Bicuspid aortic valve – state-of-the-art

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ABSTRACT

Bicuspid aortic valve (BAV) is the most frequent congenital valve disease. Currently, due to proven correlation between BAV and severe complications, including death, it is thought to be an important clinical issue. The review aims to summarize the current state of knowledge about BAV. Based on available literature, BAV epidemiology, morphology, genetics, diagnostic criteria, screening in relatives and most common complications have been described. BAV can be associated with both valve disease and aortic disease, thereby leading to increased morbidity and mortality. Additionally, significant part of the article reviews the mechanisms of formation, phenotypes and treatment of aortic aneurysm in patients with BAV.

KEYWORDS valvular heart disease, congenital defects, aorta

INTRODUCTION

Bicuspid aortic valve (BAV) is the most common congenital cardiac anomaly.1,2 Probably the first to ever visualize BAV was Leonardo da Vinci during his studies in the XVI century. Currently, due to proven correlation between BAV and severe complications, including death, it is thought to be the important clinical issue. In recent years, BAV has gained increasing interest in research and treatment.

EPIDEMIOLOGY

The estimated prevalence of BAV is 0.5 – 2% of the general population, with strong male predominance – 3:1.1,2 There are differences in the prevalence of BAV in available publications. The Table 1 shows the prevalence of BAV based on the current literature.

Most BAV cases occur sporadically. However, according to Huntington and colleagues, familial BAV has been reported with the prevalence in first-degree relatives of affected individuals being as high as 9%, suggesting an autosomal dominance pattern with reduced penetrance.3

The BAV may appear as an isolated defect or associated with other congenital cardiovascular anomalies, such as:

- coarctation of the aorta4
- ventricular septal defects5
- patent ductus arteriosus6,7
- atrial septal defect8
- hypoplastic left heart syndrome (HLHS)7,9
- mitral valve disease (mitral valve prolapsed or congenital mitral stenosis)10,11
- Ebstein’s anomaly6
- tetralogy of Fallo6
- left ventricular noncompaction12 and others.

The most common of them is coarctation of the aorta. Of patients with coarctation, approximately 50% to 85% have BAV.13,14

Furthermore, there are number of syndromes whose cardiac involvement includes BAV: Andersen syndrome, familial TAAD, Marfan syndrome, Turner syndrome, Shone’s complex and Williams syndrome.15–17

Moreover, coronary artery anomalies occur in patients with BAV more frequently than in the general population. The length of the left main coronary artery is significantly shorter than in normal in up to 90% of cases.18 There have been reports of anomalous origins of the left circumflex coronary artery and single left coronary artery.19 These variations are important considerations for ischemic heart disease.

MORPHOLOGY

The bicuspid valve is composed of two leaflets, of which one is usually larger.20,21 Structurally, BAV is heterogeneous, depending on the pattern of valve leaflet fusion:
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- type I - fusion of the right and left coronary cusp resulting in anterior – posterior commissural orientation,
- type II - fusion of the right and non-coronary cusp resulting in right and left commissural orientation,
- type III - fusion of the left and non-coronary cusp.

The most common pattern, accounting for about 75% of BAV cases, is type I. Table 2 shows type of BAV frequency based on the available literature. Type I is more common in males while type II is more common in females.

There are also other, less popular classifications of BAV. Sievers and Schmidtko attempted to establish a classification system based on a 5-year data collection of 304 surgical specimens. They reported the three characteristics required for BAV classification: number of raphes, spatial position of cusps or raphes, and functional status of the valve (presented in Table 3).

Three major types were identified:
- type 0 (no raphe),
- type 1 (one raphe),
- and type 2 (two raphes) and 24 subcategories of potential BAV configuration types.

Most frequently, BAV with one raphe was identified (type 1, n = 269) and only 21 patients had a ‘purely’ BAV with no raphe (type 0).

There were only a few cases of BAV with a double raphe described in the current literature. It is proven that there is a relation between pathogenesis, morphology and clinical manifestation of BAV, as shown in Table 4. Many scientific studies have been performed to evaluate the BAV formation. To our knowledge, there is enough evidence to decide that the type I and II of BAVs have different etiological entities.

