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Inter-ethnic differences in valve morphology, valvular dysfunction, and aortopathy between Asian and European patients with bicuspid aortic valve

William K.F. Kong[1,2], Madelien V. Regeer[1], Kian K. Poh[2], James W. Yip[2], Philippe J. van Rosendael[1], Tiong C. Yeo[2], Edgar Tay[2], Vasileios Kamperidis[1,3], Enno T. van der Velde[1], Bart Mertens[4], Nina Ajmone Marsan[1], Victoria Delgado[1], and Jeroen J. Bax[1]*

[1]Department of Cardiology, Leiden University Medical Center, Albinusdreef 2, 2300 RC Leiden, The Netherlands; [2]Department of Cardiology, National University Heart Centre, National University Health System, 5 Lower Kent Ridge Rd, 119074 Singapore; [3]Department of Cardiology, AHEPA University Hospital, St.Kiriakidis 1, PO Box 54636 Thessaloniki, Greece; and [4]Medical Statistics Department, Leiden University Medical Center, Albinusdreef 2, 2300RC Leiden, The Netherlands

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Background Transcatheter aortic valve replacement (TAVR) has been shown safe and feasible in patients with bicuspid aortic valve (BAV) morphology. Evaluation of inter-ethnic differences in valve morphology and function and aortic root dimensions in patients with BAV is important for the worldwide spread of this therapy in this subgroup of patients. Comparisons between large European and Asian cohorts of patients with BAV have not been performed, and potential differences between populations may have important implications for TAVR.

Aim The present study evaluated the differences in valve morphology and function and aortic root dimensions between two large cohorts of European and Asian patients with BAV.

Methods and results Aortic valve morphology was defined on transthoracic echocardiography according to the number of commissures and raphe: type 0 = no raphe and two commissures, type 1 = one raphe and two commissures, type 2 = two raphes and one commissure. Aortic stenosis and regurgitation were graded according to current recommendations. For this study, aortic root dimensions were manually measured on transthoracic echocardiograms at the level of the aortic annulus, sinus of Valsalva (SOV), sinotubular junction (STJ), and ascending aorta (AA). Of 1427 patients with BAV (45.2 ± 18.1 years, 71.9% men), 794 (55.6%) were Europeans and 633 (44.4%) were Asians. The groups were comparable in age and proportion of male sex. Asians had higher prevalence of type 1 BAV with raphe between right and non-coronary cusps than Europeans (19.7% vs. 13.6%, respectively; $P < 0.001$), whereas the Europeans had higher prevalence of type 0 BAV (two commissures, no raphe) than Asians (14.5% vs. 6.8%, respectively; $P < 0.001$). The prevalence of moderate and severe aortic regurgitation was higher in Europeans than Asians (44.2% vs. 26.8%, respectively; $P < 0.001$) whereas there were no differences in BAV with normal function or aortic stenosis. After adjusting for demographics, comorbidities, and valve function, the dimensions of the aortic annulus [mean difference 1.17 mm/m^2, 95% confidence interval (CI) 0.96–1.39], SOV (mean difference 1.86 mm/m^2, 95% CI 1.47–2.24), STJ (mean difference 0.52 mm/m^2, 95% CI 0.14–0.90) and AA (mean difference 1.05 mm/m^2, 95% CI 0.57–1.52) were significantly larger among Asians compared with Europeans.

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* Corresponding author. Tel: +31 71 526 2020, Fax: 31 71 526 6809, Email: j.j.bax@lumc.nl

Conclusions This large multicentre registry reports for the first time that Asians with BAV showed more frequently type 1 BAV (with fusion between right and non-coronary cusp) and have larger aortic dimensions than Europeans. These findings have important implications for prosthesis type and size selection for TAVR.

