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Original Article

Bicuspid aortic valve outcomes

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Abstract *Background:* Bicuspid aortic valve is the most common CHD. Its association with early valvular dysfunction, endocarditis, thoracic aorta dilatation, and aortic dissection is well established. *Objective:* The aim of this study was to assess the incidence and predictors of cardiac events in adults with bicuspid aortic valve. *Methods:* We carried out a retrospective analysis of cardiac outcomes in ambulatory adults with bicuspid aortic valve followed-up in a tertiary hospital centre. Outcomes were defined as follows: interventional – intervention on the aortic valve or thoracic aorta; medical – death, aortic dissection, aortic valve endocarditis, congestive heart failure, arrhythmias, or ischaemic heart disease requiring hospital admission; and a composite end point of both. Kaplan–Meier curves were generated to determine event rates, and predictors of cardiac events were determined by multivariate analysis. *Results:* A total of 227 patients were followed-up over 13 ± 9 years; 29% of patients developed severe aortic valve dysfunction and 12.3% reached ascending thoracic aorta dimensions above 45 mm. At least one cardiac outcome occurred in 38.8% of patients, with an incidence rate at 20 years of follow-up of $47 \pm 4\%$; 33% of patients were submitted to an aortic valve or thoracic aorta intervention. Survival 20 years after diagnosis was $94 \pm 2\%$. Independent predictors of the composite end point were baseline moderate–severe aortic valve dysfunction (hazard ratio, 3.19; 95% confidence interval, 1.35–7.54; $p < 0.01$) and aortic valve leaflets calcification (hazard ratio, 4.72; 95% confidence interval, 1.91–11.64; $p < 0.005$). *Conclusions:* In this study of bicuspid aortic valve, the long-term survival was excellent but with occurrence of frequent cardiovascular events. Baseline aortic valve calcification and dysfunction were the only independent predictors of events.

Keywords: Aorta; aortic valve, bicuspid; heart defects, congenital; survival

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Bicuspid aortic valve is the most common CHD,[1–3] affecting 1.3% of the population.[1] Despite advances in our knowledge, since its first descriptions, for five centuries,[4] there are still knowledge gaps and areas where further research is warranted. The heterogeneous clinical presentation and course, morbid consequences of early valvular dysfunction requiring surgery, and the possibility of life-threatening complications justifies continued efforts to understand this CHD.

The purposes of this retrospective study were to examine disease progression and cardiac outcomes in a group of adults with bicuspid aortic valve followed-up over a prolonged period of observation and to determine predictors of adverse cardiac outcomes.

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Material and methods

Study subjects

This retrospective study examined a referral population of consecutive adults with bicuspid aortic valve assessed at the ambulatory adult CHD clinic of the Santa Marta Hospital from 1990 through 2015. Patients were identified using the hospital CHD database. The inclusion criterion was bicuspid aortic valve documented on transthoracic echocardiography. Patients for whom we had no access to baseline echocardiography and those submitted to aortic valve replacement or ascending aortic graft surgery previously were excluded.

Assessments

Baseline data were obtained from the record of the patient's first visit to the ambulatory clinic. Baseline data included age, sex, reason for referral, coronary risk factors, cardiac medications, associated cardiac diseases, previous cardiac procedures, and echocardiographic parameters. Follow-up data up to September, 2015 were obtained by review of clinical records, which included summaries of ambulatory visits, procedures, and hospital admissions.

Doppler and two-dimensional transthoracic echocardiography examinations performed at baseline and during the follow-up period at the discretion of the attending physician were reviewed by one of the researchers' echocardiographer in order to standardise the variables evaluated and to ensure uniformity of results. Bicuspid aortic valve was diagnosed when only two cusps were identified in the short-axis parasternal view. The type of bicuspid aortic valve was classified into type 1, from right–left coronary cusp fusion, type 2, from right-non coronary cusp fusion, and type 3, from left-non coronary cusp fusion,[5] in patients who had not undergone previous intervention on the aortic valve and in whom leaflet orientation could be clearly visualised. Valve degeneration was evaluated according to the presence of thickening and calcification. Aortic stenosis was classified as mild (valve area >1.5 cm^2, mean Doppler gradient <25 mmHg, maximum jet velocity 2.0–3.0 m/s), moderate (valve area 1–1.5 cm^2, mean Doppler gradient 25–40 mmHg, maximum jet velocity 3.0–4.0 m/s), or severe (valve area <1 cm^2, mean Doppler gradient >40 mmHg, maximum jet velocity >4.0 m/s).[6] In all patients diagnosed before continuous-wave Doppler became available, wide valvular opening ascertained the absence of valve stenosis. Aortic regurgitation was classified as mild, moderate, or severe using an integrated approach taking into consideration the following color and continuous flow Doppler criteria: ratio of the regurgitant jet width to the left ventricular outflow tract width, ratio of the regurgitant jet area to the left ventricular outflow tract area, pressure half-time, effective regurgitant orifice area, regurgitant volume, and presence of holodiastolic retrograde flow in the descending aorta.[6,7] Other transthoracic echocardiography parameters recorded were left parasternal long-axis M-mode left ventricular end-diastolic diameter, left ventricular end-systolic diameter, end-diastolic posterior wall thickness, end-diastolic interventricular septum thickness, left atrium size, right ventricle size, end-diastolic measurements of the aortic sinus at the sinus of Valsalva level, and proximal ascending aortic dimensions. The presence or absence of left atrial enlargement, left ventricular dilatation, left ventricular hypertrophy, and right ventricular dilatation was also assessed according to criteria defined by Otto et al.[8] Dilated aortic sinus and proximal ascending aorta were defined by dimensions greater than 40 mm irrespective of body surface area.[9] The spectrum of aortic dilatation phenotypes was classified into type 1, characterised by dilated aortic root, type 2, enlargement involving the tubular portion of the ascending aorta, and type 3, dilatation of the entire ascending aorta with sinotubular junction effacement.[10] Left ventricular ejection fraction was also assessed with visual estimation[11] and two-dimensional echocardiography guidance.[12]

Outcome measures

The frequency of progression to thoracic aorta dilatation and to moderate or severe aortic stenosis or regurgitation was determined. Aortic growth rate was defined as the difference between the diameter at the first and the last follow-up echocardiogram – except in patients undergoing ascending aortic graft surgery, in which we took into account the last echocardiogram performed before surgery – divided by the time interval in years for each patient. It was considered that a rapid aortic dilatation was present when the growth rate was above average for the aortic root or the proximal ascending aorta.