Sieveld and colleges, based on animal models, suggest that type II of BAVs is caused by a defective formation of the outflow tract cushions, probably caused

<table>
<thead>
<tr>
<th>Author(s)</th>
<th>Study population (n)</th>
<th>BAV prevalence (%)</th>
<th>Male/Female</th>
</tr>
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<tbody>
<tr>
<td>Lewis and Grant</td>
<td>215</td>
<td>1.39</td>
<td>3:1</td>
</tr>
<tr>
<td>Wauchope</td>
<td>9966</td>
<td>0.5</td>
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<p>| Table 1 The prevalence of bicuspid aortic valve based on the current literature. |
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Table 2 The type of bicuspid aortic valve frequency based on the available literature.

<table>
<thead>
<tr>
<th></th>
<th>Type I</th>
<th>Type II</th>
<th>Type III</th>
</tr>
</thead>
<tbody>
<tr>
<td>R-L</td>
<td>152</td>
<td>39</td>
<td>1</td>
</tr>
<tr>
<td>R-NC</td>
<td>799</td>
<td>320</td>
<td>16</td>
</tr>
<tr>
<td>L-NC</td>
<td>85</td>
<td>28</td>
<td>2</td>
</tr>
<tr>
<td>John S. Ikonomidisi et al.</td>
<td>31</td>
<td>9</td>
<td>6</td>
</tr>
<tr>
<td>Alberto Forteza et al.</td>
<td>45</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Sabet HY et al.</td>
<td>270</td>
<td>37</td>
<td>8</td>
</tr>
<tr>
<td>Ilenia Foffa et al.</td>
<td>7</td>
<td>2</td>
<td>0</td>
</tr>
</tbody>
</table>

Total number of patients: 1863

R-L: right-coronary and left-coronary leaflet fusion; R-NC: right-coronary and non-coronary leaflet fusion; L-NC: left-coronary and non-coronary leaflet fusion.

Table 3 Sievers’ bicuspid aortic valve type for Stanford Valve-sparing Aortic Root Replacement [based on Sievers et al.23].

Three major types were identified:
- type 0 (no raphe),
- type 1 (one raphe),
- and type 2 (two raphes) and 24 subcategories of potential BAV configuration types.

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It is proven that there is a relation between pathogenesis, morphology and clinical manifestation of BAV, as shown in Table 4. Many scientific studies have been performed to evaluate the BAV formation. To our knowledge, there is enough evidence to decide that the type I and II of BAVs have different etiological entities.

Sieveld and colleges, based on animal models, suggest that type II of BAVs is caused by a defective formation of the outflow tract cushions, probably caused.
by an exacerbated nitric oxide-dependent epithelial-to-mesenchymal transformation. Furthermore, type I of BAV is the result of an anomalous embryonic outflow tract septation, presumably produced by alterations in neural crest cell behavior. However, it needs to be emphasized that there is increasing evidence of redox stress and inflammatory activation for type I, and of predominant endothelial dysfunction for type II. According to the authors, this conclusion can be extended to humans. In their opinion, this can be done because human, mouse, and hamster AVs are morphologically equivalent and the normal valve morphogenesis is similar in both rodent species and humans.

Other researchers consider BAV morphology to be highly correlated with clinical manifestation. A retrospective review of 1135 patients with BAV has shown that type I was more often associated with aortic coarctation, left heart defects (HLHS, Shone’s syndrome, mitral stenosis, left ventricular outflow tract obstruction) and less AV pathology, whereas type II of BAV was associated with more significant AV pathology. This study showed that patients with type II of BAV had more than twice the risk of aortic stenosis and regurgitation compared with other types of BAV.

Calloway and colleagues proved that there is a significant interaction between BAV morphology and age in predicting AV disease risk (Fig. 1). Type II of BAV is more likely to manifest aortic valve disease (AVD) in childhood, while type I of BAV is likely to manifest AVD in adulthood.

Mutations in a gene called NOTCH1 are noticed in people with BAV. The Notch signaling pathway is highly conserved and plays a critical role in cell differentiation during organogenesis. NOTCH1 transcripts are abundant in the mesenchyme of the outflow tract and the developing AV leaflets, what probably underlies the role of Notch signaling in AV development. Inhibition of NOTCH1 signaling down-regulates Sox9 expression and promotes valvular calcification in vitro.

Probably, the next reason for BAV is reduced endothelial nitric oxide synthase (eNOS) production, which is caused by mutation in NOS3 gene. Fernandez et al. suggest a mechanism whereby NOS3 deficiency results in abnormalities in endocardial generation of mesenchyme (EMT), which leads to failure informing separate precursor cushions for the right and non-coronary leaflets.

