Bicuspid aortic valve (BAV) has been identified as the most common heart valve anomaly and is considered to be a heritable disorder that affects various cardiovascular disorders, including aortopathy. Current topics regarding the clinical management of BAV including surgical strategies with or without concomitant aortic repair or replacement are attracting interest, in addition to the pathological and morphological aspects of BAV as well as aortopathy. However, surgical indications are still being debated and are dependent on current clinical guidelines and surgeons’ preferences. Although clinical guidelines have already been established for the management of BAV with or without aortopathy, many studies on clinical management and surgical techniques involving various kinds of subjects have previously been published. Although a large number of studies concerning the clinical aspects of BAV have been reviewed in detail, controversy still surrounds the clinical and surgical management of BAV. Therefore, surgeons should carefully consider valve pathology when deciding whether to replace the ascending aorta. In this review, we summarized current topics on BAV and the surgical management of diseased BAV with or without aortopathy based on previous findings, including catheter-based interventional management.

Keywords: bicuspid aortic valve, thoracic aortic aneurysm, aortic valve replacement, transcatheter aortic valve implantation, aortopathy

Introduction

Bicuspid aortic valve (BAV) is a common congenital cardiac malformation, with a reported incidence of between 0.6% and 2% in the general population.\(^1\) BAV has been identified as the main cause of aortic valve disease leading to surgical treatment in children and young adults. A large pathological survey revealed that BAV could result in a stenotic lesion in 75% of patients and insufficiency in 15%.\(^3\)

Although BAV is often considered to be a benign lesion early in life, the complications associated with cardiovascular diseases, including aortic stenosis (AS), aortic insufficiency (AI), infective endocarditis (IE), and aortic dilation and dissection, can result in marked increases in morbidity and mortality later in life.\(^4\)–\(^6\)

Understanding of aortic dilation associated with BAV has evolved with improvements in diagnostic technology and surgical management.\(^7\) There is a growing consensus that the ascending aorta should be replaced at the time of aortic valve replacement for bicuspid aortic valve even if it is only moderately dilated. A recent study that gathered information from a total of 100 Canadian cardiac surgeons reported that surgeons’ knowledge and attitudes toward BAV aortopathy influenced their surgical approaches. This large survey revealed significant gaps in the knowledge and attitudes of surgeons toward the diagnosis and management of BAV aortopathy, with approximately one third of cardiac surgeons stating that
they would replace an undersized ascending aorta.\textsuperscript{5} Therefore, surgeons need to be more aware of current aspects and knowledge related to BAV with or without aortopathy based on published evidence, including the various surgical techniques used for aortic valve repair and catheter-based interventional therapy.

### Pathophysiology, Morphology and Aortopathy of Bicuspid Aortic Valve

BAV is considered to be a heritable disorder with a significantly higher recurrence risk in first-degree relatives. An essential concept to avoid the risk of early death is that all-first-degree relatives undergo an echocardiographic follow-up at regular intervals regardless of the presence or absence of BAV.\textsuperscript{9} These genetic issues of BAV with other cardiovascular anomalies suggest that valve malformations can be primary to defective valvular disease or secondary to other elements of cardiovascular diseases.\textsuperscript{10} Concomitant aortopathy with BAV may also be prevalent in the relatives of BAV patients; therefore, screening for and detecting cardiovascular disease by echocardiography should be considered for these individuals.\textsuperscript{11}

Some biomedical materials such as the vascular matrix appear to be important in BAV patients. A deficiency in fibrillin-1 and increased matrix metalloproteinase (MMP) levels may result in aortic degeneration and dilatation. Both MMP-2 and MMP-9 are known to be involved in the turnover of elastic matrix components, and may affect the pathophysiology of and clinical implications for aortic degeneration and dilatation in patients with BAV.\textsuperscript{12,13} This mechanism has been suggested to play a role in the development of thoracic aortic aneurysms and morphological cusp fusion in BAV patients. This phenomenon may be more aggressive in BAV-associated ascending aorta dilatation in the right-left fusion type, and, thus, requires earlier surgical intervention.\textsuperscript{14}

The combination of mitral regurgitation due to myxomatous degeneration and BAV is sometimes recognized as having a large prolapsing anterior leaflet of the mitral valve and dilated aortic annulus with aortic insufficiency due to cusp prolapse. Toronto’s group reported that 1.8% of patients with BAV had anterior leaflet disease of the mitral valve.\textsuperscript{15} In an echocardiographic study of BAV by Schaefer and associates, the overall prevalence of myxomatous MV was 4.7% and varied according to the morphology of the aortic cups: its prevalence was 2.6% in the fused right and left cusp type and 13% in the fused right and non-coronary cusp type.\textsuperscript{16} Roberts et al. reported the combination of mitral valve prolapse and BAV, which is rare; however, a more detailed examination to detect mitral valve dysfunction is recommended for surgical BAV patients.\textsuperscript{17}