Cardiac outcomes were defined as follows: interventional, surgery/percutaneous intervention on the aortic valve or thoracic aorta; medical, death, aortic dissection, aortic valve endocarditis, congestive heart failure, arrhythmias, or ischaemic heart disease requiring hospital admission; and a composite end point of both, total events, during the follow-up period. Mortality was determined, and causes of death were classified as cardiac, non-cardiac, and unknown on the basis of review of clinical records and/or death certificates.

Statistical analysis

Data analysis was performed using SPSS version 20. Continuous data are expressed as mean ± one standard deviation, and compared using the unpaired Student t-test or Wilcoxon's rank test. Categorical data are displayed as frequencies and percentages, and compared using χ^2 tests or Fisher's exact tests wherever appropriate. The two-sided level of significance was 0.05.

Kaplan–Meier curves were generated to determine event rates. Potential predictors of cardiac outcome were evaluated by univariate Cox regression analyses. Candidate variables with a p value of <0.05 on univariate analysis were entered into multivariate Cox regression models. A stepwise, backward-elimination algorithm was used. Multivariate logistic regression

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models were also developed to predict a rapid growth at the ascending and root level separately.

Results

Baseline characteristics

We identified 287 ambulatory patients with bicuspid aortic valve followed-up in the adult CHD clinic of our institution over the past two decades. After application of exclusion criteria, 227 patients were included in the analyses. Baseline characteristics are presented in Table 1. Reasons for referral were aortic valve dysfunction in 72 patients (31.7%), thoracic aorta disease including eight cases of thoracic aorta aneurysm, 3.5%, and nine of aortic coarctation, 4.0%, transition of care from paediatric cardiology to adult cardiology (116 patients, 51.1%), and other reasons in the remaining 22, including five ischaemic heart disease, four arrhythmia, two hypertension, four heart failure, three endocarditis, two atrial septal defect, one family history of bicuspid aortic valve, and one pulmonary stenosis.

Age at first medical appointment was 28 ± 14 years (median, 21 years; range 15–72; interquartile range 19.5). Patients were predominantly male (70.5%); 27% of patients had hypertension, and 93.5% of them were receiving antihypertensive drugs. Cardiovascular medications included β-adrenergic antagonists (11.9%), calcium channel antagonists (3.2%), angiotensin-converting enzyme inhibitor/angiotensin II receptor antagonist (22.8%), diuretics (6.8%), statins (12.8%), and antiplatelet agents (5.9%).

In all, 67 patients (29.5%) had at least a previous diagnosis of other associated CHD – 18.9% had aortic coarctation, 7.5% ventricular septal defect, 1.8% atrial septal defect, 2.2% patent ductus arteriosus, and 3.5% others valvulopathies excluding aortic valve disease, such as pulmonary stenosis, mitral valve prolapse, or dysplasia. The majority of

Table 1. Baseline characteristics of study participants.

Age	(n = 227)*	Baseline echocardiogram	(n = 227)*
Mean ± SD (years)	28 ± 14	LVEDD (mean ± SD) (mm)	52 ± 7
Age >30 years [n (%)]	72 (59.1)	LVESD (mean ± SD) (mm)	32 ± 6
Age >50 years [n (%)]	24 (10.6)	LVD [n (%)]	39 (17.2)
Male sex [n (%)]	101 (70.5)	LVEF ⩾ 50% [n (%)]	221 (97.4)
Cardiovascular risk factors	(n = 219)	IVSTh (mean ± SD) (mm)	10 ± 2
Hypertension [n (%)]	60 (27.4)	PWTh (mean ± SD) (mm)	10 ± 2
Hyperlipidaemia [n (%)]	31 (14.2)	LVH [n (%)]	37 (16.2%)
Diabetes [n (%)]	5 (2.3)	LA size (mean ± SD) (mm)	34 ± 6
Smoking status [n (%)]	34 (15.5)	LAE [n (%)]	20 (8.8)
Obesity (BMI ⩾ 30)** [n (%)]	18 (8.2)	RV size (mean ± SD) (mm)	20 ± 5
Cardiovascular medications	(n = 219)	RVD [n (%)]	4 (1.8)
B-adrenergic antagonists [n (%)]	26 (11.9)	Type of bicuspid aortic valve	(n = 83)
Calcium channel antagonists [n (%)]	7 (3.2)	1/2/3 [n (%)]	53/26/4
ACE inhibitors/ARBs [n (%)]	50 (22.8)		(63.9/31.3/4.8)
Diuretics [n (%)]	15 (6.8)	Aortic valve degeneration	
Statins [n (%)]	28 (12.8)	Leaflet thickening [n (%)]	115 (53.0%)
Oral antidiabetic agents [n (%)]	5 (2.3)	Leaflet calcification [n (%)]	36 (16.6%)
Antiplatelet agents [n (%)]	16 (5.9)	Peak aortic velocity (mean ± SD) (m/s)	2.2 ± 1.0
Oral anticoagulation [n (%)]	7 (3.2)	Peak AV gradient (mean ± SD) (mmHg)	24 ± 24
Syndromes		AS severity, mild/moderate/severe [n (%)]	46/22/19
Turner [n (%)]	4 (1.8)		(20.3/9.7/8.4)
Marfan [n (%)]	1 (0.4)	AR severity, mild/moderate/severe [n (%)]	90/37/6
Associated CHD			(39.6/16.3/2.6)
CoA [n (%)]	43 (18.9)	AV dysfunction, moderate or severe [n (%)]	74 (32.6)
VSD [n (%)]	17 (7.5)	Aortic sinus dimension (mean ± SD) (mm)	31 ± 6
ASD [n (%)]	4 (1.8)	TAA dimension (mean ± SD) (mm)	35 ± 11
Others [n (%)]	13 (5.7)	Aortic dilatation (>40 mm) [n (%)]	32 (14.1)
Previous aortic valve/thoracic aorta interventions		Type of aortic dilatation	(n = 32)
Aortic valvuloplasty or valvotomy [n (%)]	10 (4.4)	1/2/3 [n (%)]	4/13/15
CoA treatment [n (%)]	(n = 43) 33 (76.7)		(12.5/40.6/46.9)

ACE = angiotensin-converting enzyme; ARB = angiotensin II receptor blockers; AR = aortic valve regurgitation; AS = aortic valve stenosis; ASD = atrial septal defect; AV = aortic valve; BMI = body mass index; CoA = aortic coarctation; IVSTh = interventricular septum thickness; LA = left atrium; LAE = left atrial enlargement; LVD = left ventricular dilatation; LVEDD = left ventricular end-diastolic diameter; LVEF = left ventricular ejection fraction; LVESD = left ventricular end-systolic diameter; LVH = left ventricular hypertrophy; PWTh = posterior wall thickness; RV = right ventricle; RVD = right ventricular dilatation; TAA = tubular ascending aorta; VSD = ventricular septal defect

*Unless otherwise indicated

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these associated diseases had successful percutaneous/surgical treatment in childhood, including 77% of the aortic coarctation cases, or had no haemodynamic significance. A total of 10 patients (4.4%) had previous aortic valvuloplasty or valvulotomy in childhood, with two of them having residual moderate aortic stenosis and regurgitation at their baseline echocardiogram.