Moreover, eNOS-produced nitric oxide (NO) is also believed to play a role in aneurysm formation.

It seems that Gata5 appears to regulate at least 2 pathways involved in differentiation of endocardial cells, namely, Tbx20 and Notch. The data suggest that absence of Gata5 results in defective valve morphogenesis and BAV formation. It was confirmed in in vivo and in vitro studies.

Furthermore, mutations in ACTA2 gene on chromosome 10q, which encode smooth muscle α-actin, cause thoracic aortic aneurysm and, in some instances, BAV.

A lot of other genes have been implicated in the etiology of BAV, they are listed in Table 5.

### GENETICS

While the heritability of BAV is now well established, genes linked to the defect remain largely unknown. Genetic heterogeneity in BAV is demonstrated by the involvement of mutations in diverse genes encoding transcription factors, extracellular matrix proteins, and signaling pathways that regulate cell proliferation, differentiation, adhesion, or apoptosis.

### DIAGNOSIS

The mainstay of diagnosis is echocardiography (trans-thoracic or transesophageal (TEE)), which can provide a definitive diagnosis in most patients (sensitivity – 92%, specificity – 96%). The parasternal short axis view allows for direct visualization of the valve cusps. In this view, the normal triangular opening shape is lost, becoming more ‘fish mouth’ like in appearance, more

### Table 4  Relation between pathogenesis, morphology and clinical manifestation of bicuspid aortic value.

<table>
<thead>
<tr>
<th>Pathogenesis</th>
<th>Oxidative stress and mediators of inflammation(^{25})</th>
<th>Formed during embryonic outflow tract septation(^{25})</th>
<th>Endothelial dysfunction(^{25})</th>
<th>Formed before embryonic outflow tract septation(^{25})</th>
<th>GATA 5 and Alk2 mutations(^{108,109})</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphology</td>
<td>Type I of BAV</td>
<td>Type II of BAV</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical manifestation</td>
<td>Coarctation of the aorta(^{106})</td>
<td>Aortic stenosis(^{106})</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Left heart defects (HLHS, Shone’s syndrome, mitral stenosis, left ventricular outflow tract obstruction)(^{106})</td>
<td>Aortic regurgitation(^{106})</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>AVD in adulthood(^{27})</td>
<td>AVD in childhood(^{27})</td>
<td></td>
<td></td>
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</tr>
<tr>
<td></td>
<td>Aortic root dilatation and asymmetric dilatation of the ascending aorta(^{34})</td>
<td>Dilatation of the ascending aorta (without root) and aortic arch(^{34})</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Higher shear stress along the aortic wall(^{110})</td>
<td>Higher incidence in males(^{22})</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Higher incidence in males(^{22})</td>
<td></td>
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</tbody>
</table>

BAV: bicuspid aortic valve; HLHS: hypoplastic left heart syndrome; AVD: aortic valve disease.
akin to the mitral valve. This is especially pronounced in systole, as in diastole the raphe can appear like a commissure of the third cusp. Furthermore, domed relief of cusps in systole and abnormally coaptation are observed on the parasternal long axis view.

The diagnostic accuracy of echocardiography in detecting BAV is good, but is less reliable when the leaflets are moderately or severely calcified or when AV stenosis is present. Zegdi and colleagues suggest that TEE color Doppler analysis might improve the accuracy of diagnosing BAV by standard TEE (sensitivity 95.5%, specificity 96.2% vs. 85% and 88%).

The bicuspid aortic valve may be accompanied by other aortopathies, which are not always detected by echocardiography. Therefore, computed tomography and cardiac magnetic resonance are used to augment the diagnostic process.

A recent study of 123 patients with confirmed BAV found that 10% of the patients were misidentified as having a tricuspid AV (TAV) using transthoracic echo and 28% had a nondiagnostic study, in comparison to 4% being misidentified as having a tricuspid valve by cardiac magnetic resonance and 2% having a nondiagnostic study. In 2002, Thiene and coworkers reported the possibility that echocardiography might not be able to correctly differentiate a bicuspid valve with a median cleft (simulating a rudimentary commissure) from a true tricuspid valve.

Finally, echocardiography remains the gold standard for the diagnosis of BAV considering the high cost of cardiac magnetic resonance.