Sievers and associates attempted to establish a classification system based on 5 years of data collected from the surgical specimens of 304 patients. Three characteristics for a systematic classification were identified according to the number of raphes, spatial position of cusps or raphes, and functional status of the valve. Type 0 has no raphe, type 1 has 1 raphe, and type 2 has two raphes. The most prevalent type of BAV was shown to be type 1 with the left-right fused type.\textsuperscript{18} Angelini and co-workers reported a relationship between the number of sinuses, origin of the coronary artery, and number of leaflets in BAV patients, in whom wide variations were observed in the architecture of valves having two leaflets. Few BAV cases have had two leaflets supported by two sinuses.\textsuperscript{19}

The clinical guidelines for BAV with aortopathy revealed that the number of patients with BAV undergoing thoracic aortic surgery has markedly increased;\textsuperscript{20} therefore, cardiovascular surgeons should possess a scientific knowledge of BAV aortopathy and precise decision-making for its surgical management. As described previously, abnormal wall stress as a consequence of pathological transvalvular flow characteristics as well as cellular and extracellular abnormalities in the aortic walls of BAV patients contribute to BAV aortopathy. The relationship between coronary cusp fusion and a more severe degree of degeneration in the ascending aorta is a novel finding. Russo et al. examined 115 patients with diseased BAV, and found a correlation between the specific anatomy of BAV with the left-right fused type and a more severe degree of wall degeneration in ascending aortic dilatation of the aortic root at a younger age.\textsuperscript{21} Davies and colleagues reported a relationship between aortopathy and BAV anatomy in 70 BAV patients who had a higher rate of aortic growth than others, with even the incidence of rupture and dissection being similar.\textsuperscript{22} Fazel and co-workers classified the four patterns of aortic dilatation: cluster I: aortic root alone; cluster II: tubular ascending aorta alone; cluster III: tubular portion and transverse arch; and, cluster IV: aortic root and tubular portion with tapering across the transverse arch. They subsequently decided on a surgical strategy based on these patterns of aortic dilatation in BAV patients.\textsuperscript{23} Aortic 3-dimensional blood flow was analyzed to investigate altered ascending aorta hemodynamics in BAV patients and its relationship with differences in cusp fusion patterns and the expression of aortopathy. The presence and type of BAV fusion was associated with changes in regional wall stress.
distribution and systolic flow eccentricity. Aortic enlargement involving tubular portions of the ascending aorta was the most common phenotype of BAV aortopathy detected among the BAV patients examined.²⁴)

Current Guidelines for the Surgical Management for Bicuspid Aortic Valve and Concomitant Ascending Aortic Dilatation

Surgical strategies and the management of BAV with aortopathy according to several current clinical guidelines have been summarized in Table 1. The U.S. guidelines indicate surgical interventions to repair aortic sinuses or replace the ascending aorta in patients with BAV if the diameter of the aortic sinuses or ascending aorta is greater than 5.5 cm (Class I, Level of evidence B). Surgical interventions to repair the aortic sinuses or replace the ascending aorta are reasonable in patients with BAV if the diameter of the aortic sinuses or ascending aorta is greater than 5.0 cm and the risk of dissection is present (family history of AD or if the rate of the increase in diameter is over 0.5 cm per year (Class IIa, Level of evidence C)). Replacement of the ascending aorta is reasonable in patients with BAV who are undergoing aortic valve surgery because of severe AS or AR if the diameter of the ascending aorta greater than 4.5 cm (Class IIa, Level of evidence C).²⁵) According to the European guidelines published in 2012, concomitant surgery should be considered for high-risk patients with BAV complicated by aortic root disease, and the ascending aorta 5.0 cm or greater in diameter.²⁶) The Canadian guidelines published in 2014 stated that surgical interventions should be considered for this population when the size of the ascending aorta is between 5.0 and 5.5 cm, accounting for patient size, particularly in the presence of other risk factors.²⁷) In contrast, the Japanese clinical guidelines for surgical and interventional treatments of valvular heart diseases published in 2012 by the Japanese Circulation Society stated that an ascending aortic diameter over 4.5 cm for patients with BAV should be replaced (class I) in consideration of the small physiques of Japanese populations.²⁸) Furthermore, an ascending aortic diameter over 4.0 cm in patients with BAV should be considered for concomitant aortic replacement at AVR (class II) and dilatation of the ascending aortic diameter of over 0.5 cm per year should be also recommended for surgical interventions.