Overall, 74 patients (32.6%) in the study group had significant aortic valve dysfunction – moderate or severe aortic stenosis or regurgitation – at baseline. Table 2 compares baseline characteristics of these patients with those without baseline aortic valve dysfunction.

At baseline, the mean diameter of the sinus of Valsalva and the proximal ascending aorta was 31 ± 6 and 35 ± 11 mm, respectively. In all, 32 patients

Table 2. Baseline characteristics of patients with and without baseline moderate–severe aortic valve dysfunction.

	Baseline AV dysfunction	No baseline AV dysfunction	P
	(n = 74)*	(n = 153)*	
Age (mean ± SD) (years)	35 ± 16	25 ± 12	< 0.001
Age >30 years [n (%)]	39 (52.7)	33 (21.6)	**<0.001**
Male sex [n (%)]	57 (77)	103 (67.3)	**0.133**
Cardiovascular risk factors	(n = 70)	(n = 149)	
Hypertension [n (%)]	24 (34.3)	36 (24.2)	0.117
Hyperlipidaemia [n (%)]	14 (20)	17 (11.4)	0.089
Diabetes [n (%)]	4 (5.7)	1 (0.7)	**<0.05**
Smoking status [n (%)]	13 (18.6)	21 (14.1)	0.394
Obesity (BMI ⩾ 30)** [n (%)]	6 (10.2)	8 (6.9)	0.451
Associated CHD			
CoA [n (%)]	4 (5.4)	39 (25.5)	**<0.001**
VSD [n (%)]	3 (4.1)	14 (9.2)	0.281
Others [n (%)]	8 (10.8)	11 (7.2)	0.356
Previous aortic valve/thoracic aorta interventions			
Aortic valvuloplasty or valvotomy [n (%)]	2 (2.7)	8 (5.2)	0.505
CoA treatment [n (%)]	(n = 4)	(n = 39)	
	1 (25)	32 (82.1)	<0.05
Baseline echocardiogram			
LVEDD (mean ± SD) (mm)	56 ± 9	51 ± 6	**<0.001**
LVESD (mean ± SD) (mm)	34 ± 7	30 ± 5	**<0.001**
LVD [n (%)]	25 (33.8)	13 (8.5)	**<0.001**
LVEF ⩾ 50% [n (%)]	71 (95.9)	150 (98)	0.394
IVSTh (mean ± SD) (mm)	11 ± 3	9 ± 2	**<0.001**
PWTh (mean ± SD) (mm)	10 ± 2	9 ± 2	**<0.001**
LVH [n (%)]	23 (31.1)	13 (8.5)	**<0.001**
LA size (mean ± SD) (mm)	36 ± 5	33 ± 5	**<0.001**
LAE [n (%)]	10 (13.5)	10 (6.5)	0.082
RV size (mean ± SD) (mm)	23 ± 5	19 ± 5	0.090
RVD [n (%)]	1 (1.4)	2 (1.3)	1.000
Type of BAV	(n = 25)	(n = 58)	
1/2/3 [n (%)]	15/9/1 (60/36/4)	38/17/3 (65.5/29.3/5.2)	0.826
AV degeneration			
Leaflet thickening [n (%)]	60 (81.1)	61 (39.9)	**<0.001**
Leaflet calcification [n (%)]	26 (35.1)	11 (7.2)	**<0.001**
Peak aortic velocity (mean ± SD) (m/s)	300 ± 125	178 ± 54	**<0.001**
Peak AV gradient (mean ± SD) (mmHg)	15 ± 10	43 ± 33	**<0.001**
Aortic sinus dimension (mean ± SD) (mm)	34 ± 6	30 ± 6	**<0.001**
TAA dimension (mean ± SD) mm)	42 ± 12	35 ± 9	<0.05
Aortic dilatation (>40 mm) [n (%)]	15 (20.3)	17 (11.1)	0.063
Type of aortic dilatation	(n = 15)	(n = 17)	
1/2/3 [n (%)]	2/6/7 (13.3/40/46.7)	2/7/8 (11.8/41.2/47.1)	0.334

AV = aortic valve; BAV = bicuspid aortic valve; BMI = body mass index; CoA = aortic coarctation; IVSTh = interventricular septum thickness; LA = left atrium; LAE = left atrial enlargement; LVD = left ventricular dilatation; LVEDD = left ventricular end-diastolic diameter; LVEF = left ventricular ejection fraction; LVESD = left ventricular end-systolic diameter; LVH = left ventricular hypertrophy; PWTh = posterior wall thickness; RV = right ventricle; RVD = right ventricular dilatation; TAA = tubular ascending aorta; VSD = ventricular septal defect

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(14.2%) had dilated thoracic aorta – that is, aortic sinus and/or proximal ascending aortic dimensions greater than 40 mm. The most frequent aortic phenotype was dilatation of the entire ascending aorta (46.9% of cases), followed closely by the isolated dilatation of tubular ascending aorta (40.6%).

Progression of disease

The 227 patients were followed-up for a mean of 13 ± 9 years (median, 11 years; range, 0.2–40.7 years; interquartile range 13.3). The frequency and age at which moderate or severe aortic valve dysfunction and aortic dilatation occurred are listed in Table 3. Overall, 66 patients (29.1%) developed severe aortic valve dysfunction during the follow-up period. The mean age of diagnosis was 43 ± 13 years.

