

Review

Research Progress of Transcatheter Aortic Valve Replacement in Aortic Valve Stenosis due to Bicuspid Aortic Valve

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Abstract

Patients with bicuspid stenosis often have anatomical characteristics such as elliptical valve rings, high and asymmetric valve calcification, unequal valve leaflets, and concomitant widening of the ascending aorta and/or transverse heart. These unfavorable factors are more likely to cause poor placement of transcatheter aortic valve replacement (TAVR) valves, poor expansion of valve stents, which can lead to reduced valve durability, residual perivalve leakage, rupture of valve rings and surrounding structures, and serious surgical related complications such as ascending aortic dissection. In summary, TAVR treatment for mitral stenosis is receiving increasing attention. In this manuscript, we reviewed the research progress of transcatheter aortic valve replacement in aortic valve stenosis due to bicuspid aortic valve.

Keywords

aortic valve stenosis; bicuspid aortic valve; transcatheter aortic valve replacement

Bicuspid aortic valve (BAV) is the most common congenital cardiac valve malformation, with an incidence of approximately 1–2% in the human population [1]. BAV has a higher incidence than tricuspid aortic valve (TAV), and BAV is associated with earlier onsets of aortic valve calcification and dilatation of the ascending aorta and aortic root [2,3]. In a previous study, patients with BAV accounted for approximately 50% of patients with aortic stenosis (AS) who underwent surgical aortic valve replacement (SAVR) [4]. Specifically, 69% of patients in the 51–60 years age group had BAV, and this proportion was reduced to 41% in patients aged 71–80 years [4], indicating that BAV is an important factor leading to AS in a relatively young population. After 20 years of development and modification, the surgical procedure of TAV replacement (TAVR) is not inferior to that of SAVR in the treatment of patients at high risk of severe AS. Results of the Placement of Aortic Transcatheter Valves (PARTNER) 3 Trial have shown

that TAVR is superior to SAVR for low-risk patients with severe AS [5–7]. Therefore, the clinical practice consensus and guidelines recommend TAVR as an important treatment modality for patients with severe AS [8]. However, BAV is more anatomically asymmetric, possibly concomitant with severe calcification, and often associated with ascending aortic diseases [2,3]. Thus, TAVR in patients with BAV is challenging and may lead to many postoperative complications [9,10]. This article reviews the applications of TAVR in patients with BAV.

Anatomical Features and Classification of BAV

Due to abnormal cusp (i.e., leaflet) development, failure to separate two adjacent cusps of the three cusps of the valve eventually leads to BAV. Typically, fused cusps are significantly larger than the unfused cusp, creating an asymmetrical structure. The fused cusps also have a distinctly raised structure, called a raphe. According to the classification system reported by Sievers and Schmidtke [11], BAV cases are divided into three categories according to the number of raphe: Type 0 (no raphe), Type 1 (one raphe), and Type 2 (two raphe). On this basis, BAV cases are subdivided into three subtypes based on the fused cusps: left–right fusion (L-R); right–noncoronary fusion (R-N); and left–noncoronary fusion (L-N). Type 1 is the most common BAV, mainly presenting as subtype L-R, while Type 0 and Type 2 are relatively rare. A study by Jilaihawi *et al.* [12] showed that the complications of TAVR were not only related to the number of raphe, but also to valve cusp morphologies (i.e., commissural conditions). They classified BAV cases into three types: tricommissural, bicommissural raphe, and bicommissural nonraphe; each type was further classified into two subtypes based on whether the ostium of the coronary artery is located on the same or contralateral side. This classification system pays more attention to the supravalvular structure to facilitate the evaluation of TAVR. In addition, the BAV cusps decline after birth, gradually showing fibrosis, calcification, and myxomatous degeneration, and patients with BAV usually have aortic dilatation [13]. According to the location, aortic dilatation is divided into four types: Cluster I, dilatation of the aortic root only;

Cluster II, dilatation of the ascending aorta; Cluster III, dilatation of the tubular ascending aorta and aortic arch; and Cluster IV, dilatation of the aortic root, ascending aorta, and aortic arch [14].

