Original Article

Bicuspid Aortic Valve Disease from Infancy to Older Age: A 25-Year Experience from an Italian Referral Center

Annachiara Benini, Giovanni Benfari, Mara Pilati, Giovanni Battista Luciani[1], Flavio Luciano Ribichini, Maria Antonia Prioli

Department of Medicine, Division of Cardiology, University of Verona, [1]Department of Surgery, Division of Cardiac Surgery, University of Verona, Verona, Italy

Abstract

Aim: Bicuspid aortic valve (BAV) is the most common congenital heart defect, with considerable risk of morbidity and mortality. The purpose of the study was to analyze clinical and echocardiographic presentation of BAV in a large-volume tertiary Italian center and to test their interaction with full age span, sex, and first diagnosis versus second referral. **Methods:** Consecutive patients of all ages diagnosed with BAV at our center from January 1988 to December 2012 were retrospectively included. Exclusion criteria were as follows: associated complex congenital cardiac disease, systemic syndrome, and previous cardiac surgery. **Results:** Eligible patients were 790, divided by age quartiles. Seventy-two percent of patients had any grade BAV dysfunction. Aortic valve stenosis was more frequent in the first (24%) and fourth (24%) quartiles. This corresponds to a double-peak stenosis severity curve, being more severe at a very young age and in the elderly. Aortic valve regurgitation was more prevalent in each quartile than stenosis, with a prevalence of 72% in the second quartile and 77% in the third quartile. This corresponds to a single-peak regurgitation severity curve, being more severe in the fourth and fifth decades of life. Patients with previously diagnosed BAV had more significant valve dysfunction in comparison to patients with first diagnosis of BAV, either stenosis (15% vs. 21%, $P = 0.024$) or regurgitation (58% vs. 68%, $P = 0.006$). **Conclusion:** The dominant BAV dysfunction in this large Northern Italian community is regurgitation, with higher severity of disease in the fourth and fifth decades of life.

Keywords: Aortic regurgitation, aortic stenosis, bicuspid aortic valve

Introduction

Bicuspid aortic valve (BAV) is the most common congenital heart defect, with a population prevalence of 0.5%–2%, with a male predominance of approximately 3:1, and with considerable risk of developing morbidity and mortality over the lifetime.[1,2] It can occur isolated or in association with additional heart defect and may occur within a syndrome.[3-6] Its most common heart-related complications are valve dysfunction and aortic dilation.[7,8] Because of the association with aortic dilation, BAV is somehow considered as an aortopathy rather than a localized valve disease.[7,9,10] Young adults with valve dysfunction could require intervention.[11-13] Death in patients with BAV can be secondary to progressive aortic valve dysfunction or endocarditis, if not treated, or rarely secondary to aortic complication (dissection or rupture).[7,8,14,15] Aortic regurgitation (AR) is highly prevalent in patients with BAV, ranging from 47% to 64%.[1,7,16-18] AR presents generally at a younger age than severe aortic stenosis (AS).[17,19] AS in BAV typically presents in the neonatal period or in the fifth or sixth decade. When valve dysfunction begins, then the progression of stenosis is probably similar to that of tricuspid valve stenosis but manifests 5–10 years earlier.[20] Limited data exist on patients with mixed AS and AR, as it is not common in BAV.[1,19] BAV-associated aortopathy has a prevalence of 40% of patients in referral center.[19] Dilation may occur in the aortic root, the tubular ascending aorta (AA), and the proximal aortic arch.[21] To our knowledge, there is no extensive study that presents prevalence and features of BAV and its related dysfunction among different age groups.

Access this article online

Quick Response Code:

Website: www.jcecho.org

DOI: 10.4103/jcecho.jcecho_115_20

Address for correspondence: Dr. Maria Antonia Prioli, Department of Medicine, Division of Cardiology, University of Verona, Piazzale Aristide Stefani 1, Verona 37126, Italy.
E-mail: antonia.prioli@gmail.com

Submitted: 15-Oct-2020 **Accepted:** 16-Jan-2021 **Published:** 21-May-2021

How to cite this article: Benini A, Benfari G, Pilati M, Luciani GB, Ribichini FL, Prioli MA. Bicuspid aortic valve disease from infancy to older age: A 25-year experience from an Italian referral center. J Cardiovasc Echography 2021;31:29-34.