Root or tubular ascending aorta diameters of >40 and >45 mm were observed in 30.8 and 12.3% of patients, respectively. The mean sinus of Valsalva dimension and proximal ascending aorta dimension was 34 ± 10 and 39 ± 9 mm at the end of an aorta mean echocardiographic follow-up of 9 ± 3 years, respectively. Dilatation progressed at faster rates in the proximal ascending aorta: the mean rate of change in aortic sinus dimension was 0.3 ± 0.6 mm/year (95% confidence interval 0.2–0.4), and the mean increase in ascending aorta dimension was 0.5 ± 0.7 mm/year (95% confidence interval 0.3–0.7). In multivariate analysis, the presence of moderate or severe aortic regurgitation and arterial hypertension was strongly associated with rapid aortic dilatation (Table 4).

Table 3. Progression of disease.

	n (%) of patients (n = 227)	Age (mean ± SD) (years)
Moderate or severe AV dysfunction	122 (44.0)	36 ± 16
Severe AV dysfunction	66 (29.1)	43 ± 13
Moderate or severe AS	78 (34.4)	39 ± 15
Severe AS	53 (19.1)	43 ± 14
Moderate or severe AR	80 (35.2)	34 ± 14
Severe AR	13 (5.7)	43 ± 11
Aortic dilatation (>40 mm)	70 (30.8)	42 ± 15
Aortic dilatation (>45 mm)	34 (12.3)	45 ± 13

AR = aortic regurgitation; AS = aortic stenosis; AV = aortic valve

Primary outcomes

The frequency and nature of outcome events are listed in Table 5. A total of seven deaths occurred (3.1%), of which two were cardiac related, two were not related to a cardiac aetiology, including one case of malignancy and one septic shock, and three were of unknown reasons. Survival was 96 ± 2 and 94 ± 2% at 10 and 20 years, respectively (Fig 1).

The composite end point – medical or interventional events – occurred in 88 patients (38.8%), with an incidence rate at 20 years of 47 ± 4% (Fig 2); 11 patients (4.8%) were diagnosed with bacterial endocarditis. Aortic dissection and stroke occurred in two (0.9%) and six patients (2.6%), respectively; moreover, seven patients (7.5%) required hospital admission for congestive heart failure (Table 5). The incidence of cardiovascular medical events was 20 ± 4% at 20 years of follow-up (Fig 2).

During the follow-up period, aortic valve or thoracic aorta interventions were performed in 74 patients (32.6%), with an incidence rate at 20 years of 39 ± 4% (Fig 3); 61 patients (26.9%) were subjected to at least one aortic valve intervention, at a mean age

Table 4. Predictors of rapidly progressive aortic dilatation.

	Univariate analysis		Multivariate analysis	
Candidate variables	**OR (95% CI)**	**p value**	**OR (95% CI)**	**p value**
Baseline age >30 years	1.37 (0.63–2.99)	0.433		
Male sex	1.16 (0.56–2.44)	0.690		
Hypertension	2.26 (1.00–5.07)	**0.049**	3.67 (1.31–10.29)	0.014
Hyperlipidaemia	2.60 (0.85–7.94)	0.093		
Smoking status	1.80 (0.65–4.96)	0.256		
Obesity	1.88 (0.50–7.10)	0.355		
Previous diagnosis of CoA	1.80 (0.65–4.96)	0.256		
Previous aorta/AV intervention	1.89 (0.85–4.19)	0.116		
Baseline aortic dilatation (>40 mm)	1.07 (0.38–3.02)	0.903		
Moderate–severe AV dysfunction	1.73 (0.82–3.63)	0.148		
Moderate–severe AS	1.38 (0.51–3.73)	0.527		
Moderate–severe AR	2.50 (1.00–6.21)	**0.049**	2.98 (1.23–7.20)	0.015

AR = aortic regurgitation; AS = aortic stenosis; AV = aortic valve; CI = confidence interval; CoA = aortic coarctation; OR = odds ratio

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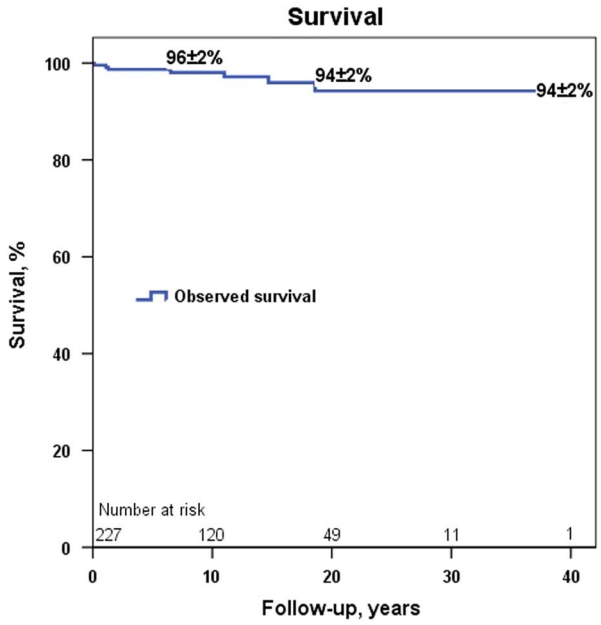

Figure 1.
Survival during the follow-up of adults with bicuspid aortic valve. Survival (± SD) at 10 years, 20 years, and end of follow-up are indicated.

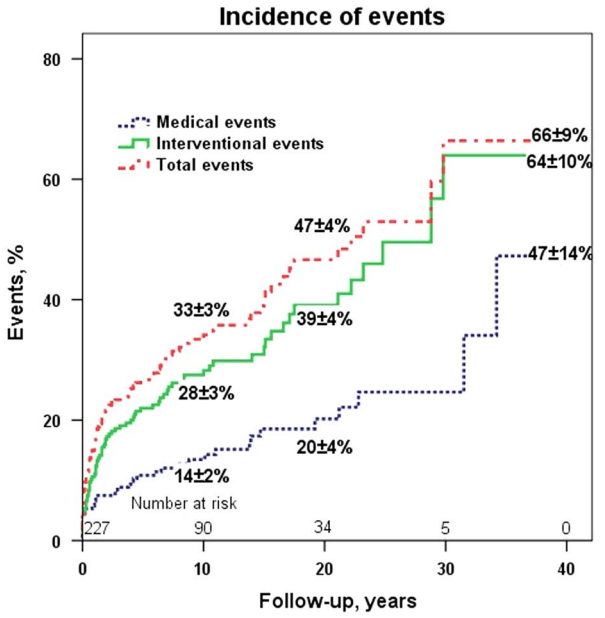

Figure 2.
Incidence of medical (death, aortic dissection, native aortic valve endocarditis, congestive heart failure, arrhythmias, ischaemic heart disease requiring hospital admission; blue dotted line), interventional (aortic valve, thoracic aorta; green solid line), and total events (medical events or interventional events; red dotted and dashed line). The event rates (± SD) at 10, 20 years, and end of follow-up are indicated.

