













## Article

# Bicuspid Aortic Valve Disease with Early-Onset Complications: Characteristics and Aortic Outcomes

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**Abstract:** Bicuspid aortic valve (BAV) is the most common congenital heart malformation in adults, but it can also cause childhood-onset complications. The presentation and clinical course of young adults who present due to BAV complications are relatively uncharacterized. In a multicenter study, we found that young people who experience significant complications related to BAV disease before age 30 are distinguished from the majority of BAV cases that manifest after age 50 by a relatively severe clinical course, with higher rates of surgical interventions, more frequent second interventions, and a greater burden of congenital heart malformations. These observations highlight the need for prompt recognition, regular lifelong surveillance, and targeted interventions to address the significant health burdens of patients with early-onset BAV complications.

**Keywords:** bicuspid aortic valve; outcomes; thoracic aortic aneurysms; coarctation; aortic surgery

## 1. Introduction

Bicuspid aortic valve (BAV) is the most common congenital heart defect, affecting 0.5–2% of the general population [1]. BAV is a clinical valvulo-aortopathy associated with a high incidence of significant cardiac complications, including aortic regurgitation or stenosis, infective endocarditis, and thoracic aortic aneurysms (TAAs) predisposing to thoracic aortic dissection [1–3]. The clinical spectrum of BAV disease ranges from lesions that are diagnosed in utero or at birth to incidental findings in asymptomatic older adults, making it a lifelong issue [2–4]. Additionally, BAV may be a feature of genetic syndromes such as Turner syndrome, Loeys–Dietz syndrome, or other congenital heart diseases [3,4]. The phenotypic manifestations of BAV and its related aortopathy are also diverse, and these variations can have significant clinical associations and implications [4,5]. Consequently, the prognosis of BAV patients varies widely. The prompt diagnosis of BAV and identification of patients who are at elevated risk for early-onset complications are essential because the treatment frequently requires intervention, frequent surveillance, and intensive medical therapies. We hypothesize that people with early-onset complications of BAV may have anatomic, clinical, or genetic predictors that distinguish them from the majority of individuals with BAV who progress along a more benign clinical course. Therefore, we selected and characterized a unique cohort of young adults who presented between ages 17 and 30 with moderate or severe BAV-related disease.

## 2. Materials and Methods

Early-onset BAV probands were recruited from 16 collaborating sites that referred eligible individuals to the data coordinating center at the University of Texas Health Science Center at Houston (UTHealth Houston). The study protocol was approved by the Committee for the Protection of Human Subjects at UTHealth Houston (HSC-MS-11-0185). All participants signed a written consent form, and study procedures were conducted in compliance with the ethical standards of the relevant national guidelines on human experimentation (HHS regulations 45 CFR part 46) and with the Helsinki Declaration of 1975, as revised in 2008. Details of the study protocol were previously published for a different analysis of the same EBAV cohort [6]. The principal inclusion criteria were BAV with a maximum aortic Z-score (root or ascending) > 4, thoracic aortic dissection, moderate or severe aortic stenosis or regurgitation, or valvular or aortic intervention prior to age 30. Individuals with genetic syndromes or clinically discovered mutations of causal BAV or HTAD genes were excluded. BAVs were classified by direct review of echocardiographic images as right–left cusp fusion if the commissures were oriented at 3–5 and 9–11 o’clock and as right–non-coronary cusp fusion if the commissures were oriented at 12–1 and 6–7 o’clock in parasternal short axis views. *t*-tests or chi-squared tests were used for comparisons between EBAV subgroups or between the EBAV cohort and published cohorts as appropriate. For comparisons with study-level data from the BAV meta-analysis, we removed 17 of 32 studies (5062 of 9441 patients) that excluded subgroups systematically or had incomplete data (Supplementary Materials Table S1 [7]).

## 3. Results

A total of 279 EBAV probands were included in this analysis. The mean age at diagnosis was 18 years. Two-thirds were male and almost 30% had other congenital heart malformations, most frequently aortic coarctation, ventricular septal defects, atrial septal defects, patent ductus arteriosus, or mitral valve abnormalities.

