Sex Differences in Phenotypes of Bicuspid Aortic Valve and Aortopathy

Insights From a Large Multicenter, International Registry

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Background—This large multicenter, international bicuspid aortic valve (BAV) registry aimed to define the sex differences in prevalence, valve morphology, dysfunction (aortic stenosis/regurgitation), aortopathy, and complications (endocarditis and aortic dissection).

Methods and Results—Demographic, clinical, and echocardiographic data at first presentation of 1992 patients with BAV (71.5% men) were retrospectively analyzed. BAV morphology and valve function were assessed; aortopathy configuration was defined as isolated dilatation of the sinus of Valsalva or sinotubular junction, isolated dilatation of the ascending aorta distal to the sinotubular junction, or diffuse dilatation of the aortic root and ascending aorta. New cases of endocarditis and aortic dissection were recorded. There were no significant sex differences regarding BAV morphology and frequency of normal valve function. When presenting with moderate/severe aortic valve dysfunction, men had more frequent aortic regurgitation than women (33.8% versus 22.2%, $P<0.001$), whereas women were more likely to have aortic stenosis (34.5% versus 44.1%, $P<0.001$). Men had more frequently isolated dilatation of the sinus of Valsalva or sinotubular junction (14.2% versus 6.7%, $P<0.001$) and diffuse dilatation of the aortic root and ascending aorta (16.2% versus 7.3%, $P<0.001$) than women. Endocarditis (4.5% versus 2.5%, $P=0.037$) and aortic dissections (0.5% versus 0%, $P<0.001$) occurred more frequently in men.

Conclusions—Although there is a male predominance among patients with BAV, men with BAV had more frequently moderate/severe aortic regurgitation at first presentation compared with women, whereas women presented more often with moderate/severe aortic stenosis compared with men. Furthermore, men had more frequent aortopathy than women. **(*Circ Cardiovasc Imaging*. 2017;10:e005155. DOI: 10.1161/CIRCIMAGING.116.005155.)**

Key Words: aortic disease ■ aortic valve stenosis ■ bicuspid aortic valve ■ endocarditis

Bicuspid aortic valve (BAV) is three times more prevalent among men than women.[1,2] However, sex differences in patients with BAV have not been extensively studied. A recent study of patients with BAV who underwent surgical aortic valve replacement showed that women presented more frequently with aortic stenosis and smaller maximal aortic diameter compared with men.[3] In addition, women were referred for surgical aortic valve replacement at an older age than men, and aortic aneurysm repair was less frequently performed in women than in men.[4] However, these results may not be extended to large unselected cohorts of patients with BAV without indication for surgery. Accordingly, this study evaluated the sex-related differences in valve morphology, valvular function at presentation (normal, stenosis, and regurgitation), aortopathy, frequency of endocarditis, and aortic dissection in a large multicenter, international registry of patients diagnosed with BAV. Specifically, the proportion of each morphological type of BAV and its relationship with valve dysfunction and aortopathy in men versus women

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were evaluated. In addition, the differences between men and women in dimensions of various aortic segments were assessed. The findings may help to establish the most appropriate clinical surveillance and management of men and women with BAV.

Methods

Patient Population

This BAV multicenter registry was established at the Department of Cardiology of the Leiden University Medical Centre (The Netherlands) in collaboration with 4 other departments of Cardiology across 4 countries (Singapore, Australia, Canada and Romania). Data were collected in accordance with regulations approved by Institutional Review Boards. In total, 2139 patients from June 1991 until November 2015 with an echocardiographic diagnosis of BAV from these 5 centers were retrospectively reviewed and included in this study. The inclusion criteria were BAV documented on transthoracic echocardiography and complete clinical record data. Completeness of clinical record data was defined by the presence of a clinical history, including demographics, anamnesis, physical examination, electrocardiographic, echocardiographic, and laboratory data. The final patient population consisted of 1992 patients with BAV. Demographic data and medical history were retrieved from the baseline data of medical record. Ethics approval was provided by institutional review boards of the research centers with permission to access to healthcare record and imaging data. Because of the retrospective study design, the requirement for written informed consent was waived.