Keywords Bicuspid aortic valve • Aortic annulus • Aortopathy

Introduction

Transcatheter aortic valve replacement (TAVR) has been shown feasible and safe in patients with bicuspid aortic valve (BAV).[1–5] Accurate assessment of the valve morphology, particularly the presence of raphe, its location and the burden of calcification, as well as the aortic root dimensions are important to select the appropriate size of the prosthesis and minimize the complications.[2] Compared with patients with tricuspid aortic valve, patients with BAV have larger dimensions of the ascending aorta (AA) but similar aortic annulus dimensions.[6] The majority of the studies reporting on the prevalence of BAV in the general population, and the clinical history of this disease concerned populations from Western World countries. Data regarding BAV disease in Asian populations are lacking in the literature and the prevalence of BAV disease among Asian populations is unclear. Currently there are no clinical studies specifically reporting potential racial differences in BAV disease between European and Asian populations. Prevalence of each morphological type of BAV and dysfunction (stenosis vs. regurgitation) and the presence of associated dilation of the aortic root and AA among Asian populations have not been explored. Characterization of the aortic valve morphology and function, aortic annulus, root, and AA dimensions are important to select the prosthesis size and evaluate the suitability for TAVR. The aims of the present study were therefore to characterize the differences between European and Asian populations on (i) the proportion of each morphological type of BAV and valve function and on (ii) the aortic annulus, root and AA dimensions and frequency of aortopathy.

Methods

Patient population

From June 1992 to March 2016, the original echocardiograms of 1472 patients diagnosed with BAV from two different centres, Leiden University Medical Centre (The Netherlands) and The National University Hospital (Singapore) were evaluated. Of these 1472 patients diagnosed with BAV, 195 patients were excluded from this study due to (i) discrepancy in bicuspid status by at least 2 experienced cardiac imaging experts, (ii) incomplete clinical record data and poor visualisation of aortic valve and/or aortic root on the echocardiogram, and (iii) neonatal echocardiograms. A total of 1427 patients with BAV were included; of these, 794 patients were Europeans and 633 were Asians. Age, sex, height, weight, body mass index, and medical history of patients were retrieved from the medical records of each centre (EPD-Vision®, Leiden University Medical Center, Leiden, The Netherlands, CPSS 2.0®, National University Hospital, Singapore). The institutional review board of each centre approved this retrospective analysis of clinically acquired data and waived the need for written patient informed consent.

Echocardiographic data

All echocardiographic studies were performed using commercially available equipment and were retrospectively remeasured for this project. Aortic valve morphology was examined in multiple parasternal long- and short-axis views. The classification of BAV used in this study has been described previously (*Figure 1*).[7] The phenotype of BAV was based on the presence and number of fusion raphes between the cusps and the spatial orientation of the cusps. The 'unicuspid' valves were included in the BAV type 2. The dimensions of the aortic annulus, sinus of Valsalva (SOV), sinotubular junction (STJ) and, the AA (5 cm distal to the STJ) were measured using the leading edge to leading edge technique during end-diastole in the parasternal long-axis views and indexed to body surface area (BSA). If possible, the largest measurements distal to the STJ were performed.[8] Data on inter- and intra-observer variability for the echocardiographic measurements of the various aortic segments in our laboratory have been previously reported.[9] The intra-observer variability, displayed as 1.96 times the standard deviation of the difference between the two measurements was 1.6 mm for the annulus, 3.2 mm for the SOV, 4.2 mm for the STJ and 5.1 mm for the AA respectively. The inter-observer variability was 2.6 mm for the annulus, 3.9 mm for the SOV, 4.3 mm for the STJ and 4.4 mm for the AA respectively.

The aortic dilation configurations included aortic root dilation only, AA dilation and diffuse involvement of the aortic root and AA.[10] We defined dilated aortic root (SOV or STJ) based on the normogram by Roman *et al.*[11] and aortopathy was defined by the presence of a dilated AA ≥40 mm. The severity of aortic stenosis and aortic regurgitation were evaluated according to current recommendations.[12,13] Left ventricular ejection fraction (LVEF) was determined by Simpson's Biplane method as per current recommendations.[8]

Clinical data

For each individual patient, clinical data were obtained from medical records, outpatient clinic visits, and inpatient hospitalisation. Sex, age, height and weight (at the time of the echocardiographic study), cardiovascular risk factors (hypertension, diabetes mellitus, smoking history, and hypercholesterolaemia) were recorded. Hypertension was defined as per recent Joint National Committee VII guideline or use of antihypertensive medication 6 months before or after the echocardiogram was obtained.[14] BSA was calculated using the Mosteller method.[15] The ethnicity information of these 1427 patients with BAV was available as European or Asian based on their country of origin.