Objectives

The aim of the study was to analyze clinical and echocardiographic presentation of BAV in a large-volume tertiary Italian center and to test their interaction with full age span and sex. Moreover, we aimed to compare patients who received a first diagnosis of BAV at our center and patients with a previously diagnosed BAV referred for a second opinion. In the present study, we focused on the prevalence of BAV disease-associated features at first presentation of patients.

Methods

Eligibility criteria

Consecutive patients of all ages diagnosed with BAV in the echocardiography laboratories of our center from January 1988 to December 2012 were retrospectively included. Exclusion criteria were as follows: associated complex congenital cardiac disease, systemic syndrome (e.g., Marfan and Turner), and previous cardiac surgery. Aortic coarctation was not considered an exclusion criterion. Our hospital is a tertiary care center in the north of Italy; therefore, patients were either first diagnosed with BAV in our center (e.g., murmur heard from the pediatrician and sports certificate) or were already diagnosed with BAV and came for second opinion or follow-up in a tertiary care center.

The study conformed to the Declaration of Helsinki and received internal review board approval, and informed consent was obtained from the participants.

Echocardiography

All the examinations were performed using Acuson Sequoia until 2009 and Philips HD15 or GE Vivid 5 from 2009 to 2012. All patients underwent clinical evaluation performed by their personal physician and comprehensive echocardiographic evaluation. BAV was diagnosed from parasternal short-axis view demonstrating the existence of only two commissures delimiting only two aortic valve cusps. The anatomy was defined according to fusion pattern, as right-left cusp fusion (RL), right-noncoronary cusp fusion (RN), or left-noncoronary cusp fusion (LN).[22-25] Aortic dimensions were measured at two-dimensional parasternal long-axis view as maximal diameters at annulus, sinuses of Valsalva, sinotubular junction, and proximal AA according to current guidelines.[26-29] Each dimension reported was obtained by the average of three consecutive measurements on each diameter. Z-scores were determined for pediatric patients, and aortic dilation was defined as a Z-score >2. In adult patients, aortic dilation was considered when AA diameter was >20 mm/m^2. AR was graded using a multiparametric approach including vena contracta, jet dimension, pressure half-time, and descending aorta evaluation. It was defined as mild, moderate, or severe. AS was graded using Doppler analysis and continuity equation. It was defined as mild, moderate, or severe. Other variables considered were the presence of mitral valve prolapse, atrial septal defect, small ventricular septal defect, and aortic coarctation.

Statistical analysis

The study population was divided by age quartiles. Continuous variables are reported as mean and standard deviation, and categorical variables are reported as percentage. Difference between continuous variables when normally distributed was tested using unpaired Student's *t*-test, and difference between categorical variables was tested using the Fisher's and Chi-square-test. Analysis was performed using SPSS software version 20.0 (SPSS, Chicago, IL, USA); significance level was set at $P < 0.05$.

Results

Overall population

Eligible patients consecutively enrolled were 790. Among them, 603 (76%) were male, with a male predominance of approximately 3:1, and the mean age was 29.6 ± 21.6 years. The most prevalent valve anatomy was R-L type, being present in 84% of patients. In our population, 171 patients (22%) had associated simple congenital heart disease and 43.1% had aortic root dilation. Among the patients with aortic dilation, 89.8% had a BAV with R-L type fusion pattern, 9.3% had a R-N type fusion pattern, and 0.9% had a L-N type fusion pattern.

