rendering the transcatheter approach feasible, efficacious and safe. *Rhythmos* 2017;12(3): 40-44.

Key Words: aortic stenosis; bicuspid aortic valve; tricuspid aortic valve; transcatheter aortic valve implantation/replacement; pacemaker implantation; paravalvular regurgitation

Abbreviations: AS = aortic stenosis; BAV = bicuspid aortic valve; CT = computed tomography; PAR = paravalvular aortic regurgitation; TAVI = transcatheter aortic valve implantation

Introduction

Bicuspid aortic valve (BAV) disease is the most common congenital cardiac malformation with a 3:1 male predominance.^{1,2} A prevalence of BAV of 0.4% to 2% has been reported in both the Western and Asian population.^{3,4} A high rate of complications by various degree of aortic valve stenosis or aortic valve regurgitation has been observed in BAV patients.⁴⁻⁶ There is also a low, albeit much higher than in tricuspid aortic valve, incidence of infective endocarditis and aortic dissection in this patient group.^{7,8} Some consider the underlying pathology leading to ascending aortic aneurysmal dilation in the context of BAV-associated aortopathy.^{8,9} BAV has also been associated with a higher incidence of intracranial

aneurysms.¹⁰ There appears to be familial clustering of BAV suggestive of genetic linkage, and international guidelines advocate that in affected families first-degree relatives of patients with BAV be screened.¹¹ Despite a male predominance among patients with BAV, presentation may be different in the two genders.¹² Men with BAV may have more frequently moderate/severe aortic regurgitation at first presentation compared with women, whereas women present more often with moderate/severe aortic stenosis compared with men. Furthermore, men appear to have more frequent endocarditis and aortopathy with aortic dissections than women.

For a long time, a bicuspid aortic valve (BAV) has not been considered an indication for transcatheter aortic valve implantation (TAVI) due to insufficient technology and poor procedural results conferred by this specific and challenging valvular anatomy leading to poor stability of the prosthetic valve and/or paravalvular regurgitation due to distorted native valve leaflets.¹³ Nevertheless, TAVI has been used to treat severe bicuspid aortic stenosis (AS), mainly in case reports and small patient series,¹⁴ as the large randomized controlled trials typically excluded bicuspid AS because of its unique anatomic features.

However, current technological advancements may be changing this landscape.^{15, 16} Patients with BAV have more challenging anatomy with altered aortic geometry, larger aortic annuli dimensions, more calcified, bulky and irregular valve leaflets compared with patients with tricuspid aortic valve. Improvements in mechanical controlled expansion may be able to reduce the risk of elliptical deployment and/ or malpositioning of the prosthetic valve. An adaptive seal may reduce paravalvular leak. Preliminary data with use of the newer generation valves show promising results of TAVI in patients with bicuspid anatomies.^{17, 18} Comparative data between patients with tricuspid and patients with BAV undergoing TAVI appear promising with equivalent success and complication rates.¹⁹ Thus, current preliminary data suggest that BAV may not be deemed a contraindication for TAVI any longer;^{14, 16, 20-22} however, further studies will be needed to confirm the results of these initial reports and to support the performance of TAVI in BAV stenosis.

BAV Morphology Classification

The most commonly used classification of BAV morphology was proposed by Sievers and Schmidtke,²³ depending on number of raphe, spatial position of cusps or raphe, and functional status of the valve, with three major types identified: *type 0 (no raphe)*, *type 1 (one raphe)*, and *type 2 (two raphe)*, followed by two supplementary characteristics, spatial position and function. A bicuspid aortic valve with one raphe (type 1)

appears to be the most common type, with the raphe usually positioned between the left (L) and right (R) coronary sinuses (*type 1, L/R*), frequently associated with a hemodynamic predominant stenosis (S) (type 1, L/R, S). Very few patients had a “purely” bicuspid aortic valve with no raphe (type 0). In another study, the presence of a raphe was associated with a higher prevalence of significant aortic stenosis and regurgitation.²⁴

In another similar, possibly more practical classification, again three BAV morphologies appear to predominate.²⁵ A *tricommissural* BAV, with 1 commissure completely fused between 2 cusps, often referred to as “functional” or “acquired” BAV; in this morphology, fusion is not seen in the basal third of the sinus and occurs at or close to the commissural level. A *bicommissural raphe type* has 2 cusps fused by a fibrous or calcified ridge of various heights, does not reach the height of the commissure; in this morphology, fusion of cusps occurs at or proximal to the basal third of the sinus, and the raphe may also vary in terms of calcification and vertical height. In the *bicommissural non-raphe type*, 2 cusps are completely fused from their basal origin but there is no visible seam; in this morphology, there are only 2 commissures with no raphe or third commissure.

