

# TAVR in Bicuspid Aortic Stenosis: Data and Current Limitations

Reviewing the current state of transcatheter aortic valve replacement in the bicuspid aortic valve and what is needed for further validation.

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**M**ultiple randomized trials and registries have resulted in the establishment of transcatheter aortic valve replacement (TAVR) for treatment of aortic stenosis in patients with an increased risk of surgery.<sup>1-8</sup> Over the past decade and with the development and maturation of TAVR, there has been a significant shift in the management of severe symptomatic aortic stenosis. Randomized clinical trials demonstrated the safety and efficacy of TAVR compared with surgical aortic valve replacement (SAVR), which resulted in approval of TAVR for severe symptomatic aortic stenosis regardless of surgical risk profile.<sup>2,4-6,9-12</sup>

## BICUSPID AORTIC VALVE BACKGROUND

### Anatomy

Bicuspid aortic valve is the most common congenital valvular heart disease and the most common cause of aortic stenosis in younger adults. It affects 1% to 2% of the United States' population, and up to 20% of these patients will require aortic valve intervention in adulthood.<sup>9,13</sup>

A bicuspid aortic valve differs from a tricuspid aortic valve in more ways than simply the number of leaflets. Some of these differences include increased incidence of aortopathy, dilation of the aortic root and ascending aorta, atypical location of coronary arteries, asymmetric leaflet calcification, larger annulus size, higher leaflet calcification, and fused raphe.<sup>9</sup>

### History with TAVR for Stenosis

Bicuspid aortic stenosis was an exclusion criterion in the randomized trials of TAVR due to the anatomic and clinical challenges of the bicuspid aortic valve, as well as the potential association of the aforementioned characteristics with failure of the early-generation TAVR systems,<sup>1</sup> which

resulted in notably worsening of both hospital outcomes and device success and increased incidence of paravalvular leak, device malposition, and aortic injury.<sup>13-14</sup> Therefore, the treatment of choice for symptomatic bicuspid aortic stenosis historically has been SAVR.<sup>13</sup>

Off-label use of TAVR for bicuspid aortic stenosis in the absence of aortopathy has increased as a result of an increased frequency of bicuspid stenosis in younger patients coupled with the recent shift toward treating low-risk surgical patients with TAVR, as well as the advances in technology and the accumulated procedural experience.<sup>13</sup> Although SAVR remains the only approved replacement strategy for low-risk patients with bicuspid aortic stenosis, special attention to the outcomes of TAVR in bicuspid aortic stenosis appears valuable.<sup>2,9,14-16</sup>

### Procedural Considerations

With advancing age, the bicuspid aortic valve undergoes a degenerative process, including fibrosis, calcification, and myxomatous degeneration of the valve cusps. Additionally, bicuspid aortic valve may be associated with aortic dilatation, which clinically can result in aortic stenosis, aortic regurgitation, endocarditis, aortic aneurysm, and dissection. Balloon valvuloplasty may lead to disruption of the fused commissures, resulting in severe aortic regurgitation. Additionally, due to positioning of the point of highest ellipticity in a stenotic bicuspid aortic valve above the aortic annulus, accurate placement of the valve is challenging, leading to higher degree of paravalvular leak. Consequences of asymmetric calcified leaflets can include the need for pacemaker, new-onset left bundle branch block, annular rupture, higher transvalvular gradients, paravalvular leak, and interference with valve expansion.<sup>17</sup>

## DATA OVERVIEW

Mylotte et al analyzed data from 12 participating centers in Europe and Canada to review baseline characteristics, procedural data, and clinical follow-up from 139 patients with bicuspid aortic valve who underwent TAVR: 48 with balloon-expandable valves and 91 with self-expandable valves.<sup>18</sup> The results were published in *Journal of the American College of Cardiology* in 2014. Bicuspid aortic valve was studied based on the Sievers and Schmidtke classification,<sup>15</sup> which uses number of raphe, spatial position of cusp or raphe, and functional status of the valve to classify valves to type 0 (no raphe), type 1 (one raphe), and type 2 (two raphe). The study showed a high incidence of postimplantation aortic regurgitation (28.4%) that was reduced to 17% when multislice CT–based transcatheter aortic valve sizing was performed.

In 2017, the first large-scale study was performed by Yoon et al.<sup>14</sup> It compared the procedural and clinical outcomes for 546 pairs of patients with bicuspid and tricuspid aortic valve stenosis after TAVR using Sapien XT (Edwards Lifesciences), CoreValve (Medtronic), or newer-generation devices (Sapien 3 [Edwards Lifesciences], Lotus [Boston Scientific Corporation], Evolut R [Medtronic]). Device success rate was defined as absence of procedure-related death, correct positioning of a single prosthetic heart valve into the proper anatomic location, and intended performance of the prosthetic heart valve.