Current Status of TAVR Treatment for BAV Patients

Because of anatomical features of BAV, the early PARTNER trials and other series of studies did not include patients with BAV-related AS [5]. With the accumulation of experience and the improvement in TAVR for patients with BAV in recent years, BAV is no longer a contraindication for TAVR.

Makkar *et al.* [15] compared the prognosis of BAV and TAV patients receiving TAVR treatment using propensity score matching based on the American Association of Thoracic Surgeons/American Heart Association (STS/ACC) transcatheter valve therapies (TVT) registration study data. A total of 81,822 patients were enrolled in the registered study consecutively, and 2691 pairs of patients who received the new generation balloon dilation valve (Sapien 3) were matched for analysis. There was no statistically significant difference in the 30 day all-cause mortality rate (2.6% vs. 2.5%, hazard ratio (HR) = 1.04, 95% confidence interval (CI): 0.74–1.47) and 1-year all-cause mortality rate (10.5% vs. 12.0%, HR = 0.90, 95% CI: 0.73–1.10) between the two groups (both $p > 0.05$). Similarly, there was no statistically significant difference between the two groups in terms of moderate or above perivalvular leakage 30 days after surgery (2.0% vs. 2.4%) and moderate or above perivalvular leakage 1 year after surgery (3.2% vs. 2.5%) (both $p > 0.05$). However, the incidence of stroke 30 days after surgery in the BAV group was higher than that in the TAV group (2.5% vs. 1.6%, HR = 1.57, 95% CI: 1.06–2.33). Fortunately, the incidence of stroke in the BAV group was not very high, and there was no statistically significant difference between the two groups in terms of 1-year improvement in quality of life scores ($p > 0.05$). Another meta-analysis on the application of TAVR in BAV and TAV patients also reached similar conclusions [16]. This meta-analysis selected 13 relevant studies and found that there was no statistically significant difference in mortality between the two groups at 30 days (odds ratio (OR) = 1.13, 95% CI: 0.88–1.46) and 1 year (OR = 1.02, 95% CI: 0.77–1.37), and there was also no statistically significant difference in stroke (both $p > 0.05$).

Potential Risks of TAVR in BAV

Paravalvular Leak and Aortic Annular Rupture

Paravalvular leak (PVL) refers to the residual leak between the implanted annulus and the annulus of the native valve of the patient after valve replacement. PVL is one of the most common complications after TAVR. The occurrence of PVL is closely related to the prognosis of patients undergoing TAVR [17,18]. Compared with TAV, BAV has a narrower diameter and its plane with the largest ellipticity is not necessarily at the annulus level but possibly above the valve annulus, appearing as a cone or trapezoid in imaging [19], which affects the precise release of the prosthetic valves and the complete expansion of the valves when the balloon is inflated, eventually leading to insufficient annulus closure and PVL. In addition, patients with BAV have asymmetric calcification, as well as relatively large, calcified valve cusps, and the fusion of cusps with calcified raphe can significantly limit the complete expansion of the prosthetic valves. These factors also lead to PVL [20]. Kanjanahattakij *et al.* [21] also confirmed in a meta-analysis of 854 cases of BAV and 3615 cases of TAV that patients with BAV were more likely to develop moderate to severe PVL after surgery (odds ratio = 1.42, 95% confidence interval [CI] [1.08, 1.87], $I^2 = 0\%$). A recent study by Jin *et al.* [22] showed that PVL of patients with TAV after TAVR was gradually improved at the 1-year follow-up, while PVL of patients with BAV and TAVR was not significantly attenuated at 1 year postsurgery. To reduce the occurrence of PVL clinically, balloon postdilation has been used to close the gap between the prosthetic valve and the native valve. However, calcified raphe and relatively large and calcified masses increase the risk of perforation of the native annulus, resulting in rupture of the aortic valve at the root [23]. Fedak *et al.* [24] reported that patients with BAV were more likely to experience aortic root injury than patients with TAV during Edwards SAPIEN XT valve placement (4.5% vs. 0.0%, $p = 0.015$). However, a smaller volume of balloon catheter dilation may not result in a significant reduction in the occurrence of PVL. Hence, the two opposite surgical complications, PVL and aortic root rupture, are particularly obvious in patients with BAV undergoing TAVR.