Studies of TAVI in patients with BAV

A preliminary systematic review of 4 case series with 86 patients and 6 case reports reported relatively favorable results of TAVI in BAV patients with initially successful procedure attained in all but one patient, however there was an 8.6% 30-day mortality and a considerable complication rate with 21% requiring a pacemaker, 14% experiencing major bleeding and 23.6% vascular access complications.²⁰ Paravalvular regurgitation was observed in 68.5% of patients, however the majority (80%) was reported as only mild. A subsequent analysis of short and mid-term pooled data from 7 observational studies comparing 149 BAV and 2096 non-BAV patients undergoing TAVI suggested that TAVI is feasible and safe in older patients with BAV.²⁶ Between the BAV and non-BAV cohorts, there was no difference in 30-day mortality (8.3% vs 9%), post-TAVI mean peak gradients (weighted mean difference, 0.36 mmHg), moderate or severe paravalvular leak (25.7% vs 19.9%), pacemaker implantations (18.5% vs 27.9%), life-threatening bleeding (8.2% vs 13.9%), major bleeding (20% vs 16.8%), conversion to conventional surgery (1.9% vs 1.2%) and vascular complications (8.6% vs 10.1%) (all P=NS).

In a retrospective multicenter analysis of 139 patients (mean age 78±8.9 years; STS score 4.9±3.4%) undergoing TAVI with the balloon-expandable (n = 48) or self-expandable valve (n = 91) systems for BAV stenosis (65.5%), regurgitation (0.7%), or mixed disease (33.8%),

procedural mortality was 3.6%, with valve embolization in 2.2% and conversion to surgery in 2.2%.²⁷ The mean aortic gradient decreased from 48.7±16.5mmHg to 11.4±9.9mmHg (p <0.0001). Post-implantation aortic regurgitation (AR) grade ≥2 occurred in 28.4% (19.6% balloon-expandable vs. 32.2% self-expandable valve, p = 0.11) but was prevalent in only 17.4% when CT-based valve sizing was performed (16.7% balloon-expandable valve vs. 17.6% self-expandable valve, p = 0.99). Thirty-day device safety, success, and efficacy were noted in 79.1%, 89.9%, and 84.9% of patients, respectively. One-year mortality was 17.5%. Major vascular complications were associated with increased 1-year mortality (OR: 5.66; p = 0.03). The authors concluded that TAVI in BAV is feasible with encouraging short- and intermediate-term clinical outcomes. Importantly, a high incidence of post-implantation AR is observed, which appears to be mitigated by CT-based valve sizing.

According to an international patient level multicenter analysis on outcomes in 108 patients with BAV undergoing TAVI, the primary outcome (a composite of 30-day mortality, stroke, life-threatening bleeding, acute kidney injury, coronary artery obstruction, major vascular complication and valve related dysfunction) occurred in ~27% of patients, mainly driven by re-intervention for valve malposition (9.3%).²² The 30-day and 1-year mortality rates were 8.3% and 16.9% respectively; with severe paravalvular regurgitation occurring in 9.6% of patients. Device success was achieved in 85.2% of cases with pacemaker insertion in 19.4%. The authors concluded that in selected patients with BAV and severe AS, TAVI appears both safe and feasible with acceptable clinical outcomes.

According to a systematic literature review of 8 case reports and 4 case series and meta-analysis of 5 case-control/cohort studies comprising 166 BAV patients, device success rate achieved for TAVI in this cohort of BAV patients was 95.2%.²⁸ The 30-day mortality rate was 8.4%, and the medium-term (range from 6 months to 2 years) mortality rate reported was 17.9%. Overall, the performance of TAVI in BAV patients was comparable to that in non-BAV patients (30-day mortality rate relative risk - RR 1.05, p = 0.87; device success rate RR = 1.00, p = 0.94; incidence of moderate to severe paravalvular regurgitation: RR = 1.25, p = 0.25). The authors concluded that TAVI may be feasible and safe for treating BAV stenosis patients. Other observational and comparative studies have also reported similar efficacy of TAVI in patients with bicuspid or tricuspid aortic valve anatomy with sustained and acceptable mid-term prosthesis hemodynamic performance.¹⁸ Newer generation prostheses appear to confer more favorable valve

performance.²⁹ Nevertheless, particularly challenging are anatomies with a large aortic annulus, whereby TAVI is rarely performed due to the risk of residual paravalvular aortic leakage.³⁰

In a multicenter study analyzing imaging with pre-procedural computed tomography (CT), TAVI achieved favorable outcomes in 130 patients with bicuspid aortic valve (BAV) stenosis, albeit with high permanent pacemaker rates.²⁵ Specifically, bicommissural BAV (vs tricommissural) accounted for ~69-96% of patients. For bicommissural bicuspid, non-raphe type (vs raphe type) BAV accounted for 9-62%. Overall rate of 30-day mortality was 3.8% and of cerebrovascular events 3.2%. The rate of new permanent pacemaker insertion was high (26.2%) and similar between balloon-expandable and self-expanding valves (25.5% vs 26.9%). Paravalvular aortic regurgitation (PAR) ≥ moderate was 18.1% overall but lower at 11.5% in those with pre-procedural CT. In the absence of pre-procedural CT, there was an excess of PAR. Predictors of PAR included intercommissural distance for bicommissural bicuspid (odds ratio -OR 1.37; p = 0.036) and lack of a baseline CT for annular measurement (OR 3.03; p = 0.018).