**SCREENING IN RELATIVES**

Because of BAV strong familial association, screening programs seem to be necessary.

According to 2010 ACC/AHA Guidelines for the Diagnosis and Management of Patients with Thoracic Aortic Disease:

- First-degree relatives of patients with BAV, premature onset of thoracic aortic disease with minimal risk factors, and/or a familial form of thoracic aortic aneurysm and dissection should be evaluated for the presence of BAV and asymptomatic thoracic aortic disease (Class I, Level of Evidence: C).
- All patients with BAV should have both the aortic root and ascending thoracic aorta evaluated for

<table>
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<th>Gene</th>
<th>Gene name</th>
<th>Chromosome</th>
<th>Human disease</th>
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<td>Turner syndrome</td>
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<tr>
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<td>5,9,13,15,18</td>
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</tr>
<tr>
<td>ACTA2</td>
<td>α-smooth muscle actin</td>
<td>10</td>
<td>Familial aortic aneurysm, Type 6</td>
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<tr>
<td>AXIN1</td>
<td>Axin-1</td>
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<td>BAV</td>
</tr>
<tr>
<td>ELN</td>
<td>Elastin</td>
<td>7</td>
<td>Cutis laxa/BAV</td>
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<tr>
<td>ENG</td>
<td>Endoglin</td>
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<td>Hereditary haemorrhagic telangiectasia</td>
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<td>FBN1</td>
<td>Fibrillin-1</td>
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</tr>
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<td>FGF8</td>
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</tr>
<tr>
<td>GATA5</td>
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<td>BAV</td>
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<tr>
<td>GATA6</td>
<td>GATA binding protein 6</td>
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<td>ASD and BAV</td>
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<td>HOXA1</td>
<td>Homeobox A1</td>
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<td>BAV</td>
</tr>
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<td>JAG1</td>
<td>JAGGED1</td>
<td>20</td>
<td>Alagille syndrome; tetralogy of Fallot</td>
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<td>KCNJ2</td>
<td>Potassium inwardly rectifying channel J2</td>
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<td>Andersen syndrome</td>
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<td>NKX2.5</td>
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<td>HLHS</td>
</tr>
<tr>
<td>NOS3</td>
<td>Endothelial nitric oxide synthase</td>
<td>7</td>
<td>BAV</td>
</tr>
<tr>
<td>NOTCH1</td>
<td>NOTCH1</td>
<td>9</td>
<td>BAV</td>
</tr>
<tr>
<td>PDIA2</td>
<td>Protein disulphide isomerase A2</td>
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<td>BAV</td>
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<tr>
<td>TGFB1</td>
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<td>Loeys–Dietz syndrome/sporadic BAV</td>
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<tr>
<td>UFD1L</td>
<td>Ubiquitin fusion degradation 1 like</td>
<td>22</td>
<td>BAV</td>
</tr>
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BAV: bicuspid aortic valve; ASD: atrial septal defect; HLHS: hypoplastic left heart syndrome.
Bicuspid aortic valve

In patients with Turner syndrome with additional risk factors, including BAV, coarctation of the aorta, and/or hypertension, and in patients who attempt to become pregnant or who become pregnant, it may be reasonable to perform imaging of the heart and aorta to help determine the risk of aortic dissection (Class IIb, Level of Evidence: C).

Furthermore, according to current AHA/ACC Guidelines for the Management of Patients With Valvular Heart Disease, many valve experts also recommend imaging screening all first-degree relatives of patients with BAV, especially if the patient has an associated aortopathy or a family history of valvular heart disease or aortopathy. On the other hand, they do not yet have data addressing the possible impact of screening on outcomes or the cost-effectiveness of this approach.

ESC 2014 Guidelines on the diagnosis and treatment of aortic diseases have the same view. Because of familial occurrence, screening of first-degree relatives should be considered (Class IIa, Level of Evidence: C).

CLINICAL MANIFESTATION

Currently, due to proven correlation between BAV and severe complications, including death, it is thought to be the important clinical issue. Although, the clinical presentation of patients with BAV can vary from severe valve disease in infancy to asymptomatic valve disease in old age, symptoms typically develop in adulthood. There is increasing awareness that patients with BAVs are at high risk for cardiovascular complications such as AV dysfunction, infective endocarditis, ascending aortic aneurysm and aortic dissection. Despite these complications, large series have confirmed that survival in asymptomatic adults with BAV is not shortened when compared with the general population.