Prosthetic Valve Thrombosis and Prosthetic Valve Durability

In TAVR, after placing the prosthetic valve frame, a new pocket-like sinus structure is formed between the prosthetic valve and the native valve, and blood flow in this new structure is slow, so this site is predisposed to prosthetic valve thrombosis [25]. The durability of the prosthetic valve is not only related to the material used, but also to whether the implanted valve is fully inflated, the degree

of eccentricity of the prosthetic valve frame, and the degree of inclination between the prosthetic valve frame and the native valve [26–28]. Insufficient valve expansion tends to collapse the prosthetic valve, increasing the resistance to blood flow through the valve [27]. The greater the centrifugal degree of the prosthetic valve frame, the easier it is to form shear and turbulence locally [28]. Moreover, the tilt of the prosthetic valve frame may also cause hemodynamic disturbances in the sinus of Valsalva and increase vascular resistance [26]. The above factors together affect the decline of the prosthetic valve. BAV has a relatively complex and asymmetric structure, and its valve opening tends to be elliptical. In addition, the degree of calcification of BAV is severe, and the sinuses of Valsalva are relatively large. Theoretically, this morphology and these abnormal hemodynamics of the prosthetic valve are more likely to occur, which may result in valve thrombosis and prosthetic valve failure. Nevertheless, existing long-term data on prosthetic valve thrombosis and prosthetic valve failure are very limited. More clinical studies on this issue are required for further clarification.

Risk of Coronary Obstruction

Compared with BAV and TAV, the sinus of Valsalva is larger in size, while coronary ostium height is basically similar [9]. The relatively long cusps may cause obstruction of the ostia of the coronary arteries during TAVR. Moreover, unlike the ostia of the coronary arteries located in the middle of the sinuses in patients with TAV, the coronary ostia in some patients with BAV are abnormally close to the native commissure of heavily calcified valve cusps, and the calcified tissue may be pushed by the prosthetic valve during TAVR, resulting in obstruction of coronary ostia [29]. Many patients with BAV need to undergo procedures to release the cusp tissue, bringing the prosthetic valve closer to the coronary artery ostia, increasing the risk of coronary obstruction [29]. A study in China comparing the complications of patients with BAV and with TAV showed that all four patients with coronary obstruction were BAV cases [30]. A large-sample study showed that a larger number of patients with BAV had coronary obstruction than patients with TAV. However, due to the low overall incidence rate, no statistically significant difference was shown in the study [31].

Permanent Pacemaker Insertion

Complete atrioventricular block is also one of the common complications of TAVR. Severe calcification in patients with BAV easily increases the pressure of the prosthetic valve on the tissue between the right and noncoronary cusps, and the deep tissue between the right and noncoronary cusps is the cardiac conduction system [32]. In addition, the intraventricular septum in patients with BAV is usually shorter than that in patients with TAV, and the pros-

thetic valves are easily placed too deep, which may cause atrioventricular block and increase the risk of permanent pacemaker implantation (PPI) [33]. A multicenter study of 139 patients with BAV showed that 23.2% of the patients ultimately required PPI [34].