TAVI in bicuspid AS appears to be associated with lower device success rate, particularly with the early-generation devices. According to a propensity score matching comparison between 546 pairs of bicuspid and tricuspid AS undergoing TAVI derived from a multicenter registry, patients with bicuspid AS had more frequent conversion to surgery (2% vs 0.2%; p = 0.006) and a significantly lower device success rate (85.3% vs. 91.4%; p = 0.002).³¹ Within the group receiving early-generation devices, bicuspid AS had more frequent aortic root injury (4.5% vs 0%; p = 0.015) when receiving the balloon-expanding device, and moderate-to-severe paravalvular leak (19.4% vs. 10.5%; p = 0.02) when receiving the self-expanding device. Among patients with new-generation devices, however, procedural results were comparable across different prostheses. The cumulative all-cause mortality rates at 2 years were comparable between bicuspid and tricuspid AS (17.2% vs 19.4%; p = 0.28).

Paravalvular Regurgitation

In BAV patients undergoing TAVI, increased rates of paravalvular leak (particularly in the absence of baseline contrast CT scan) and permanent pacemaker implantation have been observed regardless of device design and leaflet morphology.²⁵ However, newer-generation valve devices have shown more promising results in mitigating these high rates of paravalvular aortic regurgitation.^{16, 29, 30}

Pacemaker Implantation

Higher rates of pacemaker implantation after TAVI in bicuspid AS do require further investigation. Pacemaker

implantation rates reported during TAVI of BAV patients range from 14% to 50%, and are even higher than the generally high rates observed with self-expandable devices in patients with tricuspid aortic valve stenosis.²⁹ Unfortunately, newer generation devices have not curtailed these rates.³¹ Perhaps, avoiding low implantation positions may play a role.¹⁶

Technical Challenges

Close preoperative and intraoperative analyses of the aortic valve anatomy are mandatory for successful TAVI in BAV cases.³² Preprocedural multidetector computed tomographic (CT) imaging for detailed measurements of the aortic annulus, ascending aorta diameter, coronary ostia height, sinus area, sinotubular junction area, calcification and eccentricity index are all required in order to determine whether currently available valved stents may be able to fit the specific anatomy.³³

Type I BAV anatomy with left and right cusp fusion appears to have significantly better outcomes than other valve variants.²²

Conclusion

In patients with bicuspid AS, the altered valve anatomy with the elliptic shape of the BAV annulus, combined with the asymmetric heavy calcifications of the leaflets pose technical challenges for TAVI. Nevertheless, TAVI appears technically feasible, albeit a demanding procedure, and current literature cautiously supports a role of TAVI in selected BAV AS patients; however, the final role of this technique in this challenging group of patients will need to be determined from randomized controlled trials comparing TAVI with surgical replacement and studies comparing TAVI in bicuspid and tricuspid aortic valves. Technological advancements appear to play a significant and crucial role in rendering the transcatheter approach feasible, efficacious and safe.

Table 1. Parameters determining a successful TAVI procedure in patients with symptomatic severe BAV stenosis

• Pre-procedural imaging (CT-based sizing)

CT is the preferred modality for morphology delineation, calcium characterization, and quantification and can also optimally assess for aortopathy / CT annular sizing helps to select an appropriately sized implant

• Type of prosthetic valve

A newer generation low profile valve is preferable with improved sealing properties of the external sealing layer of the inflow portion

Devices moderately oversized (e.g. ~10% of the annular area) may have a low rate of AR

• Procedure

Improved accuracy of valve positioning with an improved valve delivery system

Increased operator experience and case planning

• Caveats

Cautious with valve oversizing for fear of annular rupture/should be guided by CT annular measurements

Beware of asymmetric expansion of some valves

Self-expanding valves might be more capable of conforming to the irregular orifice of the bicuspid valve but less capable of achieving a circular formation after implantation /

However, there is no conclusive evidence for an advantage of a certain type of valve in preventing AR or improving clinical outcomes

Possible higher device success rate and lower incidence of significant AR in patients with type 1L-R bicuspid valves (fusion of the left and right cusps)

Still high pacemaker implantation rates, with either balloon- or self-expandable valves, ranging from 14% to 50% / maybe associated with low implantation positions

AR = aortic regurgitation; BAV = bicuspid aortic valve; CT = computed tomography; TAVI = transcatheter aortic valve implantation

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