Statistical analysis

The SPSS version 20.0 software (Armonk, NY, USA: IBM Corp) was used for statistical analysis. Continuous variables were expressed as the mean ± standard deviation after assessment of a normal distribution, and categorical variables were expressed as frequency and percentage. The unpaired Student *t*-test was used to compare continuous variables between the groups and the χ^2 test for the comparison of categorical variables. Unadjusted and adjusted general linear models were used to evaluate the differences in aortic dimensions between populations. Age, sex,

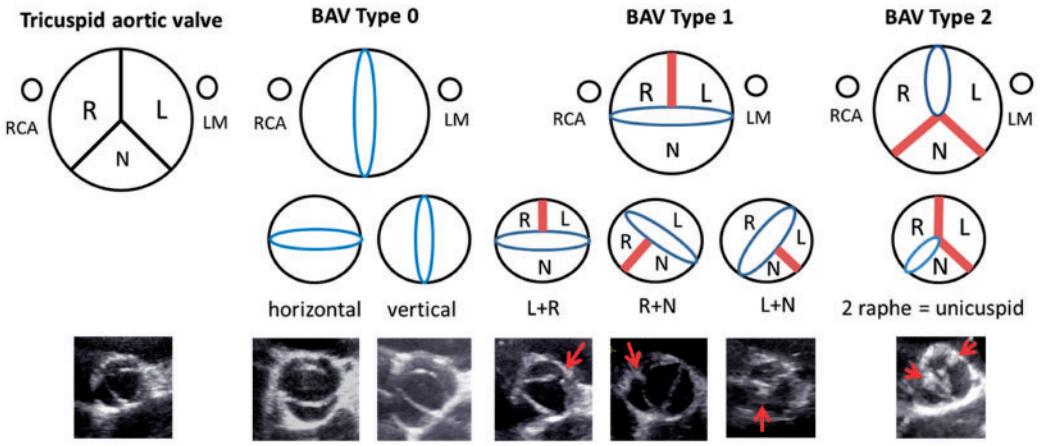

Figure 1 Schematic presentation and echocardiographic images of the different bicuspid aortic valve (BAV) morphologies. Red bands and arrows represent the raphe (commissural fusion). Type 0 denotes BAV without raphe and type 1 and 2 denote the presence of one or two raphes, respectively. The aortic valve is depicted in a cross-sectional short-axis view. The ostium of right coronary artery (RCA) is depicted on the left and the left main (LM) is on the right.

ethnicity, hypertension, dyslipidaemia, diabetes mellitus, smoking status, BAV morphology, and aortic regurgitation were included as covariates in the adjusted models. The unadjusted and adjusted mean differences and 95% confidence intervals were reported. A *P*-value < 0.05 was considered statistically significant.

Results

Patient characteristics

Patients' demographics and echocardiographic characteristics are provided in *Table 1*. Patients were separated into two groups based on their ethnicity: 794 (55.6%) were European and 633 (44.4%) were Asian. There were significant inter-ethnic differences for height, weight, BSA and cardiovascular risk factors. The Asian group had higher prevalence of hypertension, dyslipidaemia, and diabetes mellitus but lower incidence of smoking than the European group.

Differences between bicuspid aortic valve types

Overall the most prevalent BAV morphology was type 1 with fusion of the left and right coronary cusps ($n = 968$, 67.8%) whereas the type 2 BAV morphology (two raphes) was the least prevalent ($n = 8$, 0.6%). There were significant differences in the BAV morphology between the European and Asian patients. Both groups had predominantly type 1 BAV with fusion of the left and right coronary cusps (68.5% in Europeans vs. 67.0% in Asians). However, type 0 BAV (without fusion raphe) was more frequently observed among Europeans compared with Asians (14.5% vs. 6.8%, respectively; $P < 0.001$) whereas type 1 BAV with fusion raphe between the right and non-coronary cusps was more frequently observed in the Asian group compared with the European group (19.7% vs. 13.6%, respectively; $P < 0.001$).