Most patients with functionally normal BAV are asymptomatic and are diagnosed incidentally on echocardiography or when a systolic ejection sound or murmur is noted. However, Demir revealed significant LV diastolic and systolic dysfunction in subjects with BAV in the absence of significant valvular disease. His findings are hypothesis generating and verification using prospective studies is needed.

Thoracic aortic disease

Bicuspid aortic valve is associated with high risk of dilatation of the ascending aorta. A number of studies have shown that aortic diameter is larger generally in patients with BAV compared to those with normal tricuspid valves. Furthermore, retrospective cohort study included 416 consecutive patients with definite BAV diagnosed by echocardiography, proved that the 25-year risk of aneurysm formation is 26% and the risk of aortic dissection is approximately 8 times higher than in the general population.

Mechanisms of aortic aneurysm formation

There is a clear association between BAV and thoracic aortic aneurysm (TAA), however the nature of this relationship is still unknown. Generally, there are two theories of aortic aneurysm development in patients with BAV:

- the hemodynamic theory - aortic wall degeneration is caused by the abnormal post-valvular flow. It is possible then that these eccentric flow patterns may in turn lead to a differential distribution of aortic wall shear stress and subsequent flow-induced vascular remodeling of the aortic wall.
- the genetic theory - arterial wall fragility is caused by still unidentified genetic defect.

There are many evidences for hemodynamic theory of aortic aneurysm development:

- strong correlation between the degree of restriction in the conjoint cusp systolic motion (called ‘conjoint cusp opening angle’) and the severity and growth rate of the ascending aortic dilatation.
- correlation between the type of BAV with resulting eccentric transvalvular blood flow and the location of aortic aneurysm. The type I is more often associated with aortic root dilatation and asymmetric dilatation of the ascending aorta. In contrast, dilatation of the ascending aorta (without root) and aortic arch is typical for the type II.
- shear stress by way of friction on the endothelial surface, with cellular signaling cascades resulting in increased expression of matrix metalloproteinases (MMPs) and growth factors that affect matrix degradation and vascular smooth muscle cell (VSMC) apoptosis. According to in vivo studies it plays a role in pathogenesis of aortic aneurysm.
- dilatation is mainly observed on the proximal part of the aorta.
- dilatation of an initial aortic diameter can also occur in patients with abnormal TAV.
The arguments in favor of the genetic theory:

- Progression of aortic dilation in children with a functionally normal BAV excludes the hemodynamic effect as the only factor of aneurysm development.\(^{59-61}\)
- Progression of aortic dilatation is also observed in patients who underwent replacement of the aorta.\(^{62,63}\)
- Patients with BAV stenosis have larger ascending aorta diameter than patients with TAV stenosis.\(^{64}\)
- There are histological abnormalities of the ascending aorta wall in patients with BAV regardless of aortic dilatation. These changes are like those observed in patients with Marfan syndrome and they include: elastin fragmentation, cystic medial necrosis, increased amount of collagen, accumulation of mucopolysaccharides and apoptosis of VSMC.\(^{58,65}\)
- Coexistence of main pulmonary artery dilatation and BAV may result from a common developmental exposure as both originate from the embryologic conotruncus, caused by genetic defects.\(^{66,67}\)

Based on these, a combined development mechanism is likely, with genetically determined aortopathy and altered hemodynamics in the ascending aorta.

Hypothesis supported by many experiments are presented below:

- Fibrillin-1 content was reduced in BAV aortas compared with that seen in TAV aortas.\(^{66,68}\) Reduced fibrillin-rich microfibrils dissociated smooth muscle cells from elastic laminae and stimulated the cells to increase constitutive MMP activity and undergo apoptotic cell death. It might result in aortic degeneration and dilatation. Studies to date have not proven that fibrillin deficiency in patients with BAV is a primary genetic defect as can be seen in Marfan syndrome.\(^{69}\)
- Some researchers noticed that tissue samples from ascending aortic aneurysms with BAV have increased activity and expression of proteolytic enzymes known as MMPs (mainly MMP2 and MMP9) compared with aneurysms from patients with TAV. Tissue inhibitors of metalloproteinase (TIMP) lose their ability to control MMPs that affect matrix degradation.\(^{65}\) Wilton and colleagues proved that ratio of MMP2/TIMP1 in ascending aorta is greater in patients with BAV than in patients with normal TAV.\(^{70}\) The results of LeMaire’s observation were very similar if goes about ratio of MMP2/TIMP2.\(^{71}\) Ikonomidis and colleagues suggest that aortic aneurysms with each BAV morphology group possess unique signatures of MMP and endogenous tissue inhibitors. Moreover, the results suggest that the type I of BAV may be more aggressive and may justify an earlier surgical intervention.\(^{26}\)
- In contrast, in Abaci’s study of 112 patients with BAV, MMP-2 and 9 levels were not relevant for aortic dilatation.\(^{72}\) The reason of different results of these studies is unknown. It may result from small cohorts and technical problems with measuring MMP activity.
- Wagsater and colleagues studied collagen homeostasis in nondilated and dilated aorta segments from 69 patients with BAV and from 40 patients with TAV as reference. Biochemical and morphological analyses of collagen and analyses of mRNA expression demonstrate an impaired biosynthesis and posttranslational modification of collagen in aortas of patients with BAV. Their results may explain the increased aortic aneurysm formation in BAV patients.\(^{73}\)
- In aneurysm tissue from patients with BAV and Marfan’s syndrome increase transforming growing factor (TGF) β, AngII receptor and Smad3 expression was observed, what confirmed the meaning of these proteins as a possible pathogenic factors in aneurysm disease. So, losartan-mediated reduction in TGF-β expression and the cytoplasmic localization of Smad3 support a role for AT1R antagonism in the inhibition of aneurysm progression.\(^{74,75}\)

**Aneurysm phenotypes**

There are variable aneurysm phenotypes encountered in BAV. Fazel and coworkers from Stanford analyzed 64 BAV patients and described 4 patterns (Fig. 2) of aortic dilatation:\(^{57}\)

- cluster I, aortic root alone (\(n = 8, 13\%\));
- cluster II, tubular ascending aorta alone (\(n = 9, 14\%\));
- cluster III, tubular portion and transverse arch (\(n = 18, 28\%\));
- cluster IV, aortic root and tubular portion with tapering across the transverse arch (\(n = 29, 45\%\)).

The most common portion to dilate is the tubular ascending aorta with the fastest growing rate in adults (~0.4–0.6 mm/y), irrespective of BAV morphology and function.\(^{76,77}\) Furthermore, root dilatation phenotype is less common but is more often associated with type I BAV morphology and male sex.\(^{76}\) This root phenotype has been associated with faster tubular-ascending aorta dilatation and aortic regurgitation is, in turn, related to faster root dilatation and also with a higher risk of aortic dissection in a limited BAV subgroup.\(^{78}\)

Similar results were seen in the study of Sievers and Schmidtke. Aortic aneurysms (diameter 5 cm) were present in 90 (29.6\%) patients, with involvement
of the aortic root in 18 (5.9%), ascending aorta in 88 (28.9%), aortic arch in 2 (0.7%), and descending aorta in 1 (0.3%). Moreover, a significantly higher proportion of aneurysms of the ascending aorta was present in BAV type 2 (valve with two raphes) (Fig. 3).23

The age is judged to be the most likely risk factor for progression of aortic aneurysm. Aortic root size itself is related to valve morphology and the presence of significant disease of AV.2 Aortic stenosis presents a significant added risk for patients with aneurysmal disease in the face of BAV. Despite faster rates of growth, BAV has a similar rate of aortic complication than TAV.79 Similar results were seen in the study of Fernandes and colleagues. Predictors of aortic root dilatation included aortic regurgitation, absence of aortic stenosis and fusion of the right and left coronary leaflets (the type I of BAV). While predictors of ascending aortic dilatation included aortic regurgitation and absence of aortic coarctation.81

Additionally, a family history of AV disease is also associated with a significantly elevated risk of increasing ascending aortic size.80 Oliver et al. noticed that the co-existence of coarctation of aorta was the significant predictor of long-term acute aortic events (dissection or rupture) in patients with BAV.