Patient Data

Detailed clinical and imaging characteristics of patients with BAV who met the echocardiographic criteria were evaluated. Medical records were reviewed to document baseline demographics (at the time of the echocardiographic study) including age, sex, height, weight and body surface area (BSA) and cardiovascular risk factors. Body surface area was calculated with the Mosteller method.[5] Hypertension was defined as per Joint National Committee VII guideline or the use of antihypertensive medication within 6 months before or after the echocardiogram was obtained.[6]

Echocardiographic Data

Comprehensive transthoracic echocardiography was performed according to current recommendations. The first echocardiogram with the diagnosis of BAV was considered for this analysis. All echocardiographic studies were performed using commercially available equipment and were retrospectively analyzed without knowledge of the clinical data. Left ventricular ejection fraction was calculated using the Simpson method.[7]

Aortic valve morphology was obtained in multiple parasternal long- and short-axis views. Diagnosis of BAV was based on transthoracic echocardiographic short-axis views showing the existence of only 2 commissures in systole. The BAV was classified according to Sievers classification (Figure 1).[8] The "unicuspid" aortic valves were included in the type 2 BAV.

Valve function was classified as normal, stenotic, or regurgitant. Aortic stenosis and aortic regurgitation were graded as mild, moderate, or severe on the basis of the European Association of Cardiovascular Imaging and the American Society of Echocardiography recommendations.[9,10]

For the evaluation of aortopathy, various segments of the aortic root–the sinus of Valsalva (SOV), sinotubular junction (STJ) and 5 cm distal to the STJ, the ascending aorta (AA)–were measured by using the leading edge to leading edge technique in the parasternal long-axis view perpendicular to the centerline of the aorta.[11] Enlarged aortic root dimension (SOV and STJ) was based on the nomogram by Roman et al,[12] and aortopathy was defined by an AA diameter of ≥40 mm. The classification of aortic dilatation configurations was as follows (Figure 2): dilatation of the aortic root (including SOV or STJ), isolated dilatation of the AA, and diffuse dilatation of the aortic root and AA.[13]