We divided then the population by age quartiles, the mean age of the subgroups was 3.8 ± 3.3 years, 18.1 ± 4.7 years, 37.6 ± 6.2 years, and 59.2 ± 8.3 years, respectively, and male sex was always prevalent, ranging from 71% to 81%. A typical BAV (R-L type) was the most frequent in all the quartiles. Aortic diameters increased with age, in particular sinus diameter was found to be 23.9 ± 7.4 mm in the first quartile and 39.9 ± 5.8 mm in the last one, while AA diameter ranged from 18.6 ± 5.2 mm to 44.5 ± 6.5 mm. The highest prevalence of aortic root dilation was found in the third quartile (55%), but also in the fourth quartile, it was quite high (49%). Associated simple congenital heart diseases were more frequent in the first quartile (39%), in particular considering aortic coarctation (29%), atrial septal defect (4%), and small ventricular septal defect (3%). Mitral valve prolapse was found to be more frequent in the third (10%) and fourth quartiles (8%). Other characteristics are reported in Table 1.

Valve dysfunction according to age at diagnosis

In the overall BAV population, 568 patients (72%) had aortic valve dysfunction (stenosis/regurgitation) of any grade including mild, and this prevalence slowly increased with age. Analyzing age quartiles, we see that its prevalence nearly doubled between the first quartile (46%) and the fourth one (85%). Aortic valve stenosis was more frequent in the first (24%) and fourth (24%) quartiles. Despite similar percentage, the severity of stenosis was slightly higher in the fourth quartile, where 14% of patients had > moderate stenosis, while in the first one, only 10% of patients had significant stenosis. Aortic valve regurgitation was in general more prevalent in each quartile than stenosis, with a prevalence of 72% in the second quartile, 77% in the third quartile, and 72% in the fourth quartile. In the last two quartiles, both 30% of

patients had >moderate regurgitation. Regarding the finding of combined BAV stenosis and regurgitation, it was present in only 66 patients (8%) in the overall population, being nearly double in the fourth quartile in comparison to the first one (13% vs. 7%). In the fourth age quartile, there was also the highest prevalence of combined >moderate stenosis and regurgitation (3%) [Supplementary Table 1].

Figure 1 displays probability to present with any grade of aortic valve stenosis, which slightly increases with age, while the probability to present with any grade of aortic valve regurgitation increases from 50% with diagnosis at 10 years to nearly 90% at 80 years. This trend was maintained also dividing male and female population [Supplementary Figure 1]. In Figure 2, the severity of aortic valve stenosis varies significantly with age, even if the probability to present with BAV stenosis does not vary significantly among the full age span. Namely, prevalence does not correspond to severity of that specific valvulopathy. In fact, diagnosis of AS in BAV both at a very young age and in the elderly prompts a higher severity of the valvulopathy. This corresponds to

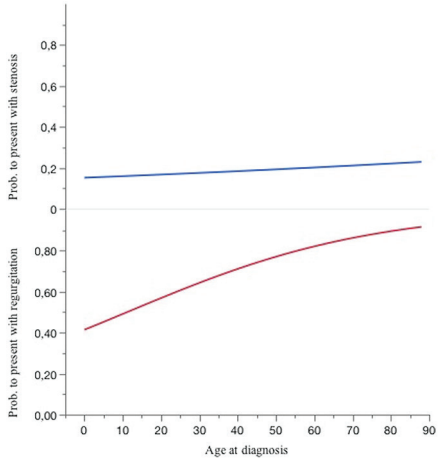

Figure 1: Probability to present with aortic stenosis and regurgitation, according to age at diagnosis of bicuspid aortic valve

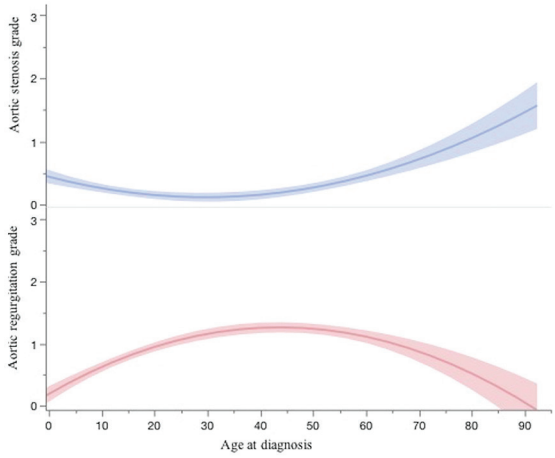

Figure 2: Grade of aortic stenosis and regurgitation, according to age at diagnosis of bicuspid aortic valve