Valve function

In both groups of patients, the prevalence of a normal functioning BAV was similar (12.6% vs. 12.3%, $P = 0.936$). Overall, significant aortic stenosis was more prevalent than significant aortic regurgitation (*Table 1*). Of interest, the European group had higher incidence of significant aortic regurgitation than the Asian group (44.2% vs. 26.8%, respectively; $P < 0.001$). There was no difference in the grades of aortic stenosis between the two groups.

Aortic dimensions and bicuspid aortopathy

The majority of patients showed normal dimensions of the aortic root and AA (67.8% among Europeans vs. 70.9% among Asians). The prevalence of dilated aortic root only and dilated AA only did not differ between the two groups. The most striking difference was in the prevalence of diffusely dilated type of aortopathy, which was more frequent in the European group than in Asian group (14.4% vs. 8.7%, respectively; $P = 0.008$).

There were significant differences in the aortic dimensions between the two groups (*Table 1*). The indexed diameters of the aortic annulus, SOV, STJ, and AA were significantly larger in the Asian group compared with the European group. These differences remained statistically significant after adjusting for age, sex, ethnicity, hypertension, dyslipidaemia, diabetes mellitus, smoking, morphology of BAV, and aortic valve dysfunction (*Table 2*).

Discussion

The main findings of our study (in which echocardiograms of 1427 patients were remeasured) are summarized as follows: there were significant differences in the BAV morphological types between the European and Asian patients, with type 0 being more frequently observed among Europeans, whereas type 1 with fusion raphe

Table 1 Clinical and echocardiographic characteristics of the patients with bicuspid aortic valve

	All Patients ($n = 1427$)	European ($n = 794$)	Asian ($n = 633$)	*P*-value
Age (years)	45.2 ± 18.1	44.4 ± 18.0	46.1 ± 18.2	0.093
Male gender (%)	1026 (71.9)	566 (71.3)	460 (72.7)	0.594
Body surface area (m^2)	1.84 ± 0.26	1.93 ± 0.25	1.75 ± 0.22	<0.001
Height (cm)	171.0 ± 11.6	175.9 ± 10.6	164.7 ± 9.6	<0.001
Weight (kg)	72.6 ± 16.9	78.0 ± 16.7	65.7 ± 14.7	<0.001
Hypertension	433 (30.7)	187 (24.0)	246 (38.9)	<0.001
Dyslipidaemia	352 (24.7)	143 (18.0)	209 (33.1)	<0.001
Diabetes mellitus	129 (9.1)	47 (5.9)	84 (13.3)	<0.001
Smoking	232 (16.5)	154 (19.4)	84 (13.3)	0.002
Morphology of BAV				<0.001
Type 0	158 (11.1)	115 (14.5)	43 (6.8)	
Type 1 L+R	968 (67.8)	544 (68.5)	424 (67.0)	
Type 1 R+N	233 (16.3)	108 (13.6)	125 (19.7)	
Type 1 L+N	60 (4.2)	22 (2.8)	38 (6.0)	
Type 2	8 (0.6)	5 (0.6)	3 (0.5)	
Aortic stenosis				0.138
None	515 (44.2)	350 (44.4)	265 (44.0)	
Mild	242 (17.4)	132 (16.8)	110 (18.3)	
Moderate	238 (17.1)	1264 (15.7)	114 (18.9)	
Severe	295 (21.2)	182 (23.1)	113 (18.8)	
Aortic regurgitation				<0.001
None	445 (31.2)	273 (34.4)	172 (27.2)	
Mild	461 (32.3)	170 (21.4)	291 (46.0)	
Moderate	308 (21.6)	212 (26.7)	96 (15.2)	
Severe	212 (14.9)	139 (17.5)	73 (11.6)	
Normal valve function	178 (12.5)	100 (12.6)	78 (12.3)	0.936
Aortic dimensions				
Aortic annulus indexed diameter (mm/m^2)	12.6 ± 1.9	12.2 ± 1.8	13.2 ± 1.9	<0.001
Sinus of Valsalva indexed diameter (mm/m^2)	18.7 ± 3.6	18.1 ± 3.3	19.6 ± 3.7	<0.001
Sinotubular junction indexed diameter (mm/m^2)	15.7 ± 3.4	15.6 ± 3.5	15.9 ± 3.2	<0.001
Ascending aorta indexed diameter (mm/m^2)	20.1 ± 4.2	19.7 ± 4.0	20.7 ± 4.5	<0.001
Pattern of aortic dilation				0.008
Normal	987 (69.2)	538 (67.8)	449 (70.9)	
Dilated aortic root only	133 (9.3)	73 (9.2)	60 (9.5)	
Dilated ascending aorta only	138 (9.7)	69 (8.7)	69 (10.9)	
Diffuse dilation of aorta	169 (11.8)	114 (14.4)	55 (8.7)	
LVEF (%)	62.3 ± 12.4	62.8 ± 12.8	61.7 ± 11.8	0.088