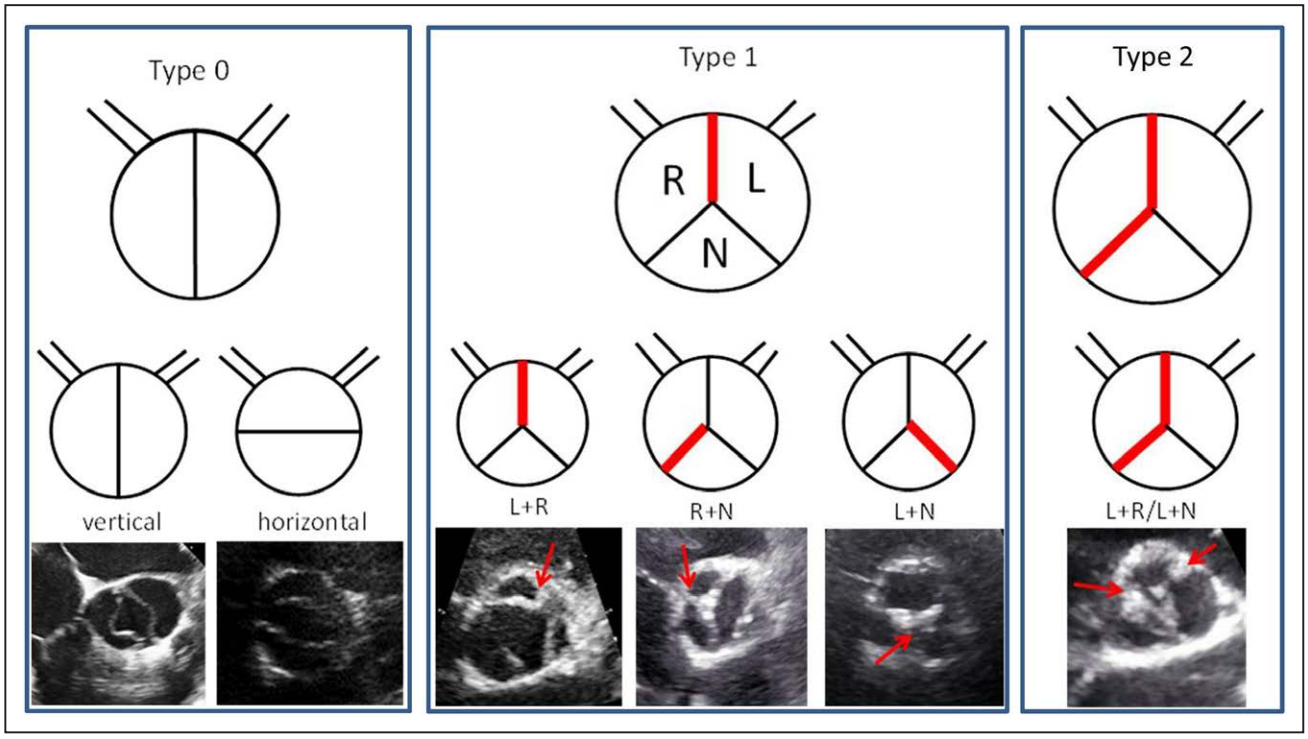

Figure 1. Correspondence between the classification of Sievers et al[8] and 2-dimensional echocardiographic views of bicuspid aortic valves (BAVs). Aortic valves are visualized from the short-axis views (from a left ventricular view). Red bands and arrows represent the raphe (commissural fusion). Type 0 denotes BAVs with 2 cusps, 2 commissures but no raphe, and types 1 and 2 denote BAVs with 1 or 2 fusion raphes, respectively.

Statistical Analysis

Continuous variables are expressed as mean±SD deviation after the assessment of a normal distribution, and categorical variables as frequency and percentage. The unpaired Student *t* test was used to compare continuous variables between the groups. The χ^2 test or the Fisher exact test were used to compare categorical variables as appropriate. Demographic variables as well as valvular and aortic characteristics of men and women with BAV were compared using general linear models for continuous variables and χ^2 tests for categorical variables. Association of valve morphology and function with aortopathy was determined using general linear models to examine differences of least square means. Unadjusted and adjusted general linear models were used to evaluate the differences in aortic dimensions between the groups. The unadjusted and adjusted mean differences and 95% confidence intervals were reported. A *P* value of <0.05 was considered statistically significant. SPSS version 20.0 software (IBM Corp, Armonk, NY) was used for statistical analysis.

Results

Patient Characteristics

Table 1 outlines the demographic variables of the patient population. The final population consisted of 1992 patients; of these, 1424 (71.5%) were male and 568 (28.5%) were female. There were no differences in the mean age at diagnosis between the 2 groups (46.8±17.5 versus 46.6±19.2 years, *P*=0.77). There were significant sex differences for height, weight, and BSA. The prevalence of hypertension, diabetes mellitus, smoking and dyslipidaemia was similar between the 2 groups.

Sex Differences in BAV Morphology

In the overall population, the most common BAV morphology was type 1 with fusion raphe between the left and right coronary cusps (n=1368, 68.7%) and the least frequent was the type 2 BAV with 2 raphe (n=8, 0.4%). Because of the low number of patients included in type 2 BAV, this group of patients was excluded from the analysis. There were no significant differences between men and women in terms of BAV morphology. Both groups had predominantly type 1 BAV with fusion of the left and right coronary cusps (69.1% versus 67.6%, respectively; *P*=0.63) followed by type 1 BAV with fusion of the non- and right coronary cusps (16.8% versus 17.5%, respectively; *P*=0.63) and type 0 BAV (9.5% versus 11.6%, respectively; *P*=0.63).

Sex Differences in Aortic Valve Function

The prevalence of aortic valve dysfunction was common in both groups of patients, with only 15.3% of patients with normal valve function (15.4% in men versus 14.8% in women, *P*=0.71). When presenting with moderate/severe aortic valve dysfunction, men had more frequently aortic regurgitation than women (33.8% versus 22.2%, *P*<0.001), whereas women were more likely to have aortic stenosis (34.5% versus 44.1%, *P*<0.001).

Sex Differences in Aortic Dimensions and Aortopathy

There were significant differences in the aortic dimensions between the groups as shown in Table 2. The linear dimensions of the SOV, STJ, and AA were significantly larger in men compared with women. However, after adjustment for age, BSA, hypertension, dyslipidaemia, diabetes mellitus, smoking, aortic valve dysfunction, and left ventricular ejection fraction, the SOV and STJ diameters remained significantly larger in men compared with women, whereas the differences in AA diameter were not statistically significant (Figure 3).

Aortopathy was common in the overall population (n=697, 35%). Men presented more frequently with isolated aortic root dilatation (14.2% versus 6.7%, *P*<0.001) and diffuse dilation of the aorta (16.2% versus 7.3%, *P*<0.001) when compared with women.