Table 1: Clinical and echocardiographic characteristics of the overall population (left column) and by age quartiles (right columns)

	Overall	I age quartile	II age quartile	III age quartile	IV age quartile
n	790	197	197	198	198
Age, years	29.6±21.6 (0.0-88.0)	3.8±3.3 (0.0-10.0)	18.1±4.7 (10.1-27.1)	37.6±6.2 (27.7-47.6)	59.2±8.3 (47.7-88.0)
Male sex, *n* (%)	603 (76.3)	147 (75.0)	160 (81.0)	141 (71.0)	155 (78.3)
BSA, m^2	1.5±0.6	0.7±0.4	1.6±0.4	1.8±0.3	1.8±0.4
Any valve dysfunction, *n* (%)	568 (71.9)	90 (46)	146 (74.1)	163 (82.3)	169 (85.3)
Stenosis, *n* (%)	138 (17.5)	47 (23.9)	16 (8.1)	27 (13.6)	48 (24.2)
Stenosis ≥ moderate, *n* (%)	71 (9.0)	20 (10.2)	11 (5.6)	13 (6.6)	27 (13.6)
Regurgitation, *n* (%)	491 (62.2)	56 (28.4)	141 (71.6)	152 (76.8)	142 (71.7)
Regurgitation ≥ moderate, *n* (%)	169 (21.4)	8 (4.1)	42 (21.3)	59 (29.8)	60 (30.3)
R-L type, %	84.1	83.8	81.2	87.9	84.3
R-N type, %	13.4	14.7	13.7	8.6	15.7
L-N type, %	2.5	1.5	5.1	3.5	0
Annulus diameter, mm	266, 21.6±5.8	104, 17.4±5.7	67, 23.3±4.3	52, 25.1±4.2	43, 24.5±3.4
Sinus diameter, mm	269, 31.4±9.1	101, 23.9±7.4	68, 32.2±6.5	51, 37.0±5.0	49, 39.9±5.8
STJ diameter, mm	266, 27.3±8.5	101, 20.3±6.6	68, 27.6±5.4	52, 33.4±5.5	45, 35.8±5.1
Ascending aorta diameter, mm	281, 32.5±12.0	80, 18.6±5.2	71, 30.8±6.3	57, 38.7±8.2	73, 44.5±6.5
Aortic root dilation, %	43.1	18.8	23.5	54.6	49
Any simple congenital heart disease, *n* (%)	171 (21.6)	77 (39.1)	34 (17.3)	39 (19.7)	21 (10.6)
Aortic coarctation, *n* (%)	98 (12.4)	58 (29.4)	19 (9.6)	17 (8.6)	4 (2.0)
Atrial septal defect, *n* (%)	9 (1.1)	7 (3.6)	1 (0.5)	1 (0.5)	0
Small ventricular septal defect, *n* (%)	10 (1.3)	6 (3.0)	3 (1.5)	1 (0.5)	0
Mitral valve prolapse, *n* (%)	50 (6.3)	7 (3.6)	8 (4.1)	20 (10.1)	15 (7.6)

BSA: Body surface area, R-L type: Right-left type fusion, R-N type: Right-noncoronary type fusion, L-N type: Left-noncoronary type fusion, STJ: Sinotubular junction

a "double-peak" stenosis curve in Figure 2. Regarding AR, the probability to present with a significant regurgitation is higher in the fourth and fifth decades of life, while diagnosis in the elderly is most frequently associated with a less severe valvulopathy. Therefore, the regurgitation curve in Figure 2 has a single peak.