Aortic Events after Isolated Aortic Valve Replacement in Bicuspid Aortic Valve Patients

After initial primary isolated AVR in patients with BAV, BAV can be considered as a risk factor for late aortic events, AD, and the formation of aneurysms in the ascending aorta. The incidence of acute aortic events after isolated AVR is very low in BAV patients. However, Russo et al. reported high incidences of AD (10%) and ascending aortic aneurysms (6%), and consequently recommended prophylactic replacement even for a mildly enlarged ascending aorta.²⁹) Since a paradigm shift has been recognized in the clinical management of BAV aortopathy, surgical indications were stated as previously described because of the lower incidence of aortic complications following isolated aortic valve replacement in BAV patients without severe aortopathy.

Table 1  Current clinical guidelines for the surgical management of bicuspid aortic valve with aortopathy

<table>
<thead>
<tr>
<th>Guideline</th>
<th>Year (version)</th>
<th>The size of surgical indication for concomitant aortic replacement for AA</th>
<th>Class of evidence</th>
<th>Level of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>AHA/ACC²⁵)</td>
<td>2014</td>
<td>5.5 cm</td>
<td>I</td>
<td>B</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5.0 cm or family history of AD or the rate of increase in diameter ≥0.5 cm per year</td>
<td>IIa</td>
<td>C</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4.5 cm in patients undergoing AVR because of severe AS or AI</td>
<td>IIa</td>
<td>C</td>
</tr>
<tr>
<td>ESC/EACTS²⁶)</td>
<td>2012</td>
<td>5.0 cm</td>
<td>IIa</td>
<td>C</td>
</tr>
<tr>
<td>Canada²⁷)</td>
<td>2014</td>
<td>5.0~5.5 cm</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>JCS (Japan)²⁸)</td>
<td>2012</td>
<td>4.5 cm</td>
<td>I</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4.0 cm</td>
<td>IIa</td>
<td>N/A</td>
</tr>
</tbody>
</table>

Recent studies have consistently reported low incidences of aortic events following AVR in patients with BAV, as shown in Table 2. Among 153 consecutive patients with BAV stenosis, only 3% of patients were required aortic surgery due to progressive aortic aneurysm, in which previously recognized concomitant ascending aortic dilatation of 40–50 mm at initial isolated AVR. Following 15 years clinical experience after isolated AVR, there was no aortic dissection or rupture, and a markedly lower risk of adverse aortic events.\(^{30}\) In a large-scale study with 1286 patients over a median follow-up of 12 years, there were only 1% documented cases of AD, 0.9% of ascending aortic replacements, and 9.9% of progressive aortic enlargement.\(^{31}\) Apart from these findings, aortic events involving AD and the formation of aneurysms were very low incidence after AVR with BAV.\(^{32,33}\) Therefore, the routine and prophylactic replacement of a mildly dilated ascending aorta may not be recommended because of the uncommon incidence of reoperation after primary AVR in BAV patients.\(^{34,35}\)

**Clinical Outcomes and Durability of Bicuspid Aortic Valve Repair**

Aortic valve repair avoids anticoagulation and prosthetic valve-related complications could provide many advantages for patients with BAV. Various techniques have been described for the repair of BAV including resection of the flail segment of the prolapsing leaflet, annuloplasty, and resection of the raphe. However, the durability of diseased BAV repair has been questioned with long-term clinical outcomes and durability being suspected and debated. Fraser Jr and associates examined 72 consecutive patients who underwent leaflet resection, and showed that freedom from aortic valve reoperation probabilities at 12 and 24 months were 94% and 89.5%, respectively.\(^{36}\) Cosgrove and co-workers reported that 75% had BAV and aortic valve repair for aortic cusp prolapse effectively eliminated AI without causing AS among the 28 consecutive patients examined who underwent aortic valvuloplasty for AI caused by leaflet prolapse.\(^{37}\) Following the initial surgical efficacy of BAV repair, Kari et al. performed concomitant cusp repair by cusp-free margin shortening to correct prolapse. By using this surgical manipulation, the freedom from reoperation was 90% at 6 years, while freedom from AR of more than grade 2 was 100%.\(^{38}\) The reconstruction of BAV with AI is another technique that has been performed for over 10 years; however, information regarding long-term results remains limited. With a follow-up now reaching up to 13 years and a larger patient cohort, reconstruction of BAV can be performed reproducibly with good early results, freedom from reoperation at 5 and 10 years were 88% and 81%,\(^{39}\) Boodhwani et al. presented their 13 years of experience with a functional and systematic approach to BAV repair. At the 5- and 8-year follow-ups, freedom from aortic valve reoperation were 94% and 83%, respectively. The repair of bicuspid valves for AI was found to be a feasible and attractive alternative to mechanical valve replacement in young patients.\(^{40}\) The most recent novel studies reported that BAV repair was likely to be safe and durable with low mortality, a low prevalence of reoperation, and good long-term survival.\(^{41,42}\)