When dividing men and women with BAV into aortic dimensions <40 mm, 40 to 44 mm, 45 to 49 mm, 50 to 54 mm, and ≥55 mm, men had significantly higher percentage of individuals with aortic dilatation between 40 to 44 mm (24% versus 17%) and 45 to 49 mm (14% versus 9%) when compared with women (*P*<0.001, Table 3).

Endocarditis and Aortic Dissection

In the overall population, endocarditis was recorded in 78 (3.9%) patients during a median follow-up of 5.4 years after the index echocardiography. The frequency of endocarditis was higher in men than in women (4.5% versus 2.5%, *P*=0.037). All aortic dissections (n=9) were observed in men.

Discussion

This large multicenter, international registry reported on the sex differences in patients with BAV: men and women had equal proportion of each morphology type of BAV. Men with BAV had more frequently moderate/severe aortic regurgitation at first presentation compared with women, whereas women presented more often with moderate/severe aortic stenosis compared with men. The overall prevalence of aortopathy

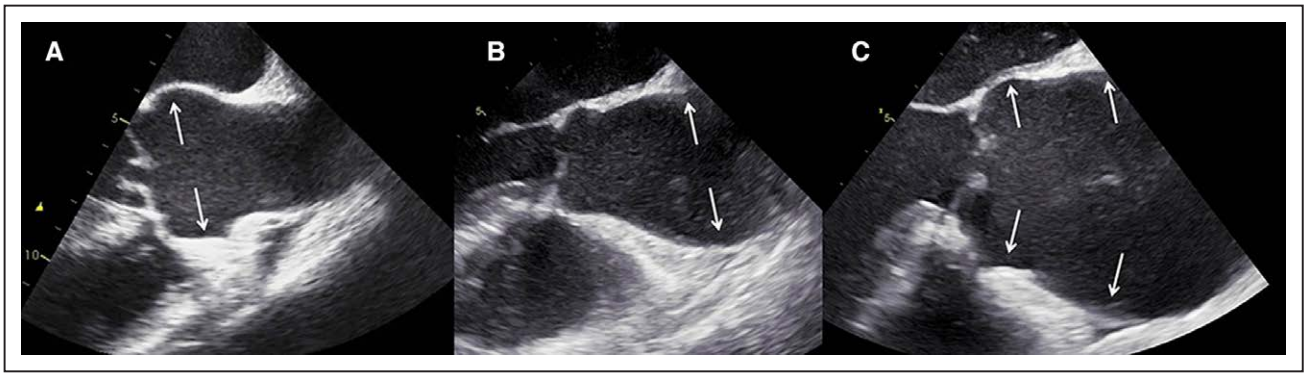

Figure 2. The classification of aortopathy: dilatation of the aortic root (including sinus of Valsalva or sinotubular junction) (**A**), isolated dilatation of the ascending aorta (**B**), and diffuse dilatation of the aortic root and ascending aorta (**C**). The arrows indicate the dilated levels.

Table 1. Baseline and Echocardiographic Characteristics of the Male and Female Patients With BAV