Valve Thrombosis

After TAVR is inserted into the artificial valve frame, a pocket like new sinus structure is formed between the new artificial valve and the main valve, and the blood flow in this structure is slow, making it a common site for valve thrombosis [25]. The durability of valves is not only related to the materials used in artificial valves, but also closely related to whether the valve is fully inflated, the degree of eccentricity of the valve frame, and the degree of tilt between the valve frame and the valve body [26–28]. Insufficient expansion of the valve can easily cause the artificial valve to fold, increasing the resistance of blood flow through the valve [27]. The greater the degree of centrifugation of the valve holder, the easier it is to form shear forces and turbulence locally [28]. The tilt of the valve frame can also cause hemodynamic disturbances in the aortic valve sinus and increase blood flow resistance [26], which together affect the failure of artificial valves. For BAVs with relatively more complex and asymmetric structures, their valve openings tend to be elliptical, with severe calcification and larger Valsalva sinuses. Theoretically, they are more prone to abnormalities in artificial valve morphology and hemodynamics, leading to valve thrombosis and worsening of artificial valve failure. However, long-term data on valve thrombosis and valve failure in BAV patients after TAVR surgery is still very limited, and further clinical research is needed to clarify this.

Infective Endocarditis

Infective endocarditis (IE) is a rare but serious complication following transcatheter aortic valve replacement (TAVR). Despite substantial improvements in the TAVR procedure and its expansion to younger and healthier patients, the incidence of IE after TAVR remains stable, with incidence rates similar to those reported after surgical aortic valve replacement.

Although data from the infective endocarditis after TAVR international registry showed that the isolated involvement of the TAVR prosthesis was the most frequent presentation (48%), the involvement of mitral valve (native or prosthetic valve), cardiac devices, or right-side IE accounted for 14.7%, 3.9%, and 1.4% respectively [35,36]. Nearly one-third of the patients (31.3%) had IE with at least 2 cardiac structures affected [35]. Interestingly, differences in TAVR platform design may influence the location and development of vegetations. Although vegetations located on the TAVR valve leaflets are the most common in both self-expanding valves (SEVs) and balloon-expandable valves

(BEVs), SEVs more frequently presented vegetations anchored to the stent frame than BEVs did (34% vs. 19%) [37]. Although IE after TAVR is recognized as a subtype of prosthetic valve endocarditis, this condition represents a particularly challenging scenario given its unique clinical and microbiological profile, the high incidence of IE-related complications, the uncertain role of cardiac surgery, and the dismal prognosis in most patients with TAVR-IE.

Impact of New-Generation Valves and Optimized TAVR Strategies on BAV

Most of the early clinical studies on TAVR in BAV patients used first-generation prosthetic valves, which were designed according to the anatomical characteristics of TAV. With the improvements in valve technology, the new generation of valves has gradually overcome some of the aforementioned potential risks brought by BAV. For example, a layer of pericardial skirt is sewed on the periphery of the valve frame of the Evolut PRO system to further close the gap between the prosthetic valve and the patient's tissue to reduce the risk of PVL [38]. A study has shown that the Edwards SAPIEN 3 valve increases radial force support, while using polyethylene terephthalate to design the outer skirt to better accommodate the morphology of the irregular annulus and asymmetrically calcified cusps in patients with BAV, thereby reducing the risk of PVL [39]. In China, considering the characteristics of severe calcification and the high proportion of BAV in patients undergoing TAVR, the Venus A-valve with enhanced radial force is more conducive to pushing calcified masses. Existing research has confirmed that the new generation of valves has obvious advantages in the treatment of patients with BAV. A study applying propensity score matching on 2726 patients with BAV and 79,096 patients with TAV showed no significant differences in 30-day and 1-year mortality, the incidence of moderate-to-severe PVL, and valve hemodynamics. Although the risk of stroke within 30 days postsurgery was higher in patients with BAV than in patients with TAV, no significant difference in the incidence of stroke was found between the two groups at the 1-year follow-up [40]. Another large-sample study using TAVR to treat patients with BAV and TAV at low surgical risk showed no significant differences in 30-day and 1-year mortality and the incidences of stroke and intraoperative complications (e.g., intraoperative conversion, coronary obstruction, PPI, cardiac perforation, prosthetic valve thrombosis, and moderate-to-severe PVL) between the two groups [37].