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

Table 2 Univariable and multivariable analysis of aortic measurements

	Unadjusted analysis			Adjusted analysis[a]		
	Difference	(95% CI)	*P*-value	Difference	(95% CI)	*P*-value
Aortic annulus (mm)	0.98	0.78–1.18	<0.001	1.17	0.96–1.39	<0.001
Sinus of Valsalva (mm)	1.53	1.15–1.91	0.001	1.86	1.47–2.24	<0.001
Sinotubular junction (mm)	0.31	0.06–0.68	0.097	0.52	0.14–0.90	0.008
Ascending aorta (mm)	0.97	0.52–1.43	<0.001	1.05	0.57–1.52	<0.001

CI: confidence interval.
[a]Adjusted for: age, gender, ethnicity, hypertension, dyslipidaemia, smoking, diabetes mellitus, and aortic regurgitation.

between the right and the non-coronary cusps was more often present in Asians; in addition, the European group had higher prevalence of significant aortic regurgitation and diffusely dilated type of bicuspid aortopathy compared with the Asian group; furthermore, the dimensions of the aortic annulus, SOV, STJ, and AA indexed for BSA were significantly larger among Asians as compared with Europeans correcting for several demographic, clinical and echocardiographic variables. These findings may have important implications for prosthesis type and size selection for TAVR.

Prevalence of bicuspid aortic valve and dysfunction across different ethnicities

There is limited information regarding the prevalence of BAV in Asian individuals. In a community-based cross-sectional study including 14 530 Chinese children, the prevalence of BAV was 7.9%.[16] However, data regarding morphology of BAV were not provided. Lee *et al.*[17] reported a prevalence of BAV of 0.16% ($n = 38$) in 23 291 Korean patients undergoing health screening between 2005 and 2010, with a predominance of male gender (92%). The majority of patients showed type 1 BAV configuration with a fusion raphe between the right and the left coronary cusps (63%) followed by the fusion between right and non-coronary cusps (29%), in line with the current findings.

Bicuspid aortic valve is frequently associated with valve dysfunction. In the present study, 12.5% of the overall population showed normal valve function, whereas significant aortic regurgitation was noted in 36.5% and significant aortic stenosis in 38.9%. The European patients more often had significant aortic regurgitation as compared with the Asian patients. Lee *et al.*[17] also showed that among 23 291 Korean individuals with BAV, aortic stenosis was more prevalent than aortic regurgitation (40% vs. 13%, respectively). The higher prevalence of significant aortic regurgitation in European patients may be related to the higher prevalence of aortopathy (particularly diffusely dilated pattern) compared with Asian patients. Of interest, when Caucasian patients and African–Americans with BAV were compared, no differences in prevalence of significant aortic stenosis or aortic regurgitation were detected.[18]

Aortic dilation and aortic phenotype across ethnicities

It has been suggested that specific BAV configurations are associated with aortopathy. The different configuration of BAV may lead to altered flow patterns, different wall strain, shear stress and other stress factors, which can affect the aortic media's integrity differently. Russo *et al.*[19] described, in 115 consecutive patients with BAV who underwent surgery of the AA, more fibrosis, medionecrosis, cystic medial necrosis, smooth muscle cell orientation and elastic fragmentation and inflammation in the AA of patients with fusion of the left and the right coronary cusps compared with other configurations. Using time-resolved three-dimensional phase contrast magnetic resonance imaging, Stephens *et al.*[20] demonstrated greater asymmetric wall shear stress in type 1 BAV with fusion of the left and right coronary cusps compared with type 0 BAV after valve sparing aortic root replacement. However, Mahadevia *et al.*[21] using four-dimensional flow magnetic resonance imaging observed that patients with type 1 BAV with fusion of the right and non-coronary cusps had more frequently dilation of the aortic root only or diffuse dilation of the AA and aortic arch whereas patients with type 1 BAV with fusion of the left and the right coronary cusps showed more frequently dilation of the tubular AA.