	All Patients (n=1992)	Men (n=1424)	Women (n=568)	*P* Value
Age, y	46.7±17.9	46.8±17.5	46.6±19.2	0.77
Body surface area, m^2	1.89±0.26	1.94±0.26	1.76±0.22	<0.001
Height, cm	171.9±11.6	174.7±11.3	164.9±9.3	<0.001
Weight, kg	76.2±18.0	79.1±18.1	68.8±15.4	<0.001
Hypertension, n (%)	650 (34.2)	463 (32.5)	187 (32.9)	0.75
Dyslipidaemia, n (%)	509 (26.8)	364 (25.6)	145 (25.5)	0.98
Diabetes mellitus, n (%)	201 (10.7)	153 (10.7)	48 (8.5)	0.15
Smoking, n (%)	305 (16.3)	230 (16.2)	78 (13.7)	0.49
Morphology of BAV, n (%)				0.63
Type 0	201 (10.1)	135 (9.5)	66 (11.6)	
Type 1 L+R	1368 (68.7)	984 (69.1)	384 (67.6)	
Type 1 R+N	328 (16.5)	239 (16.8)	89 (15.7)	
Type 1 L+N	87 (4.4)	60 (4.2)	27 (4.8)	
Type 2	8 (0.4)	6 (0.4)	2 (0.4)	
Normal valve function, n (%)	304 (15.3)	220 (15.4)	84 (14.8)	0.71
Aortic stenosis, n (%)				<0.001
None	88 (45.4)	687 (48.2)	200 (35.2)	
Mild	327 (16.7)	220 (15.4)	107 (18.9)	
Moderate	344 (17.6)	241 (16.9)	103 (18.2)	
Severe	397 (20.3)	250 (17.6)	147 (25.9)	
Aortic regurgitation, n (%)				<0.001
None	782 (39.3)	531 (37.3)	251 (44.3)	
Mild	602 (30.2)	411 (28.9)	191 (33.7)	
Moderate	367 (18.4)	278 (19.5)	89 (15.7)	
Severe	240 (12.1)	203 (14.3)	37 (6.5)	
Aortopathy, n (%)				<0.001
Normal	1295 (65.0)	859 (60.3)	436 (76.8)	
Dilated aortic root only	240 (12.0)	202 (14.2)	38 (6.7)	
Dilated ascending aorta only	185 (9.3)	132 (9.3)	53 (9.3)	
Diffuse dilatation	272 (13.7)	231 (16.2)	41 (7.3)	
Endocarditis, n (%)	78 (3.9)	64 (4.5)	14 (2.5)	0.037
Aortic dissection, n (%)	9 (0.5)	9 (0.6)	0	0.057
LVEF, %	60.6±12.0	60.1±12.2	61.9±11.5	<0.001

Values are mean±SD or n (%). BAV indicates bicuspid aortic valve; LVEF, left ventricular ejection fraction; type 1 L+N, type 1 BAV with fusion of the left and noncoronary cusps; type 1 L+R, type 1 BAV with fusion of the left and right coronary cusps; and type 1 R+N, type 1 BAV with fusion of the right and noncoronary cusps.

was higher in men than in women. Men had larger SOV and STJ but similar diameters of AA compared with women after adjustment for covariates. Endocarditis was more common in men than in women, whereas the incident cases of aortic dissection occurred only in men.

Sex Differences in BAV Morphology and Valve Function

The results of this study confirm the male predominance of BAV with a male:female ratio of 3:1.[14] To date, sex differences in terms of BAV morphology have not been extensively studied. About BAV morphology, data from the GenTAC registry presented at the 2015 American Heart Association Scientific Sessions meeting showed that among 424 patients with unoperated BAV, men had more frequently type 1 BAV with fusion between the left and right coronary cusps than women (81.5% versus 69.0%, *P*=0.03), whereas type 1 BAV with fusion between the right and noncoronary cusps was more frequently observed in women (18.5% versus 31.0%, *P*=0.03).[15] In contrast, the results of this study (n=1992 patients) showed that

Table 2. Unadjusted and Adjusted Analyses of Aortic Measurements Between Men and Women With Bicuspid Aortic Valve

	All Patients (n=1992)	Men (n=1424)	Women (n=568)	Unadjusted Analysis			Adjusted Analysis*		
				Difference	95% CI	*P* Value	Difference	95% CI	*P* Value
Aortic root									
Aortic annulus, mm	23.3±3.3	23.9±3.3	21.8±2.9	2.06	1.73–2.39	<0.001	0.88	0.58–1.19	<0.001
Sinus of Valsalva, mm	34.7±6.5	35.7±6.5	32.1±5.5	3.61	2.99–4.22	<0.001	1.77	1.21–2.33	<0.001
Sinotubular junction, mm	29.7±6.5	30.4±6.7	27.9±5.5	2.54	1.91–3.18	<0.001	0.73	0.14–1.32	0.016
Tubular ascending aorta, mm	36.7±7.7	37.3±7.7	35.4±7.4	1.97	1.22–2.72	<0.001	0.51	-0.22–1.24	0.17

CI indicates confidence interval.

*Adjusted for age, body surface area, hypertension, hyperlipidaemia, diabetes mellitus, smoking, aortic valve stenosis/regurgitation, and left ventricular ejection fraction.

type 1 BAV (fusion between left and right coronary cusps) was the most prevalent configuration without sex difference (69.1% in men versus 67.6% in women, *P*=0.63).