of 44 ± 13 years. Aortic stenosis was the most common indication for intervention (64% of cases). Only four patients later required aortic valve re-operation – those subjected to aortic valve repair, percutaneous valvulotomy, and one of the aortic homograft required an aortic valve replacement later on during the follow-up. The 20-year aortic valve surgery incidence was 35 ± 4% (Fig 4). In total, 35 patients (15.4%) underwent a thoracic aorta intervention – 60% of cases for aortic dilatation, 37% for aortic coarctation, and only one case for aortic dissection. The indications for surgical intervention for aortic dilatation were aortic diameter ⩾ 45 mm and need for a concomitant aortic valve surgery (71.4% of cases); aortic diameter ⩾ 50 mm and presence of other risk factors for aortic dissection (9.5%); and aortic diameter ⩾ 55 mm in the remaining four patients (19%). There was only one patient who required aortic re-operation, submitted initially for isolated ascending aortic graft and later required a Bentall procedure. The 20-year incidence of surgery for aortic dilatation was 13 ± 3%. A total of 13 patients required surgery for aortic coarctation, with four cases of re-coarctation, leading to a 20-year rate of 6 ± 2% (Fig 5). The peak invasive transcoarctation of the aorta gradient was 60 ± 35 mmHg at the time of the intervention.

Cardiac events according to presence or absence of baseline moderate–severe aortic valve dysfunction are presented in Fig 6. The incidence rate of the composite end point and of interventional events at 20 years of follow-up in patients with no baseline aortic valve dysfunction was 33 ± 5 and 26 ± 5%, respectively, which was significantly lower ($p < 0.001$) compared with the rates of events in those with baseline moderate–severe aortic valve dysfunction.

Predictors of primary outcomes

The candidate variables examined by univariate analysis are shown in Tables 6 and 7. None of the variables were highly correlated with each other ($r < 0.7$). On multivariate analysis, the independent predictors of the composite end point were baseline moderate or severe aortic valve dysfunction (hazard ratio, 3.19; 95% confidence interval 1.35–7.54; $p < 0.01$) and aortic valve leaflets calcification (hazard ratio, 4.72; confidence interval, 1.91–11.64; $p < 0.005$). The independent predictors of interventional events – thoracic aorta and aortic valve interventions – were age above 30 years (hazard ratio, 2.59; confidence interval, 1.12–5.99; $p < 0.05$), hypertension (hazard ratio, 2.49; confidence interval, 1.07–5.80; $p < 0.05$), hyperlipidaemia (hazard ratio, 3.46; confidence interval, 1.15–10.43; $p < 0.05$), moderate or severe aortic stenosis (hazard ratio, 7.65; confidence

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Table 5. Cardiac outcomes.

	Total of patients (n = 227)	Age (mean ± SD) (years)	Baseline AV dysfunction (n = 74)	No baseline AV dysfunction (n = 153)	p
Composite end point [n (%)]	88 (38.8)	41 ± 14	48 (64.9)	40 (26.1)	**<0.001**
Medical* [n (%)]	38 (16.7)	43 ± 15	22 (29.7)	16 (10.5)	**<0.001**
Death	7 (3.1)	41 ± 14	4 (5.4)	3 (2)	0.219
Cardiac death	2 (0.9)	44 ± 16	2 (2.7)	0 (0)	0.105
Aortic valve endocarditis	11 (4.8)	34 ± 10	7 (9.5)	4 (2.6)	**<0.05**
Aortic dissection	2 (0.9)	40 ± 13	2 (2.7)	0 (0)	0.105
Hospital admission for heart failure	7 (3.1)	48 ± 20	4 (5.4)	3 (2)	0.219
Hospital admission for stroke	6 (2.6)	41 ± 17	4 (5.4)	2 (1.3)	0.090
Hospital admission for arrhythmias	12 (5.3)	50 ± 14	4 (5.4)	8 (5.2)	1.000
Hospital admission for CAD	6 (2.6)	48 ± 13	4 (5.4)	2 (1.3)	0.090
Interventional* [n (%)]	74 (32.6)	42 ± 14	43 (58.1)	31 (20.3)	**<0.001**
Intervention on aortic valve	61 (26.9)	44 ± 13	42 (56.8)	20 (13.1)	**<0.001**
AV intervention for AS	39 (17.2)	45 ± 13	28 (37.8)	12 (7.8)	**<0.001**
AV intervention for AR	17 (7.5)	45 ± 13	10 (13.5)	7 (4.6)	**<0.05**
AV intervention for endocarditis	6 (2.6)	41 ± 12	5 (6.8)	1 (0.7)	**<0.05**
Intervention on thoracic aorta	35 (15.4)	42 ± 16	17 (23)	18 (11.8)	**<0.05**
TA intervention for aortic dilatation	22 (9.7)	47 ± 13	14 (18.9)	8 (5.2)	**<0.005**
TA intervention for CoA	13 (5.7)	34 ± 19	2 (2.7)	11 (7.2)	0.231
TA intervention for aortic dissection	1 (0.4)	31	1 (1.4)	0 (0)	0.326
Type of intervention					
Mechanical aortic valve replacement	35 (15.4)				
Bioprosthetic aortic valve replacement	6 (2.6)				
Aortic homograft	2 (0.9)				
Aortic valve repair	2 (0.9)				
Percutaneous aortic valvulotomy	1 (0.4)				
Ascending aortic graft and AV replacement	19 (8.4)				
Ascending aortic graft	4 (1.8)				
Percutaneous angioplasty for CoA	6 (2.6)				
Prosthetic patch aortoplasty for CoA	5 (2.2)				
Resection of CoA and end-to-end anastomosis	3 (1.3)				

AR = aortic regurgitation; AS = aortic stenosis; AV = aortic valve; CAD = coronary artery disease; CoA = aortic coarctation; pts = patients; TA = thoracic aorta

*Categories are not mutually exclusive

interval, 2.97–19.73; $p < 0.001$), and moderate or severe aortic regurgitation (hazard ratio, 4.17; confidence interval, 1.63–10.43; $p < 0.005$).