First diagnosis

Patients first diagnosed with BAV in our center were 448, while patients already diagnosed with BAV which came for second opinion or follow-up were 342. The mean age was comparable in the two groups (30.4 ± 23.3 and 28.4 ± 19.3, respectively, $P = 0.19$), and male sex was predominant in both the groups. As expected, patients with previously diagnosed BAV had more significant valve dysfunction versus patients with first diagnosis of BAV, either stenosis (15% vs. 21%, $P = 0.024$) or regurgitation (58% vs. 68%, $P = 0.006$). In particular, severe stenosis was almost twofold in patients with previously diagnosed BAV (6% vs. 13%, $P = 0.002$), and also, severe regurgitation was significantly higher in that group (18% vs. 26%, $P = 0.007$). We can see a slightly higher prevalence of typical BAV (R-L type) in the group already diagnosed (81% vs. 88%, $P = 0.023$), while the prevalence of other anatomy was quite similar. Moreover, in already diagnosed patients, aortic annulus diameter was significantly bigger (20.6 ± 6.3 mm vs. 22.6 ± 5.1 mm, $P = 0.005$), while other diameters and the prevalence of aortic root dilation did not vary significantly. Finally, associated simple congenital heart diseases were present in both the groups with a similar prevalence, but aortic coarctation (10% vs. 16%, $P = 0.007$) was more prevalent in the group already diagnosed with BAV, while atrial septal defect was present only in patients with a first diagnosis of BAV in our center (2% vs. 0%, $P = 0.003$). Other characteristics, including aortic diameters, are reported in Table 2.

The rate of new diagnosis was stable during the time of the study, ranging from 50% of patients in 2003–2007 to 63% of patients in 2008–2012 ($P = 0.22$) [Figure 3]. The 5-year trend showed moreover minor and not significant fluctuation over

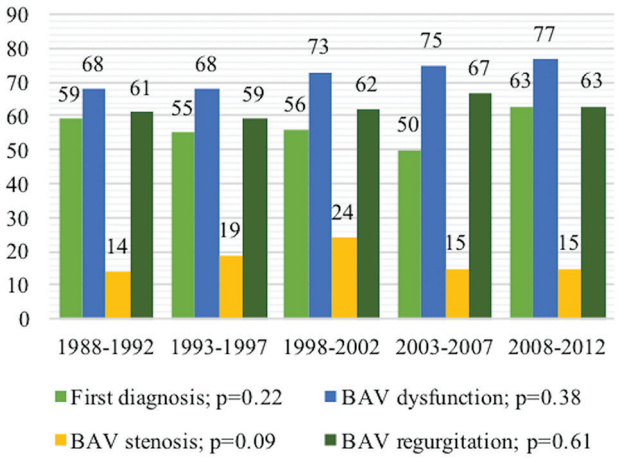

Figure 3: 5-year trend of first diagnosis, bicuspid aortic valve dysfunction, bicuspid aortic valve stenosis and bicuspid aortic valve regurgitation; *P* values refer to change in prevalence over time

Table 2: Comparison between patients with first diagnosis of bicuspid aortic valve and patients with a previously diagnosed bicuspid aortic valve

	First diagnosis of BAV	Referral of previously diagnosed BAV	*P*
n	448	342	
Age, years	30.4±23.3	28.4±19.3	0.19
Male sex, *n* (%)	346 (77.2)	253 (74.0)	0.20
BSA, m^2	1.4±0.6	1.6±0.5	0.004
Valve dysfunction, *n* (%)	302 (67.4)	262 (76.6)	0.008
Stenosis, *n* (%)	66 (14.7)	72 (21.1)	0.024
Stenosis ≥ moderate, *n* (%)	28 (6.3)	43 (12.6)	0.002
Regurgitation, *n* (%)	259 (57.8)	232 (67.8)	0.006
Regurgitation ≥ moderate, *n* (%)	80 (17.9)	89 (26.0)	0.007
R-L type, %	80.7	88.1	0.023
R-N type, %	16.5	9.8	0.20
L-N type, %	2.8	2.1	0.80
Annulus diameter, mm	20.6±6.3	22.6±5.1	0.005
Sinus diameter, mm	30.6±9.4	32.3±8.7	0.14
STJ diameter, mm	26.6±8.9	28.1±8.0	0.17
Ascending aorta diameter, mm	31.5±12.7	33.4±11.3	0.18
Aortic root dilation, %	43.8	42.1	0.71
Any simple congenital heart disease, *n* (%)	92 (20.5)	79 (23.1)	0.42
Aortic coarctation, *n* (%)	43 (9.6)	55 (16.1)	0.007
Atrial septal defect, *n* (%)	9 (2.0)	0	0.003
Small ventricular septal defect, *n* (%)	8 (1.8)	2 (0.6)	0.13
Mitral valve prolapse, %	31 (6.9)	19 (5.6)	0.42

BSA: Body surface area, R-L type: Right-left type fusion, R-N type: Right-noncoronary type fusion, L-N type: Left-noncoronary type fusion, STJ: Sinotubular junction, BAV: Bicuspid aortic valve

time regarding the prevalence of valve dysfunction ($P = 0.38$), stenosis ($P = 0.09$), and regurgitation ($P = 0.61$).