We compared the demographics of the EBAV cohort to the previously published meta-analysis data for 4379 adults with typical presentations of BAV disease and a retrospective cohort study of 652 adult Olmsted County, Minnesota, residents with BAV [7–9]. The

authors of the Olmstead County study defined a complex valvulo-aortopathy phenotype that is similar to the EBAV phenotype, except for the inclusion of syndromic and complex congenital cases that were excluded from the EBAV cohort (18% of complex cases). The results highlight the relative youth of the EBAV and complex cohorts, with mean ages of 14–18 years at diagnosis, compared to the meta-analysis of the adult BAV cohorts, with a mean age of 52 years at diagnosis (Table 1). The overall rates of aortic valve regurgitation and stenosis in the EBAV and complex valvulo-aortopathy cohorts were similar. The mean aortic pressure gradient (18 mmHg) and peak velocity (2.5 m/s) of both groups are consistent with mild aortic stenosis. However, aortopathy was more pronounced in the EBAV cohort, as evidenced by a larger aortic Z-score (3.2) than the complex cohort (2.2). The mean left ventricular ejection fraction (LVEF) of the EBAV probands ( $60 \pm 7\%$ ) was significantly lower than the meta ( $63 \pm 5\%$ ) or complex ( $64 \pm 9\%$ ) BAV groups, but there were no EBAV probands with reduced LV systolic function (LVEF < 50%).

**Table 1.** Characteristics of EBAV cohort and comparison to published BAV cohorts.

	EBAV	N	Meta	<i>P</i> <sub>meta</sub>	Complex	<i>P</i> <sub>complex</sub>
Age at presentation, years	18	78	52 ± 7	<0.01	14 ± 12	<0.01
Male, %	67	252	67 ± 14	1.0	63	0.49
AS, %	31	204	49 ± 24	<0.01	25	0.29
AR, %	38	204	28 ± 18	<0.01	47	0.15
AS+AR, %	11	204	20 ± 17	<0.01	-	-
Family member with BAV, %	32	155	6.4	<0.01	-	-
LVEF	60 ± 7.2	45	63 ± 5.0	<0.01	64 ± 9.4	<0.01
AV pressure gradient, mmHg	18 ± 14	33	-	-	19 ± 18	0.75
AV peak velocity, m/s	2.5 ± 1.0	38	-	-	2.5 ± 1.1	1.0
Maximum Z-score	3.2 ± 2.2	23	-	-	2.3 ± 2.5	0.09

Categorical variables are described by number and percentage (%). Continuous variables are described by mean and standard deviation. n: number of EBAV participants with available data; Meta: meta-analysis of 4379 adult BAV cases [8]; EBAV: bicuspid aortic valve with early-onset complications requiring intervention prior to age 30; Complex: 90 BAV probands with complex valvulo-aortopathy phenotype, as defined by Yang et al. [3]; AR: aortic regurgitation, mild or greater in severity; AS: aortic stenosis, mild or greater in severity; LVEF: left ventricular ejection fraction; AV: aortic valve; *P*<sub>meta</sub>: *p*-value for EBAV vs. meta-analysis; *P*<sub>complex</sub>: *p*-value for EBAV vs. complex valvulo-aortopathy cohort.

The overall rate of aortic interventions in the EBAV cohort was 50% during a mean follow-up period of 3.8 years. Half of the participants had their first surgery in childhood (mean age 7), and 25% had their first surgery as adults (mean age 33). One-third of the adult surgeries were second operations after a childhood surgery. Aortic valve repair or replacement with mechanical prostheses (17), bioprostheses (8), or homografts (2) was the single most common indication for intervention (44%). One-quarter underwent the isolated repair of the ascending aorta and 21% had combined valve and aortic operations (Bentall or David). Fifteen probands (22%) required at least one additional intervention after their index operation. Eight of the initial interventions occurred in childhood and required reinterventions before age 25. The most frequent indications for reintervention were aortic aneurysm repair and aortic valve replacement. The median time between the first and second interventions was 14 years. Half of those who underwent aortic surgery required an intervention within 30 months of diagnosis. There was only one reported aortic dissection (Type A) in a 36-year-old EBAV proband without syndromic features or a family history of aortic dissection. Comparable data on the reintervention rates were not available for the meta-analysis or complex valvulo-aortopathy cohorts.

While most EBAV probands had left–right cusp fusion (68%), right–non-coronary cusp fusion was more prevalent in the EBAV cohort (32%) than in the Olmstead County cohort, an outpatient cohort of adults with BAV who were followed for more than twenty years in community settings (14%) [8]. The proportion of EBAV probands who had at least one relative with BAV (32%) was significantly higher than the estimates from the

BAV meta-analysis (6.4%) [9,10]. More than one-third of the EBAV probands (35%) were diagnosed with TAAs. In the subgroup of these individuals who had available images, the location of the maximum aortic diameter was evenly divided between the root (16 cases) and the proximal ascending aorta (18 cases).