Discussion

In this study of 227 patients with bicuspid aortic valve followed-up in a tertiary hospital centre, with a mean age of 28 ± 14 years and a male:female ratio of ~2 : 1, 29.1% developed severe aortic valve dysfunction and 12.3% attained thoracic aorta diameters above 45 mm; 39% of patients had at least one primary cardiac event during a mean follow-up of 13 years. The most frequent events were aortic valve surgery for aortic stenosis (17.2% of patients), ascending thoracic aorta surgery for aortic dilatation (9.7% of patients), and aortic valve surgery for aortic regurgitation (7.5% of patients). The fact that aortic stenosis requiring surgery was the principal morbid event is concordant with previous population-based and tertiary-referral-based studies.[5,13,14] We highlight not only its frequency, with a 20-year incidence of 24 ± 4%, but also the younger age at its occurrence, at a mean age of 45 ± 13 years, lower than the average 5–10 years earlier than that expected for tricuspid aortic stenosis described in the literature.[15]

Only a few published articles have estimated rates of progressive aortic dilatation in adults with bicuspid aortic valves with a long follow-up period. Thanassoulis et al[16] estimated the annual rate of aortic enlargement in 156 bicuspid aortic valve patients followed-up for 3.8 years, and 68 patients were evaluated during nearly 4 years by Ferencik et al.[17] Our study included 227 patients, with a mean duration of aorta dimensions follow-up of 9 years, both higher than those in previously described studies. Dilatation progressed at faster rates in the proximal ascending aorta, which is consistent with that described in those studies. We also found that the presence of aortic valve dysfunction, especially baseline moderate-to-severe aortic regurgitation, has a repercussion in rate of aortic dilatation, which is

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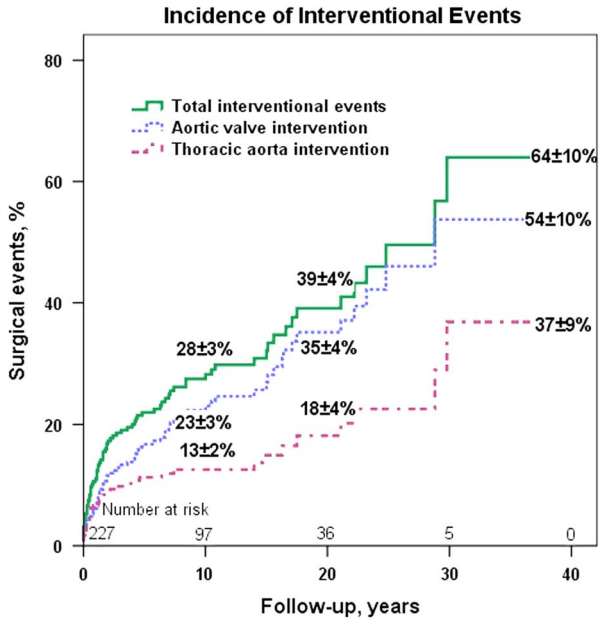

Figure 3.
Incidence of total interventional events (aortic valve, thoracic aorta; green solid line), aortic valve intervention (blue dotted line), and thoracic aorta intervention (pink dashed and dotted line). The event rates (± SD) at 10 years, 20 years, and the end of follow-up are indicated.

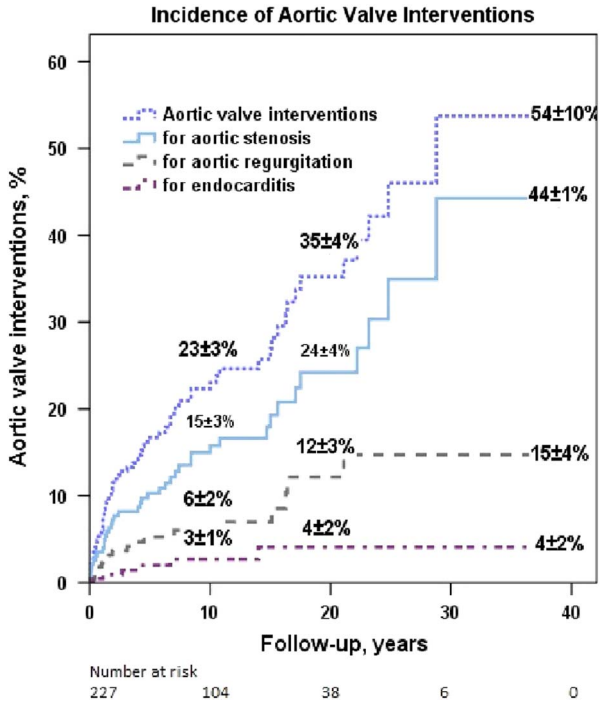

Figure 4.
Incidence of total aortic valve intervention (for aortic stenosis, aortic regurgitation, endocarditis; blue dotted line), aortic valve intervention for aortic stenosis (blue solid line), for aortic regurgitation (grey dashed line), and for endocarditis (purple dashed and dotted line). The event rates (± SD) at 10, 20 years, and the end of follow-up are indicated.

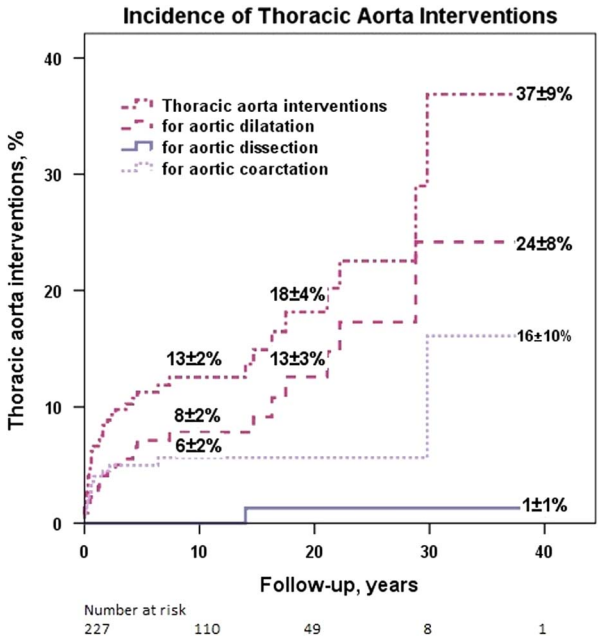

Figure 5.
Incidence of total thoracic aorta intervention (for aortic dilatation, aortic dissection, aortic coarctation; pink dashed and dotted line), thoracic aorta intervention for aortic dilatation (pink dashed line), for aortic coarctation (purple dashed line), and for aortic dissection (purple solid line). The event rates (± SD) at 10, 20 years, and the end of follow-up are indicated.

consistent with previously published studies.[16,18] The increased stroke volume imposed by aortic regurgitation enhances proximal ascending aorta wall stress, which can ultimately lead to faster aorta expansion and explain this result.