Discussion

The main value of the present study is the extensive evaluation of prevalence and severity of BAV in a large population of consecutive patients. Overall, 72% of patients had aortic valve dysfunction, with this prevalence increasing with age. We presented the differences in stenotic versus regurgitant phenotype. The dominant BAV dysfunction in this Northern Italian community is regurgitation and not stenosis. When diagnosed, AR often does not have clinical manifestation and indeed can be diagnosed during a screening echocardiography examination done for other reasons (sports certificate and abnormal heart murmur). Regurgitation is more frequent from third to fifth decades of life, being more severe in the third and fourth age quartiles. The single-peak, namely parabolic, regurgitation curve [Figure 2] confirms this observation regarding severity. On the other side, stenosis was represented by a double-peak curve, being more frequent in the first and fourth quartiles of age, but its severity did not follow exactly prevalence, being higher in the fourth quartile. The double-peak stenosis curve [Figure 1] confirms this trend of severity, according to the possible clinical presentation of a neonatal stenotic BAV or a calcific stenotic BAV in the elderly.

The present study brings novel information to existing literature.[17] Indeed, our overall mean age is slightly lower than almost all mean age reported.[1,9,19] This aspect can be explained by the fact that our tertiary cardiologic care center has a pediatric print and collaborated with sports medicine. The prevalence of stenosis more than moderate is slightly lower than reported (16.7%–37%), while the prevalence of regurgitation more than moderate was in the trend reported (13.3%–32%).[1,2,16,17,19,30] These findings can be explained by the calcified aortic stenotic valves in the elderly, which sometimes are missed as bicuspid since the severe calcification. Analyzing other features of our BAV population, male sex is predominant, with a male-to-female ratio of approximately 3:1, and the most frequent BAV was R-L type, according to literature.[1,9,19] The prevalence of aortic root dilation was higher in the third and fourth quartiles, as a result of progression of BAV-associated aortopathy, aging, and possibly other risk factors such as arterial hypertension. Associated simple congenital heart diseases were more frequent in the first quartile: none of atrial and small ventricular septal defects required cardiac surgery, most of atrial septal defects probably resolved in the 1st year of life. Only mitral valve prolapse was more frequent in the third and fourth quartiles, since it is a progressive disease through life.

One of the most interesting aspects of our population is that we could analyze separately patients with first diagnosis of BAV and patients come for a second referral; this helps distinguish primary care patients versus tertiary care patients. The mean age was quite similar in the two groups, making them comparable and showing that we have a globally young population, not only young pediatric patients come for a second referral. Patients already diagnosed with BAV had significantly more valve dysfunction, since the finding of valve dysfunction prompted for more advanced screening. Moreover, also aortic annulus diameter was significantly bigger in this group, since the BAV valvulopathy and aorthopathy were more advanced. Regarding associated simple congenital heart disease, atrial septal defect was present only in patients with a first diagnosis, probably resolving in few years. Aortic coarctation was more prevalent in the group already diagnosed with BAV; this can be explained since aortic coarctation is often early diagnosed thanks to symptoms or abnormal heart murmur, prompting the clinician to look for other possible associated cardiac heart defects, as BAV disease.

Study limitations

All limitations of a retrospective study apply. First of all, our results cannot be considered representative of the entire population, since in our neighborhoods, there are other tertiary care centers, to which patients can refer for cardiac evaluation, with only little crossover with our center. The second point is that patients included in the study could present minor congenital heart disease and aortic coarctation, which could affect features of presentation of BAV. Another limitation is inherent to the serial echocardiographic measurements during the age span in which data were collected. The very long time of the study could be considered a limitation, since ultrasound machines and echocardiographic recommendation underwent major refinements. However, the rate of new diagnosis and prevalence of BAV dysfunction showed no significant fluctuation over time, revealing a stable trend even with newer echocardiographic technique [Figure 3].