Grotenhuis and colleagues showed that the evaluation of the elastic properties of the ascending aorta (measured by cardiac magnetic resonance (CMR)) might be used to identify patients at risk of progressive dilatation of the aorta. In addition, reduced aortic wall elasticity was associated with severity of AR and degree of LV hypertrophy. Future longitudinal studies are required to investigate the predictive value of aortic stiffness in patients with BAV disease.81

4D flow magnetic resonance was used to assess blood flow patterns in the thoracic aorta. Michael D. Hope and colleagues, using CMR, provided clear evidence that abnormal, eccentric flow in the ascending aorta of a subgroup of BAV patients is associated with elevated and asymmetric wall shear stress, which may place them at risk for aneurysm. It would be a noninvasive method of risk stratifying the sizeable population of patients with BAV and it can be useful to decision regarding the concomitant replacement of the ascending aorta in patients undergoing operations for bicuspid valve disease.31

In summary, monitoring of aortic dimensions, AV competence, elastic properties of aorta and systolic blood flow in the ascending aorta measured by CMR, seems indicated in the long-term follow-up of BAV patients.

According to 2014 AHA/ACC Guidelines for the Management of Patients With Valvular Heart Disease operative intervention to repair the aortic sinuses or replace the ascending aorta is:

- indicated 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).
- reasonable in patients with BAVs if the diameter of the aortic sinuses or ascending aorta is greater than 5.0 cm and a risk factor for dissection is present (family history of aortic dissection or if the rate of increase in diameter is ≥0.5 cm per year) (Class: IIa, Level of Evidence: C).

Furthermore, replacement of the ascending aorta is reasonable in patients with BAV who are undergoing AV surgery because of severe aortic stenosis (AS) or aortic regurgitation (AR) if the diameter of the ascending aorta is greater than 4.5 cm (Class: IIa, level of Evidence: C).

It should be noted that the 2010 ACC/AHA Guidelines for the Diagnosis and Management of Patients With Thoracic Aortic Disease also recommend that:

- Patients with BAV should undergo elective operation at smaller diameters (4.0 to 5.0 cm depending on the condition) to avoid acute dissection or rupture (Class I, Level of Evidence: C).
- Elective aortic replacement is reasonable for patients with BAVs, when the ratio of maximal ascending or aortic root area (πr²) in cm² divided by the patient’s height in meters exceeds (Class IIa, Level of Evidence: C).

According to 2012 ESC Guidelines on the management of valvular heart disease surgery should be considered in patients with BAV who have aortic root disease with maximal ascending aortic diameter ≥50 mm with risk factors (coarctation of the aorta, systemic hypertension, family history of dissection or increase in aortic diameter 2 mm/year) (Class IIa, Level of Evidence: C).

For patients with BAV who have an indication for surgery on the AV, lower thresholds can be used for concomitant aortic replacement (>45 mm). However, according to the Guidelines Authors, insufficient data are available to make a recommendation.

The recent 2014 ESC Guidelines on the diagnosis and treatment of aortic diseases recommend that in patients with BAV, surgery of the ascending aorta is indicated in case of:

- aortic root or ascending aortic diameter >55 mm (Class I, Level of Evidence: C).
- aortic root or ascending aortic diameter >50 mm in the presence of other risk factors (coarctation of the aorta, systemic hypertension, family history of dissection, or increase in aortic diameter >3 mm/year) (Class I, Level of Evidence: C).
Aortic valve disease

Aortic stenosis is the most common complication of BAV. The incidence of aortic stenosis increased progressively with age. Fenoglio Jr and colleagues demonstrated that 46 percent of patients with BAV over age 50 years and 73 percent over age 70 years had some degree of stenosis. It is correlated with progression of AV degeneration especially calcification and fibrosis. The morphology of BAV is an important determinant of the risk for aortic stenosis. Calloway and colleagues showed that the type II of BAV is associated with earlier appearance of aortic stenosis compared with other types of BAV.

Beppu and colleagues observed that progression of cusp sclerosis was faster in patients with antero-posteriorly located cusps than in those with right-left-located cusps and was faster in those with eccentric cusps than in those with symmetric cusps. Patients with aortic stenosis comorbid with BAV undergo AV replacement almost 5 years earlier than patients with TAV.

Despite, most aortic stenosis cases appear in adults, congenital aortic stenosis is the important clinical issue and BAV is correlated with 80-95% of these cases. Aortic stenosis seems to strongly depend on the asymmetry of the valve.

Bicuspid aortic valves may progress and become calcified, thus leading to varying degrees of severity of aortic regurgitation. In a large retrospective cohort study of 350 patients with BAV any degree of aortic regurgitation was present in 247 patients (59%). Nonetheless, severe and requiring surgical treatment aortic regurgitation is rare. In a study by Sabet et al., among 542 patients undergoing AV replacement 13% had pure aortic regurgitation.