Ozaki et al. had recently developed a unique and novel technique for original aortic valve reconstruction with an autologous pericardium and described the surgical treatment of BAV with original aortic valve reconstruction using a harvested pericardium treated with 0.6% glutaraldehyde solution. Tricuspidization provided good opening and closure of the aortic valve with excellent hemodynamics by encircling the aorta with a felt strip at the level of the commissure, which prevented future dilatation of the aorta at the commissure level.\(^{43,44}\) They also showed that original aortic valve reconstruction was feasible for patients aged less than 60 years in 57 patients with bicuspid

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**Table 2** Aortic events following initial isolated aortic valve replacement in patients with bicuspid aortic valve

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>No. of cases</th>
<th>Mean follow-up (years)</th>
<th>AD</th>
<th>AAR</th>
<th>Other events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Girdauskas</td>
<td>2012</td>
<td>153</td>
<td>11.5</td>
<td>0 (0%)</td>
<td>5 (3%)</td>
<td>N/A</td>
</tr>
<tr>
<td>McKeller</td>
<td>2010</td>
<td>1286</td>
<td>12</td>
<td>13 (1%)</td>
<td>11 (0.9%)</td>
<td>Progressive aortic</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>replacement: 127 (9.9%)</td>
</tr>
<tr>
<td>Goland</td>
<td>2007</td>
<td>252</td>
<td>8.9</td>
<td>N/A</td>
<td>1 (0.4%)</td>
<td>N/A</td>
</tr>
<tr>
<td>Borger</td>
<td>2004</td>
<td>201</td>
<td>10.3</td>
<td>1 (0.5%)</td>
<td>7 (3.5%)</td>
<td>N/A</td>
</tr>
<tr>
<td>Russo</td>
<td>2002</td>
<td>50</td>
<td>19.5</td>
<td>5 (10%)</td>
<td>3 (6%)</td>
<td>Sudden death: 7 (14%)</td>
</tr>
</tbody>
</table>

AD: aortic dissection; AAR: ascending aortic replacement (required reoperation cases); N/A: not applicable
valves, and freedom from reoperation was 98.9% with 76 months of follow-up. Doss et al. reported similar techniques, but the report discussed whether or not repair of secondary valve lesions and small valve coaptation was possible. The pericardial patch augmentation technique, which was performed on 16 patients, increased the coaptation surface, and consequently provided reliable early competence of reconstructed BAV with triangular resection of the prolapse and direct suturing of the edges of the fused leaflet. Pretre et al. described 12 patients with tricuspidization of the valve, which this unique crown-like annulus improved coaptation of the cusps and could lead to more reliable outcomes.

A previous study reported that root stabilization with the reimplantation technique appeared to significantly improve the durability of repaired BAV over that with subcommissural annuloplasty. In BAV repair, root replacement with the reimplantation technique stabilized the ventriculooaortic junction, thereby improving valve morbidity with a low gradient, and has been associated with improved outcomes. In contrast, although progressive ascending aortic dilatation after AVR for BAV is well documented, progressive dilatation of nonreplaced sinuses no subsequent aortic event has occurred. Separate valve and graft repair remains a reasonable surgical option in the setting of AVR for BAV with ascending aortic dilatation provided the sinuses of Valsalva are not significantly enlarged.

### Clinical Potential on Transcatheter Aortic Valve Implantation for Bicuspid Aortic Valve

BAV is generally considered to contraindicate transcatheter aortic valve implantation (TAVI) because of the poor stability of the prosthetic valve or paravalvular regurgitation due to distortion of the native valve leaflets. Although several novel series have been reported including case reports on TAVI in BAV patients, little is known about the biomechanical requirements for TAVI in the setting of BAV disease. Acceptable outcomes may depend on anatomical features, such as the extent and location of valve calcification, bulky leaflets, and an enlarged root. An enlarged root may increase the risk of transcatheter heart valve displacement, distortion, or malfunctioning. One of the main reasons for this is the presumed risk of residual aortic regurgitation (AR) and a higher rate of relevant AR over grade 2 after TAVI was identified among patients with BAV. In addition, it is difficult to dilate the bicuspid valve into a completely circular shape due to the morphology of BAV itself. Therefore, the Medtronic Core Valve