It is not surprising that baseline aortic valve dysfunction had independently predicted the occurrence of a primary cardiac event, a fact that is consistent with the results of the most recent major studies that addressed this issue.[13,14] In these patients, the incidence rate of the composite end point at 20 years of follow-up was as high as 75 ± 7%, which is clearly representative of the significant morbidity associated with bicuspid aortic valve. It should also be noted that even those patients without baseline aortic valve dysfunction are at risk of having events, with a 20-year incidence of 33 ± 5 and 26 ± 5% of total events and interventional events, respectively.

Aortic valve leaflet calcification was also an independent predictor of the occurrence of a cardiac event. Turbulent flow through a bicuspid aortic valve, which has an altered architecture, plays a role in premature valve degeneration and calcification,[19] which ultimately progresses to aortic valve dysfunction. Thus, patients with valve degeneration, even if they had a normally functioning bicuspid valve, need

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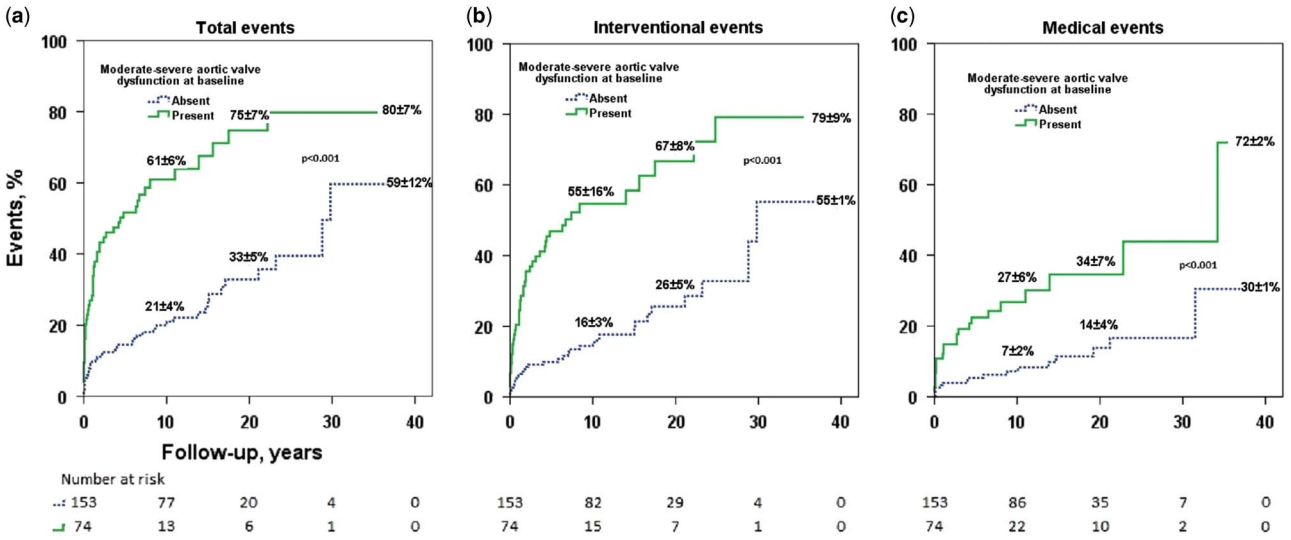

Figure 6.
*Incidence of events during follow-up according to the presence (green solid line) or absence (blue dashed line) of moderate or severe aortic valve dysfunction at baseline (including moderate or severe aortic stenosis or regurgitation). (**a**) Incidence of total events (medical and interventional). (**b**) Incidence of interventional events (aortic valve, thoracic aorta). (**c**) Incidence of medical events (death, aortic dissection, native aortic valve endocarditis, congestive heart failure, arrhythmias, and ischaemic heart disease requiring hospital admission). The event rates (± SD) at 10, 20 years, and the end of follow-up are indicated.*

Table 6. Predictors of total events.

	Univariate analysis		Multivariate analysis	
Candidate variables	**HR (95% CI)**	**p value**	**HR (95% CI)**	**p value**
Baseline age >30 years	8.59 (4.55–16.24)	**<0.001**	1.22 (0.38–3.94)	0.742
Male sex	0.77 (0.43–1.37)	0.367		
Hypertension	4.43 (2.36–8.31)	**<0.001**	1.88 (0.77–4.58)	0.165
Hyperlipidaemia	8.68 (3.38–22.25)	**<0.001**	1.56 (0.50–4.85)	0.444
Diabetes mellitus	2.37 (0.39–14.47)	0.351		
Smoking status	2.58 (1.22–5.43)	**<0.05**	2.29 (0.81–6.46)	0.118
Obesity	0.82 (0.26–2.56)	0.733		
Previous diagnosis of CoA	1.32 (0.67–2.58)	0.419		
Previous aorta/AV intervention	0.69 (0.35–1.36)	0.281		
TAA dilatation (>40 mm)	6.14 (2.61–14.43)	**<0.001**	1.31 (0.37–4.62)	0.655
Moderate–severe AV dysfunction	5.22 (2.87–9.49)	**<0.001**	3.19 (1.35–7.54)	<0.01
Moderate–severe AS	2.99 (1.37–6.53)	**<0.01**	3.08 (0.78–12.12)	0.108
Moderate–severe AR	2.08 (0.93–4.62)	0.073		
Leaflet thickening	4.63 (2.49–8.60)	**<0.001**	1.96 (0.63–6.07)	0.244
Leaflet calcification	17.18 (6.32–46.72)	**<0.001**	4.72 (1.91–11.64)	<0.005
LVH	4.16 (1.95–8.88)	**<0.001**	2.20 (0.84–5.76)	0.108
LVD	3.07 (1.50–6.29)	**<0.005**		
LVEF <50%	3.26 (0.59–18.20)	0.178		
LAE	4.37 (1.61–11.87)	**<0.005**	2.18 (0.55–8.65)	0.269
RVD	1.46 (0.09–23.89)	0.791		

AR = aortic regurgitation; AS = aortic stenosis; AV = aortic valve; CI = confidence interval; CoA = aortic coarctation; HR = hazard ratio; LAE = left atrial enlargement; TA = thoracic ascending aorta; LVD = left ventricular dilatation; LVEF = left ventricular ejection fraction; LVH = left ventricular hypertrophy; RVD = right ventricular dilatation

closest follow-up than those without it[13]; however, other mechanisms rather than turbulent flow could be involved in development of bicuspid aortic valve degeneration. As previously described for tricuspid aortic valves, some cardiovascular risk factors showed significant association with progression of disease.[20–22] This probably applies to bicuspid valves as well, and could be a possible explanation for our findings of hyperlipidaemia and hypertension as independent predictors of interventional events.