Conclusion

To our knowledge, this is the largest Italian registry reporting prevalence and features of BAV in a regional community. The dominant BAV dysfunction in this Northern Italian community is regurgitation. It is mandatory to search for significant regurgitation when a bicuspid aortic valve is diagnosed, especially in the third to fifth decades, with a careful follow-up, since it can be associated with significant medical and surgical morbidity over the life of affected individuals.

Ethical clearance

The study conformed to the Declaration of Helsinki and informed consent was obtained from the subjects.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Michelena HI, Desjardins VA, Avierinos JF, Russo A, Nkomo VT, Sundt TM, *et al*. Natural history of asymptomatic patients with normally functioning or minimally dysfunctional bicuspid aortic valve in the

community. Circulation 2008;117:2776-84.
2. Tzemos N, Therrien J, Yip J, Thanassoulis G, Tremblay S, Jamorski MT, *et al*. Outcomes in adults with bicuspid aortic valves. JAMA 2008;300:1317-25.
3. Fernandes SM, Sanders SP, Khairy P, Jenkins KJ, Gauvreau K, Lang P, *et al*. Morphology of bicuspid aortic valve in children and adolescents. J Am Coll Cardiol 2004;44:1648-51.
4. Ciotti GR, Vlahos AP, Silverman NH. Morphology and function of the bicuspid aortic valve with and without coarctation of the aorta in the young. Am J Cardiol 2006;98:1096-102.
5. Merkx R, Duijnhouwer AL, Vink E, Roos-Hesselink JW, Schokking M. Aortic diameter growth in children with a bicuspid aortic valve. Am J Cardiol 2017;120:131-6.
6. D'Ascenzi F, Valentini F, Anselmi F, Cavigli L, Bandera F, Benfari G, *et al*. Bicuspid aortic valve and sports: From the echocardiographic evaluation to the eligibility for sports competition. Scand J Med Sci Sports 2021 Mar;31:510-20.
7. Michelena HI, Khanna AD, Mahoney D, Margaryan E, Topilsky Y, Suri RM, *et al*. Incidence of aortic complications in patients with bicuspid aortic valves. JAMA 2011;306:1104-12.
8. Edwards WD, Leaf DS, Edwards JE. Dissecting aortic aneurysm associated with congenital bicuspid aortic valve. Circulation 1978;57:1022-5.
9. Michelena HI, Della Corte A, Prakash SK, Milewicz DM, Evangelista A, Enriquez-Sarano M. Bicuspid aortic valve aortopathy in adults: Incidence, etiology, and clinical significance. Int J Cardiol 2015;201:400-7.
10. Peeters FE, Van der Linden N, Thomassen AL, Crijns HJ, Meex SJ, Kietselaer BL. Clinical and echocardiographic determinants in bicuspid aortic dilatation: Results from a longitudinal observational study. Medicine (Baltimore) 2016;95:e5699.
11. Fernandes S, Khairy P, Graham DA, Colan SD, Galvin TC, Sanders SP, *et al*. Bicuspid aortic valve and associated aortic dilation in the young. Heart 2012;98:1014-9.
12. Fernandes SM, Khairy P, Sanders SP, Colan SD. Bicuspid aortic valve morphology and interventions in the young. J Am Coll Cardiol 2007;49:2211-4.
13. Holmes KW, Lehmann CU, Dalal D, Nasir K, Dietz HC, Ravekes WJ, *et al*. Progressive dilation of the ascending aorta in children with isolated bicuspid aortic valve. Am J Cardiol 2007;99:978-83.
14. Michelena HI, Katan O, Suri RM, Baddour LM, Enriquez-Sarano M. Incidence of infective endocarditis in patients with bicuspid aortic valves in the community. Mayo Clin Proc 2016;91:122-3.
15. Roberts CS, Roberts WC. Dissection of the aorta associated with congenital malformation of the aortic valve. J Am Coll Cardiol 1991;17:712-6.