In addition to the advancement of prosthetic valves, with the accumulation of surgical experience, increasingly optimized surgical strategies also promote the application of TAVR in patients with BAV. The first is the prosthetic valve selection strategy. Given the differences in anatomical structures between BAV and TAV, traditional selection

of prosthetic valves is based on the size of the valve ring, which often leads to relatively frequent surgical complications. Therefore, some scholars adopted a downsizing strategy when selecting prosthetic valves for some patients with severe calcification to achieve good surgical outcomes [41]. In addition, some scholars [42] recommended supra-annular sizing strategies, including the level of implantation at the raphe plane, i.e., to analyze the valve structure using computed tomography (CT) to determine the actual anchoring plane of the prosthetic valve, thereby determining the valve size. For patients with BAV, Petronio *et al.* [43] combined the degree of calcification and the length of fused raphe based on CT evaluation and further increased or decreased the size of the prosthetic valve to achieve a 100% implantation success rate, a low PPI rate, and absence of moderate-to-severe PVL. The above methods are all static evaluations, which fail to accurately evaluate the shape of the valve under high blood flow. Therefore, Chinese experts and scholars have proposed a strategy to evaluate the supra-annular structure using a balloon and to select the prosthetic valve size according to the supra-annual structure. A study of TAVR in BAV based on this strategy achieved a 100% success rate of the operation, and no patients in the study developed moderate-to-severe PVL or required PPI treatment [44].

In addition, accurate preoperative evaluation strategies also greatly reduce the risk of complications in patients with BAV during TAVR. Existing mature CT and esophageal ultrasonography technologies can be used to accurately quantify and evaluate various parameters, such as annulus size and the degree of calcification of the aortic valve, facilitating the formulation of individualized surgical strategies. In addition, computer modeling and three dimension (3D) printing technologies have gradually become more accurate, intuitive, and effective methods for preoperative evaluations. Based on various parameters of the aortic valve, computer modeling technology can be used to reconstruct the anatomical structure of the aortic valve of the patient, and 3D printing technology is used to materialize the aortic valve structure, thereby helping surgeons to observe the 3D anatomical features of the aortic valve intuitively and to reduce the risk of complications during surgery [45]. Studies have shown that these technologies accurately predict not only the occurrence of postoperative PPI in patients with BAV, but also the severity and location of postoperative PVL through computer-simulated hemodynamic analysis [46,47]. These simulated data also provide a basis for the surgeons to formulate surgical strategies and to reduce the risk of various surgical complications.

Future Directions for Research and Clinical Practice in TAVR for BAV

Valve Durability

All biological valves face durability issues. According to tissue fatigue data accurately simulated by computers, the durability of TAVR valve leaflets is expected to be 7.8 years shorter than that of SAVR biological valve leaflets. In clinical practice, the incidence of severe valve structural damage during the mid-term (5–8 years) of TAVR valve is 1.3%, the incidence of valve failure is 4.6%, and the 10-year biological valve failure rate of SAVR is 5.6% [48]. Although the 5-year follow-up results show that the durability of TAVR valves is not inferior to SAVR valves in both high-risk and low-risk patient groups [49], TAVR valves still lack long-term follow-up results exceeding 10 years. The 5-year follow-up results of a comparative study between self-expanding valve and balloon-expanding valve showed no significant difference in the incidence of biological valve failure and severe valve structural damage [50]. The new generation TAVR valves use different decellularization methods for different valve leaflet materials (such as bovine pericardium or pig pericardium) to achieve the goal of delaying calcification and increasing durability. At the same time, the durability of the new generation of valves, which aims to reduce perivalvular leakage by adding “skin” and improving “sealing”, and to more accurately release the valve and increase its recyclable function, remains unknown and requires further long-term follow-up to confirm. In addition, pure polymer materials for heart valves which is more durable and has better anti-thrombotic performance than biopolymer valves have also made progress.