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>No. of cases</th>
<th>Country</th>
<th>Device</th>
<th>Access route</th>
<th>Prosthetic shape</th>
<th>Mean PG (mmHg)</th>
<th>AR (≥2+)</th>
<th>Follow-up (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bauer et al.</td>
<td>2014</td>
<td>38</td>
<td>Germany</td>
<td>ES:12 MCV:26</td>
<td>TF:31, TA:6</td>
<td>N/A</td>
<td>5.5</td>
<td>9 (25%)</td>
<td>N/A</td>
</tr>
<tr>
<td>Kochman et al.</td>
<td>2014</td>
<td>28</td>
<td>Poland</td>
<td>ES:5 MCV:23</td>
<td>TF:22, TA:3</td>
<td>N/A</td>
<td>10.3</td>
<td>6 (22%)</td>
<td>11.4</td>
</tr>
<tr>
<td>Costopoulos et al.</td>
<td>2014</td>
<td>21</td>
<td>Italy</td>
<td>ES:8 MCV:13</td>
<td>TA:1 TF:13, TA:5</td>
<td>N/A</td>
<td>10.0</td>
<td>4 (19%)</td>
<td>8</td>
</tr>
<tr>
<td>Hayashi et al.</td>
<td>2013</td>
<td>21</td>
<td>France</td>
<td>ES:11 MCV:10</td>
<td>TA:5 TF:14, TA:1</td>
<td>Elliptical</td>
<td>10.8</td>
<td>10.6</td>
<td>Central 13.4</td>
</tr>
<tr>
<td>Himbert et al.</td>
<td>2012</td>
<td>15</td>
<td>Canada</td>
<td>ES:11 MCV:15</td>
<td>TA:5 TF:7, TA:4</td>
<td>Circular</td>
<td>13.4</td>
<td>3 (27%)</td>
<td>N/A</td>
</tr>
<tr>
<td>Wijesinghe et al.</td>
<td>2010</td>
<td>11</td>
<td>Canada</td>
<td>ES:11 MCV:12</td>
<td>TA:5 TF:7, TA:4</td>
<td>Circular</td>
<td>13.4</td>
<td>3 (27%)</td>
<td>N/A</td>
</tr>
</tbody>
</table>

*Author did not state the degree of aortic valve regurgitation applicable.*
system (MCS), which incorporates a balloon-expandable valve, has been suggested due to sufficient radial strength for a bicuspid valve.\textsuperscript{53,54} Himbert et al. documented 15 cases of BAV using the MCS, with acceptable short-term hemodynamic and clinical improvements.

Another concern regarding postoperative complications associated with TAVI for BAV is AR with or without paravalvular leakage because of its specific anatomical characteristics. They identified several factors that precluded the use of TAVI in patients with BAV:\textsuperscript{54} (1) the high frequency of larger aortic annular diameters, which is not suitable for currently available transcatheter valves, (2) increased risks of paravalvular AR and annular rupture, and (3) associated lesions of the ascending aorta. Heavily calcified elliptic bicuspid valves are also considered to be a contraindication to TAVI because of the risk of stent-valve displacement, distortion, or malfunctioning. The elliptic shapes of the bicuspid valve annulus, together with the presence of asymmetric heavy calcifications, are known to be important factors when attempting to achieve a good stent-valve position, deployment, and functioning. Delgado et al. advocated the efficacy of MDCT for TAVI in BAV patients, in which MDCT could provide exact information on aortic valve anatomy with accurate sizing of the aortic annulus, the length of the coronary cusp, and relationship between the coronary ostia and aortic annulus.\textsuperscript{55} Although O’Sullivan et al. showed the implications of BAV for TAVI including case reports and current series,\textsuperscript{56} we here summarized clinical series of the early outcomes of TAVI for BAV with the most recently published studies in Table 3.\textsuperscript{52–54,57–59} Close preoperative and intraoperative analyses of the aortic valve anatomy are mandatory for successful TAVI in BAV cases. Further studies are needed to confirm the feasibility of implanting commercially available stent valves into selected bicuspid AS, and mid-term and long-term echocardiographic studies are mandatory in order to obtain more information on stent functioning in BAV in terms of stress, durability, leaflet tears, deterioration, dislodgement, malfunctioning, early stenosis, or paravalvular leaks.

**Conclusion**

Bicuspid aortic valve is a genetic and heritable disorder associated with various cardiovascular diseases including aortopathy showing ascending aortic dilatation. Surgical management has been established by the current clinical guidelines, and concomitant aortic repair should be considered if a dilated aorta is detected.

**Conflict of Interest**

There is no conflict of interest to declare.

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