16. Rodrigues I, Agapito AF, de Sousa L, Oliveira JA, Branco LM, Galrinho A, *et al*. Bicuspid aortic valve outcomes. Cardiol Young 2017;27:518-29.
17. Masri A, Svensson LG, Griffin BP, Desai MY. Contemporary natural history of bicuspid aortic valve disease: A systematic review. Heart 2017;103:1323-30.
18. Yang LT, Benfari G, Eleid M, Scott CG, Nkomo VT, Pellikka PA, *et al*. Contemporary differences between bicuspid and tricuspid aortic valve in chronic aortic regurgitation. Heart 2020;317466.
19. Masri A, Kalahasti V, Alkharabsheh S, Svensson LG, Sabik JF, Roselli EE, *et al*. Characteristics and long-term outcomes of contemporary patients with bicuspid aortic valves. J Thorac Cardiovasc Surg 2016;151:1650-9.e1.
20. Roberts WC, Ko JM. Frequency by decades of unicuspid, bicuspid, and tricuspid aortic valves in adults having isolated aortic valve replacement for aortic stenosis, with or without associated aortic regurgitation. Circulation 2005;111:920-5.
21. Habchi KM, Ashikhmina E, Vieira VM, Shahram JT, Isselbacher EM, Sundt TM 3rd, *et al*. Association between bicuspid aortic valve morphotype and regional dilatation of the aortic root and trunk. Int J Cardiovasc Imaging 2017;33:341-9.
22. Roberts WC. The congenitally bicuspid aortic valve. A study of 85 autopsy cases. Am J Cardiol 1970;26:72-83.
23. Angelini A, Ho SY, Anderson RH, Devine WA, Zuberbuhler JR, Becker AE, *et al*. The morphology of the normal aortic valve as compared with the aortic valve having two leaflets. J Thorac Cardiovasc Surg 1989;98:362-7.
24. Sievers HH, Schmidtke C. A classification system for the bicuspid aortic valve from 304 surgical specimens. J Thorac Cardiovasc Surg 2007;133:1226-33.
25. Michelena HI, Chandrasekaran K, Topilsky Y, Messika-Zeitoun D, Della Corte A, Evangelista A, *et al*. The bicuspid aortic valve condition: The critical role of echocardiography and the case for a standard nomenclature consensus. Prog Cardiovasc Dis 2018;61:404-15.
26. Baumgartner H, Hung J, Bermejo J, Chambers JB, Edvardsen T, Goldstein S, *et al*. Recommendations on the echocardiographic assessment of aortic valve stenosis: A focused update from the European association of cardiovascular imaging and the American society of echocardiography. J Am Soc Echocardiogr 2017;30:372-92.
27. Erbel R, Aboyans V, Boileau C, Bossone E, Bartolomeo RD, Eggebrecht H, *et al*. 2014 ESC Guidelines on the diagnosis and treatment of aortic diseases: Document covering acute and chronic aortic diseases of the thoracic and abdominal aorta of the adult. The Task Force for the Diagnosis and Treatment of Aortic Diseases of the European Society of Cardiology (ESC). Eur Heart J 2014;35:2873-926.
28. Nishimura RA, Otto CM, Bonow RO, Carabello BA, Erwin JP, Guyton RA, *et al*. 2014 AHA/ACC Guideline for the Management of Patients with Valvular Heart Disease: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation 2014;129:e521-643.
29. Nishimura RA, Otto CM, Bonow RO, Carabello BA, Erwin JP, Fleisher LA, *et al*. 2017 AHA/ACC Focused Update of the 2014 AHA/ACC Guideline for the Management of Patients With Valvular Heart Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Circulation 2017;135:e1159-95.
30. Michelena HI, Suri RM, Katan O, Eleid MF, Clavel MA, Maurer MJ, *et al*. Sex differences and survival in adults with bicuspid aortic valves: Verification in 3 contemporary echocardiographic cohorts. J Am Heart Assoc 2016;5:e004211.