In the article published in *Journal of the American College of Cardiology*, the investigators concluded that when comparing TAVR in bicuspid versus tricuspid valves, bicuspid valves had a similar prognosis but a lower device success rate. Importantly, although procedural differences were noted in early generation devices (ie, more frequent aortic root injury when receiving the balloon-expanding device, moderate to severe paravalvular leak when receiving the self-expanding device), no difference was noted with new-generation devices. Thirty-day all-cause mortality, stroke, life-threatening bleeding, major vascular complication, and stage two and three acute kidney injury were similar in both groups.<sup>14</sup>

Makkar et al analyzed 2,691 propensity score–matched pairs of bicuspid and tricuspid aortic stenosis patients who underwent TAVR with a balloon-expandable valve (third generation) from the Society of Thoracic Surgeons (STS)/American College of Cardiology (ACC) Transcatheter Valve Therapies (TVT) registry from June 2015 to November 2018.<sup>1</sup> Primary outcomes were 30-day and 1-year all-cause mortality and stroke, and secondary outcomes were procedural complications, valve hemodynamics, and quality of life measured by New York

Heart Association class and Kansas City Cardiomyopathy Questionnaire score. Results were reported in *JAMA* in 2019. At 30 days and 1 year, all-cause mortality and valve hemodynamics (moderate or severe paravalvular leak) were not significantly different in the two groups. However, the 30-day stroke rate and the procedural complications requiring surgical intervention were significantly higher in the bicuspid group—although the latter was < 1% in both groups. It was suggested that the greater calcium burden of the bicuspid aortic valve may have required more frequent balloon dilation before and after valve replacement, which, in addition to the complexity of the cases, may have contributed to higher stroke rates. This raises the possibility of a lowered incidence of stroke with routine use of cerebral embolic protection devices.<sup>1</sup>

More recently, a 2021 *JAMA* paper by Makkar et al studied the differences in mortality and stroke in low-surgical-risk patients who underwent TAVR for bicuspid versus tricuspid aortic stenosis.<sup>19</sup>

Forrest et al performed a similar analysis using the STS/ACC TVT registry wherein 929 propensity-matched patients who underwent TAVR with the Evolut R or Evolut Pro (Medtronic) self-expanding valves were studied, and outcomes of patients with bicuspid versus tricuspid aortic stenosis were compared.<sup>9</sup> It was concluded that all-cause mortality, stroke, and valve hemodynamics did not differ between the two groups at 30 days or 1 year.

Although the time of the procedure in the Forrest et al study was longer in the bicuspid group, other procedural characteristics were similar (type of anesthesia used, access site, device success). No significant differences were noted in in-hospital events, including the following: mortality, stroke, coronary obstruction, pacemaker implantations, vascular complications, and postprocedural length of stay. A higher rate of aortic valve surgical intervention was recorded in the bicuspid group. Significantly less moderate or severe aortic valve regurgitation was reported in patients who received the Evolut Pro valve. Echocardiographic analysis was used to assess valve hemodynamics.<sup>9</sup>

A study of national trends and in-hospital outcomes revealed an increased use of TAVR for bicuspid aortic valve, from 0.39% in 2011 to 4.16% in 2014, with a significantly decreased length of stay in the hospital.<sup>13</sup> During the same timeframe, vascular complications, need for blood transfusion, and requirement for open cardiac surgery have also declined after TAVR for bicuspid aortic valve.

Another review used the National Inpatient Sample database from 2012 to 2016 to compare outcomes of hospitalizations for TAVR versus SAVR for bicuspid

aortic stenosis and, in a secondary analysis, TAVR for bicuspid versus tricuspid aortic stenosis.<sup>20</sup> Compared with SAVR, TAVR in bicuspid aortic valves showed a higher incidence of complete heart block and permanent pacemaker insertion but similar in-hospital mortality. No difference was seen between TAVR and SAVR for cardiac arrest, cardiogenic shock, acute kidney injury, hemopericardium, tamponade, and acute stroke. Patients with older age, female sex, history of heart failure, chronic lung disease, chronic kidney disease, chronic liver disease, coronary artery disease, diabetes, and history of smoking were more likely to undergo TAVR for bicuspid aortic stenosis; patients with peripheral artery disease and obesity were more likely to be selected for SAVR for bicuspid aortic stenosis.

A more focused look into bicuspid aortic valve morphology was performed by Yoon et al in 2020.<sup>20</sup> They reviewed data from 1,034 CT-confirmed bicuspid aortic valve patients who underwent TAVR with new-generation devices (Sapien 3, Evolut R/Pro, etc.). Unlike previous studies, the CT images and bicuspid aortic valve morphology were analyzed and assessed by a central core laboratory. It was concluded that calcified raphe and excess leaflet calcification were independent predictors of 2-year all-cause mortality, and patients with both features had more frequent procedural complications. Additionally, both aortic root injury and moderate to severe paravalvular regurgitation increased in the presence of both predictors (from 1.7% to 4.5% and from 3.2% to 6.5%, respectively).

If bicuspid aortic valve anatomic characteristics are reviewed in detail, and in the absence of the highest-risk phenotype, TAVR with new-generation devices in intermediate- and low-risk patients is comparable to SAVR with similar risk profile.<sup>21</sup>

## CONCLUSION

TAVR in comparison with SAVR seems to be a safe and effective therapy in patients with severe bicuspid aortic valve stenosis in the absence of aortopathy and high-risk anatomic features. However, further clinical trials and prospective studies aimed at comparing SAVR with TAVR in low-risk patients are needed to have a better understanding of the long-term results of this growing technology. ■

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