The etiology of aortic regurgitation in patients with BAV is complex. There are several hypotheses about the development of regurgitation:

- aortic root dilatation or dissection.
- complication of infective endocarditis.
- myxoid degeneration of the AV.
- fibrous strands (as embryonic remnants), which lead to poor coaptation of the cusps.

According to recent ESC Guidelines on the management of valvular heart disease patients with BAV stenosis or regurgitation are qualified to surgical treatment under the same conditions as patients with diseases of TAV.

Infective endocarditis

Because of virtual disappearance of rheumatic fever in the developed world BAVs are likely to become the most important intrinsic cardiac predisposition for infective endocarditis (IE). Presence of aortic regurgitation and existence of degenerative AV disease predispose to infective valve endocarditis in patients with BAV. In cohort study includes 642 patients with BAV, AV endocarditis occurred in 13 patients. While in another study, 4 out of 212 patients with BAV developed IE during a follow-up of 20 years during a mean follow-up of 9 years. The annual incidence in infective endocarditis in patients with BAV is about 0.1% to 0.23%.

Lamas and Eykyn analyzed 30 cases of BAV endocarditis in patients who presented to St. Thomas’ Hospital from 1970 through 1998. These represented 12.3% of the all cases of native valve endocarditis. All patients were male, and their mean age was 39 years. Viridans streptococci were responsible for 42% of cases and staphylococci for 30%. There was a high incidence of serious complications (72% heart failure; 30% perianular abscesses). Surgery was required during the initial admission in 82% of cases. Overall mortality was 14%, and surgical mortality was 9%.

According to 2015 ESC Guidelines for the management of infective endocarditis prophylactic antibiotics are not recommended for dental or surgical procedures in patients with BAV. Nevertheless, these patients should be advised of the importance of dental and cutaneous hygiene.

The detection of BAV should increase the index of clinical suspicion of endocarditis if such patients also have fever and malaise. It is important, because of high incidence of serious complications and high mortality.
CONCLUSIONS

The BAV:
- is the most common congenital cardiac anomaly, affecting 0–5–2% of the general population with strong male predominance 3:1.
- may appear as an isolated defect or associated with other congenital cardiovascular anomalies, especially with coarctation of the aorta.
- is structurally heterogeneous, depending on the pattern of valve leaflet fusion and the most common is type I (fusion of the right and left coronary cusp).
- It is proved that there is a relation between pathogenesis, morphology and clinical manifestation of BAV.
- A lot of genes have been implicated in etiology of BAV (e.g.: NOTCH1, NOS3, GATA5, ACTA2).
- The mainstay of diagnosis is transthoracic echocardiography.
- Because of familial occurrence, screening of first-degree relatives should be considered.
- the clinical presentation of patients with BAV can vary from severe valve disease in infancy to asymptomatic valve disease in old age.
- patients with BAVs are at high risk for cardiovascular complications such as AV dysfunction, infective endocarditis, ascending aortic aneurysm and aortic dissection. Aortic stenosis is the most common complication of BAV.
- Generally, there are two theories of aortic aneurysm development in patients with BAV. Based on the evidence, a combined development mechanism is likely, with genetically determined aortopathy and altered hemodynamics in the ascending aorta.
- There are variable aneurysm phenotypes encountered in BAV. Fazel described 4 patterns of aortic dilatation.
- monitoring of aortic dimensions, AV competence, elastic properties of aorta and systolic blood flow in the ascending aorta measured by CMR, seems indicated in the long-term follow-up of BAV patients.
- Isolated, normally functioning BAV does not require treatment but the detection of BAV should increase the index of clinical suspicion of endocarditis if such patients also have fever and malaise.
- The main method of treatment aortic aneurysm in patients with BAV is surgery, but there have been disputes about indications and optimal timing of operation.
- According to recent ESC Guidelines on the management of valvular heart disease patients with BAV stenosis or regurgitation are qualified to surgical treatment under the same conditions as patients with diseases of TAV.
- According to 2009 ESC Guidelines on the prevention, diagnosis, and treatment of infective endocarditis prophylactic antibiotics are not recommended for dental or surgical procedures in patients with BAV.

Author contribution
All authors contributed equally to this paper.

Conflict of interests
Authors declare no potential conflict of interest.

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REFERENCES
Bicuspid aortic valve