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Table 7. Predictors of Interventional events.

	Univariate analysis		Multivariate analysis	
Candidate variables	**HR (95% CI)**	**p value**	**HR (95% CI)**	**p value**
Baseline age >30 years	8.03 (4.27–15.09)	**<0.001**	2.59 (1.12–5.99)	**<0.05**
Male sex	0.68 (0.37–1.23)	0.198		
Hypertension	4.02 (2.15–7.52)	**<0.001**	2.49 (1.07–5.80)	**<0.05**
Hyperlipidaemia	6.57 (2.84–15.20)	**<0.001**	3.46 (1.15–10.43)	**<0.05**
Diabetes Mellitus	3.09 (0.50–18.89)	0.223		
Smoking status	2.66 (1.26–5.59)	**<0.05**	2.52 (0.96–6.60)	0.059
Obesity	0.77 (0.23–2.57)	0.672		
Previous diagnosis of CoA	1.29 (0.64–2.57)	0.474		
Previous aorta/AV intervention	1.76 (0.84–3.70)	0.134		
TAA dilatation (>40 mm)	5.12 (2.31–11.32)	**<0.001**	1.91 (0.61–5.96)	0.267
Moderate–severe AV dysfunction	5.46 (2.97–10.02)	**<0.001**	1.85 (0.59–5.83)	0.295
Moderate–severe AS	7.57 (3.57–16.06)	**<0.001**	7.65 (2.97–19.73)	**<0.001**
Moderate–severe AR	2.49 (1.26–4.93)	**<0.01**	4.17 (1.63–10.43)	**<0.005**
Leaflet thickening	3.86 (2.02–7.41)	**<0.001**	1.63 (0.70–3.81)	0.257
Leaflet calcification	8.01 (3.63–17.68)	**<0.001**	1.59 (0.48–5.26)	0.446
LVH	3.86 (1.85–8.08)	**<0.001**	1.02 (0.34–3.05)	0.970
LVD	2.94 (1.44–6.00)	**<0.005**	1.88 (0.61–5.80)	0.275
LVEF <50%	4.31 (0.77–24.11)	0.096		
LAE	2.34 (0.93–5.92)	0.071		
RVD	2.00 (0.12–32.79)	0.627		

AR = aortic regurgitation; AS = aortic stenosis; AV = aortic valve; CI = confidence interval; CoA = aortic coarctation; HR = hazard ratio; LAE = left atrial enlargement; TA = thoracic ascending aorta; LVD = left ventricular dilatation; LVEF = left ventricular ejection fraction; LVH = left ventricular hypertrophy; RVD = right ventricular dilatation

Incidence of medical events was almost half of interventional events, with a 20-year incidence of $20 \pm 4\%$. In total, 11 patients (5%) had at least an episode of infectious endocarditis during the follow-up, slightly higher than the 2–3% reported in previous population-based and tertiary-referral-based studies.[13,14,23] Surgical treatment, however, was required in only 54% of these patients, which is similar to rates described for general population endocarditis[24] and far below the 75% reported in a recent multi-centre observational study.[25] Another encouraging observation was the low rate of dissection, with only two cases in the 227 patients analysed (0.07%/patient-year), similar to that observed by Tzemos et al (0.1%/patient-year)[14] and Michela et al (0.03%/patient-year).[26] The overall relatively lower dissection incidence in bicuspid aortic valve could be partially explained by prophylactic aortic repair, the larger diameters at which dissection occurs compared with tricuspid aortic valve patients with ascending aortic dissection,[9] and also by the higher proportion of bicuspid aortic valve patients with no progression of aortic dilatation compared with the aortic root in Marfan syndrome patients.[27]

Study limitations

First, our study has limitations related to the enrolment of cases from a single tertiary centre. This could have led to overestimation of the severity of valvular lesions, aortic dimensions, and rates of progression as our patients might have had more advanced BAV than those in community-based studies. Another fact that may contribute to this overestimation is our cohort including ~30% patients with associated CHD and 50% patients previously followed-up by paediatric cardiologists. This probably represents a higher morbidity population than adults in community receiving a new diagnosis of bicuspid aortic valve. Therefore, the morbidity associated with bicuspid aortic valve could be overestimated as compared with that in the general population.

Second, we would like to highlight the fact that the studied population included mostly young adults and were relatively free of baseline aortic dilatation. This may have led to a predilection for valve events in follow-up, as age and diameter of the aorta are two of the main predictors of aorta events

Third, we also acknowledge the inability to evaluate other important contributing factors for outcomes as data were retrospectively collected.

To conclude, with major improvements in echocardiography during the study period, with higher reliable measurements of the severity of aortic valve disease since the emergency of continuous-wave Doppler, we consider that adequate techniques were used throughout the study period to rank the severity of aortic valve function, always following the state of

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art. We are also aware that the transthoracic echocardiography measurements of the thoracic aorta are substantially lower than those measured by more accurate methods such as gate CT[28] or MRI, and as we did not compare the diameters between these methods in patients analysed by the two techniques we cannot ensure that the rate of thoracic aorta dilatation is underestimated in our study.

Conclusions

In this tertiary referral centre study of adults with bicuspid aortic valve, the long-term survival was excellent but with occurrence of frequent cardiovascular events, mainly aortic valve or thoracic aorta interventions. Patients with aortic valve dysfunction and leaflets calcification at baseline were at higher risk for cardiac events. Not only age and moderate or severe aortic valve stenosis and regurgitation were independent predictors of interventional events but also were cardiovascular risk factors such as hypertension and hyperlipidaemia. Even those with no baseline aortic valve dysfunction had a high 20-year incidence rate of interventional events. Therefore, all patients with bicuspid aortic valve will need serial evaluations of aortic dimensions and aortic valve, with a periodicity dictated by the clinical condition and individual risk factors.

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Conflicts of Interest

None.

Ethnical Standards

This research does not involve human and/or animal experimentation. All authors have contributed to the study design and data acquisition, analysis, and interpretation. The presented manuscript was reviewed and approved by all authors.

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