BAV with Ascending Aortic Dilation

At present, guidelines recommend simultaneous SAVR and ascending aortic repair (Class IIa) for patients with BAV and ascending aortic dilation diameter ≥ 45 mm. However, it should be noted that we do not have direct evidence that TAVR increases the incidence of ascending aortic events in patients with BAV and concomitant ascending aortic dilation. According to short-term follow-up data of one year, there was no progress in ascending aortic dilation after TAVR compared to preoperative, whether it was for the mitral valve or the tricuspid valve [51]. Moreover, the follow-up results of up to 15 years have shown that for patients who have not yet formed BAV with concomitant ascending aortic aneurysm, simple valve replacement may increase the probability of ascending aortic aneurysm formation after surgery, but the probability of aortic dissection is very low, and there is no significant difference compared to patients with tricuspid valve [52]. This suggests that as-

ending aortic dilation after valve replacement alone does not necessarily lead to clinical outcomes of aortic dissection or rupture.

Computer Modeling and 3D Printing Technology

Computer modeling and 3D printing technology are gradually becoming more accurate, intuitive, and effective preoperative evaluation methods. It reconstructs the anatomical structure of the patient's aortic valve using computer modeling techniques by inputting various parameters of the patient's aortic valve, and solidifies the structure using 3D printing technology, helping the surgeon visually and stereoscopically observe the anatomical features of each patient and deduce possible complications during surgery. Research [47,48] shows that this technology not only accurately predicts the occurrence of postoperative PPI in BAV patients, but also accurately determines the severity and location of postoperative PVL through computer simulated hemodynamic analysis.

Conclusion and Outlook

The TAVR field is developing rapidly, but valve durability, severe calcification of the BAV, ascending aortic dilation, risk of coronary artery occlusion, and simple aortic valve regurgitation remain significant challenges. In the future, we will mainly explore in two aspects: optimization of the TAVR treatment process, and innovation and improvement of TAVR valves.

The optimization of TAVR treatment process, including the prognostic value of imaging evaluation, the effectiveness and safety of emerging technologies related to TAVR, including chimney supports, BASILICA, brain protection technology, and combined EVAR technology; Clarification of the optimal anti-thrombotic regimen after TAVR surgery; This requires our clinical doctors not only to perform a surgery well, but also to actively participate in the systematic planning and clinical trial projects. Multi-center, large-scale and long-term clinical data can truly provide strong evidence for us to solve problems, or change clinical practice guidelines. The innovative improvement of TAVR valves is a fundamental measure to address valve durability, the risk of coronary occlusion, and the challenge of simple aortic regurgitation. On the one hand, seeking or creating more durable valve materials or artificial valve processing methods. On the other hand, designing more ideal valves with a wider range of anatomical indications can address the shortcomings of TAVR valves in terms of insufficient ability, stability, and preservation of coronary pathways in the simultaneous treatment of AS and aortic regurgitation (AR). This requires close collaboration among multiple disciplines such as medicine, engineering, and materials science. The innovative development of medicine in

the future is a long and arduous task, and the combination of medicine and engineering is the strongest support on the development path.

To summarize, TAVR is a safe and effective treatment for BAV-related AS. However, the anatomical complexity of BAV, the rejuvenation of patients with BAV, and the characteristics of ascending aortic lesions associated with BAV still challenge the implementation of TAVR in patients with BAV. SAVR is still an important means for the treatment of BAV-associated AS. With the improvement of valve technology and valve materials, problems such as poor valve durability will be gradually resolved in the future. We also believe that TAVR indications will expand to all age groups and all valve types to benefit more patients.

Author Contributions

Data collection and writing manuscript—LC, literature search—LJ, MZ and XC, analysis and/or interpretation—ZW. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

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Conflict of Interest

The authors declare no conflict of interest.

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