#### 4. Discussion

The principal objective of this study was to investigate the health burden of people with early-onset complications of BAV disease. The mean age at presentation of the EBAV cohort was 18 years. In contrast, the mean age at presentation of the adult BAV patients from 15 prospective studies was 52 years (Table 1) [7]. Only 14% of the participants in the largest natural history study of adult BAV disease were less than 30 years old at presentation [9]. Thus, the EBAV cohort is an extreme phenotype sample of BAV disease that is relatively uncharacterized. The proportions of women (33% vs. 28%) and family members with a BAV (32% vs. 6%) were both substantially higher than the estimates for community-living adults with typical presentations of BAV disease [9–11]. We also observed that the ‘root phenotype’ of BAV aortopathy (root > ascending aortic diameter), which predisposes to aortic regurgitation and was identified as a potential biomarker of genetically triggered or early-onset disease, appears to be enriched in EBAV probands [1]. Aortic regurgitation tends to be more pronounced in individuals with less common BAV morphologies, such as R-N cusp fusion, who were also overrepresented in the EBAV cohort [5]. These observations underscore the increased burden of BAV-related complications and signal the probable enrichment of highly penetrant genetically triggered disease in the EBAV cohort [9,10,12]. Thus, familial screening may be especially beneficial to individuals with early-onset BAV disease for the timely diagnosis of relatives who may also be at risk for early complications.

The comparative analysis identified stark contrasts between the prognosis of the EBAV cohort and cohorts with typical later-onset BAV disease that becomes clinically apparent after age 50. We hypothesized that early diagnosis may predict a more severe disease course due to additional congenital heart malformations and more frequent reinterventions. We confirmed that the EBAV participants required surgical interventions at a higher rate (50% vs. 27% over 20 years), underwent second interventions more frequently within 15 years of their index procedures (22% vs. 4–10% in a recent meta-analysis of surgical outcomes), and had twice as many concomitant congenital heart malformations than older BAV patients that comprise the majority of the longitudinal BAV study cohorts [5,8,13]. Even with these potentially aggravating factors, it is notable that we only observed one aortic dissection in the EBAV cohort. However, many individuals underwent elective aortic replacement before they might otherwise have undergone dissection.

Most of the EBAV participants who required more than one procedure had the initial aortic repair in childhood and underwent a subsequent aortic valve repair or replacement before age 25. The necessity of repeated surgical interventions in such a young population has significant implications for life expectancy and quality of life. Moreover, the long-term durability of valve interventions in this population remains uncertain, raising the possibility that they may require future interventions [11]. In the Olmstead County study, the subgroup of individuals with complex valvulo-aortopathy, defined similarly to EBAV, were found to have decreased long-term survival [3].

The EBAV cohort represents a small subset (10–15%) of BAV cases, even with our multicenter approach, and we acknowledge the limitations related to the subgroup analysis of a rare phenotype. Some phenotypic data for the adult and complex BAV cohorts were not available for comparison.

#### 5. Conclusions

The high event rate of young individuals who present due to symptomatic BAV disease highlights the critical importance of prompt recognition, lifelong surveillance, and targeted interventions to address the significant health burdens related to the EBAV or complex valvulo-aortopathy phenotype. This study also demonstrates the potential

value of familial screening or genetic testing to identify relatives who may be at risk for BAV-related complications. The genetic biomarkers derived from larger cohort studies may eventually prove useful to predict complications and promote personalized treatment algorithms for BAV disease.

**Supplementary Materials:** The following supporting information can be downloaded at <https://www.mdpi.com/article/10.3390/hearts5030018/s1>, Table S1: Studies from the meta-analysis by Hardikar et al. included for comparison with the EBAV cohort.

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**Institutional Review Board Statement:** The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national guidelines on human experimentation (HHS regulations 45 CFR part 46) and with the Helsinki Declaration of 1975, as revised in 2008, and that the study has been approved by the Committee for the Protection of Human Subjects at the University of Texas Health Science Center at Houston on 1 July 2012 (HSC-MS-11-0185).

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**Data Availability Statement:** The original contributions presented in the study are included in the article/Supplementary Materials; further inquiries can be directed to the corresponding author.

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