In terms of valve function, this study showed that men and women had comparable rates of normal valve function (15.3%). However, the majority of patients had some grade of valve dysfunction (84.7%). Significant aortic regurgitation was more frequently observed in men at first presentation, whereas women were more likely to present with significant aortic stenosis. Similarly, in the preliminary results of the GenTAC registry, the prevalence of normal valve function was 15%, men had more frequently aortic regurgitation compared with women (43.8% versus 25.0%, *P*=0.003) and women presented more frequently with aortic stenosis (30.0% versus 18.6%, *P*=0.033).[15]

On the basis of the high prevalence of valve dysfunction in patients with BAV, close echocardiographic monitoring is needed both in men and in women. Of interest, the type of valve dysfunction (stenosis or regurgitation) was not related to valve morphology but was related to sex suggesting other pathophysiological factors influencing the development of stenosis or regurgitation. This link should be further elucidated in future studies.

Sex Differences in Aortic Dimensions and Aortopathy

The higher frequency of aortopathy in men with BAV compared with women has been previously described in an autopsy study, including 162 patients.[16] In this study, men showed more frequent aortic dilatation (at the level of SOV and STJ) compared with women (Table 2, adjusted analysis). This may explain the higher prevalence of aortic regurgitation in men compared with women. Andrei et al[4] reported larger aortic dimensions in men when compared with women (43.6±7.9 mm versus 38.8±9.3 mm, respectively; *P*<0.001), but the location of the aortic dilatation was not specified. Of interest, the prevalence of hypertension was not different between men and women. One of the possible hypotheses underlying these differences is that undefined characteristics of the X chromosome protect women from developing aortopathy. For example, women with deficiency of X chromosome (Turner syndrome) have higher risk of BAV, aortic dilatation, aneurysm and dissection than women with normal chromosome (46, XX).[17] There have been few clinical and animal studies on the contribution of sex hormones to the development of aortic dilatation and aneurysm.[18–20] Alternatively, as suggested by Zhang et al,[18] there are some missing X-related factors that increase susceptibility to testosterone during early stages of development in an animal model. Experimental models of aortic aneurysm indicated that administration of testosterone promotes aortic aneurysm formation, whereas estrogen could prevent this process through reducing extracellular matrix-degrading enzymes.[18,19,21,22] Aortic distensibility, elasticity and stiffness can affect aortic dilatation in the BAV populations.[23] In cardiac MRI studies, women had higher aortic distensibility than men.[24] It is postulated that some intrinsic factors within the aortic wall, such as the cross-linking of extracellular matrix, could increase the aortic stiffness and prevent aortic dilatation in women with BAV.[25] These findings suggest that the evaluation of men with BAV should have specific focus on aortic dimensions. Whether the surveillance should be different in men than in women remains unknown because this study was cross-sectional. However, the higher frequency of aortic dissection in men than in women suggests that men with BAV should have regular follow-up of aortic dimensions with 3-dimensional imaging techniques, such as magnetic resonance or computed tomography, to determine the timing of surgery, particularly among those with fast growth rate.

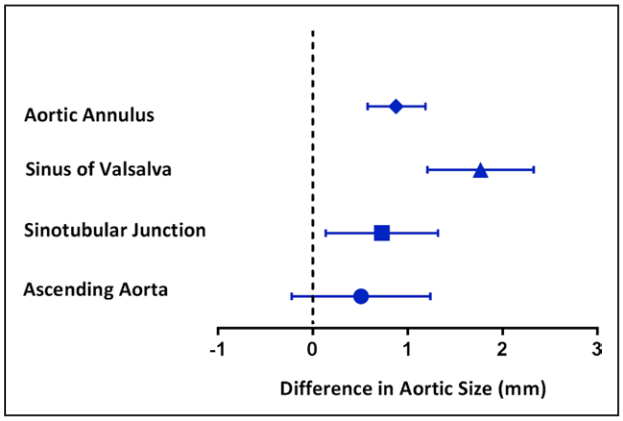

Figure 3. Female patients with bicuspid aortic valve (BAV) have smaller aortic root dimensions. Absolute differences in various aortic dimensions between men and women with BAV after adjustment for age, body surface area, hypertension, dyslipidaemia, smoking, diabetes mellitus, aortic valve dysfunction, and left ventricular ejection fraction. Women have a smaller aortic annulus, sinus of Valsalva and sinotubular junction but not ascending aorta compared with male patients. Data are shown as mean with 95% confidence intervals.

Table 3. Sex Distribution of Aortic Dimensions According to Established Cut-Off Values

Aortic Dilatation Cut-Off Values	Men, n=1424 (%)	Women, n=568 (%)
<40 mm	795 (56)	402 (70)
40–44 mm	344 (24)	96 (17)
45–49 mm	200 (14)	51 (9)
50–54 mm	56 (4)	14 (3)
≥55 mm	29 (2)	5 (1)

BAV Complications in Men and Women

On the basis of the earlier case series, the frequency of BAV endocarditis was estimated to range between 10% and 30%.[26] However, high rates were probably because of reporting bias in earlier studies, and more recent estimates of the frequency of endocarditis are much lower at 2%.[16] There is a strong male predominance among patients with BAV endocarditis.[27,28] In this study, the frequency of endocarditis among men was 4.5% compared with 2.5% in women. Whether the higher frequency of endocarditis in men is related to the higher prevalence of aortic regurgitation in BAV remains unclear.

The most feared complication in patients with BAV is aortic dissection, due to the high associated mortality rate. In a previous study, including 416 patients with BAV, aortic dissection occurred in 2 patients over a mean follow-up of 16 years, indicating the low incidence of this complication but still significantly higher than in the general population.[29,30] All aortic dissections occurred in men and male sex is a recognized risk factor for this complication.[31] However, Beller et al[32] did not manage to show any difference in percentage of patients with BAV presenting with dissection according to sex (25.8% versus 20.0%, P=0.4). This is most likely because of referral bias as in their study only patients with aneurysms of the AA eligible for cardiac surgery were retrospectively analyzed.[32] Nevertheless, the higher frequency of aortic complications among men with BAV compared with women suggests the need of close control of aortic dimensions over time.

Study Limitations

This study has all the inherent limitations of any retrospective study. The true prevalence of BAV with no functional abnormality may be underestimated since the majority of patients were referred for echocardiography because of the presence of clinical signs of stenosis/regurgitation. In addition, echocardiographic data were not analyzed in a core laboratory. However, the collaborators are experienced cardiologists from high volume referral centers with high expertise in valvular heart disease. For the assessment of the different segments of the thoracic aorta, MRI and computed tomography are preferred over transthoracic echocardiography. However, their use is limited because of relatively low availability and associated radiation, respectively. Finally, data on familial BAV were not systematically available.

Conclusions

From this large multicenter, international registry of patients with BAV, the disparities between men and women in terms of valve morphology and dysfunction as well as aortopathy and aortic dimensions were shown. There were no sex differences in terms of aortic valve morphologies. However, when presenting with moderate/severe valve dysfunction, men with BAV were more likely to present with significant aortic regurgitation, whereas women were more likely to present with significant aortic stenosis. Furthermore, men had higher overall frequency of aortopathy involving the aortic root or AA. Finally, complications, such as valve endocarditis and aortic dissection, were observed more frequently in men.

Acknowledgments

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Disclosures

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CLINICAL PERSPECTIVE

Bicuspid aortic valve is 3× more prevalent among men than women. However, the sex differences regarding type of bicuspid valve morphology and function at presentation and frequency of aortopathy, aortic dissection, and endocarditis are not well known. The present large multicenter, international registry including 1992 patients confirmed that bicuspid aortic valve is more frequently observed among men than women, but there are no differences in terms of valve morphology. In contrast, men presented more often with moderate/severe aortic regurgitation, whereas women presented more frequently with moderate/severe aortic stenosis. Interestingly, the type of valve dysfunction was not associated with the valve morphology, suggesting other pathophysiological determinants of the development of aortic stenosis or regurgitation. Furthermore, men had more frequently isolated dilatation of the sinus of Valsalva or sinotubular junction and diffuse dilatation of the aortic root and ascending aorta than women. Complications, such as endocarditis and aortic dissection, were more frequently recorded in men. These findings suggest that evaluation of bicuspid aortic valve in men should have specific focus on aortic dimensions and detection of potential complications over time. Whether the surveillance in men and women with bicuspid aortic valve should be different cannot be answered by this present study because of the cross-sectional design.

Sex Differences in Phenotypes of Bicuspid Aortic Valve and Aortopathy: Insights From a Large Multicenter, International Registry

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