In addition, the presence of aortic stenosis or aortic regurgitation has been also associated with the presence of aortopathy. Dilation of the tubular part of the AA was more frequently associated with aortic stenosis, suggesting post-stenotic dilation, whereas aortic root dilation was more prevalent in aortic regurgitation, and unrelated to the presence or severity of stenosis.[22]

Furthermore, the association between BAV and thoracic aortic aneurysms is well-established and it has been estimated that up to 20% of individuals with BAV may develop AA aneurysms.[23] Patients with TGFBR2 and ACTA 2 mutations have a slightly increased risk of this complication.[24,25] In addition, a recent report has shown that genetic variants in MAT2A predispose individuals to thoracic aortopathy.[26] In the present study, genetic testing was not performed. It may well be that differences in genetics and flow haemodynamics influenced the results.

Implications for transcatheter aortic valve replacement

Experience regarding TAVR in patients with BAV is accumulating. Several registries have demonstrated that TAVR is feasible and safe in these patients.[1,3–5] New-generation bioprosthetic valves were associated with less paravalvular leak and higher device success rate than early-generation devices.[27] However, the incidence of significant paravalvular regurgitation is still relatively high compared to patients with tricuspid aortic valves.[1,3–5] Multi-detector row computed tomography provides more precise measurements of the aortic annulus as compared with two-dimensional echocardiography to select the appropriate prosthesis size and its use has been associated with a reduction in the incidence of this complication.[2] Compared with tricuspid aortic valves, BAV show larger dimensions of the aortic annulus, SOV and AA and therefore, larger sizes of the transcatheter aortic valve prostheses may be needed.[5] In addition, BAV shows more frequently eccentric annular calcification compared with tricuspid valves which may influence the expansion of the prosthesis and lead to gaps between the prosthesis frame and the host annulus and subsequent paravalvular regurgitation. However, it remains unknown whether the different configuration of the BAV may also impact on the results of TAVR. The present study provides valuable information by describing the differences in BAV morphology and aortic root dimensions between Europeans and Asians. While type 1 BAV with fusion between the right and left coronary cusps was the most prevalent configuration, Asians showed higher frequency of type 1 BAV (with fusion between the right and non-coronary cusps) than Europeans. In addition, after adjusting for several demographic, clinical and BAV morphology and function, Asians showed larger indexed dimensions of the aortic annulus, root and AA compared to Europeans. These findings may be of importance in the development of new devices that may be more suitable for these anatomies than the currently available prostheses. In addition, when selecting patients with BAV for TAVR it is important to consider the need for aortic intervention. Current recommendations base the indication of aortic surgery on non-indexed dimensions of the aortic root and AA.[28]

The present results show that, based on non-indexed measurements, Europeans have more frequently diffuse dilation of the aorta whereas isolated dilation of the AA is more frequent among Asians. However, when indexing the dimensions for BSA, Asians have larger dimensions than Europeans.

Study limitations

The main limitation is the retrospective nature of this study. The analysis and re-assessment of the images were not performed blinded to ethnic origin. Some cases of dilated AA could be missed as the distal part of the AA could have been visualized inadequately during transthoracic echocardiography due to the limitation of this two-dimensional modality. The use of different ultrasound systems may have influenced the accuracy of the measurements. Technological advances of the last years may have resulted in better accuracy. With high sensitivity and specificity, transthoracic echocardiography will remain the main imaging modality for surveillance of BAV and aortopathy progression since multi-detector computed tomography and cardiac magnetic resonance may be less accessible.[29] There is possible referral bias as the centres of the study are tertiary referral hospitals for valve surgery and therefore the prevalence might not reflect the real prevalence of BAV in the general population.

Conclusions

There is significant heterogeneity in BAV and aortic dimensions across European and Asian patients. Type 1 BAV with fusion between the left and the right coronary cusps is the most frequent phenotype in both groups. However, type 0 (without raphe) is more frequently observed in Europeans and fusion raphe between the right and the non-coronary cusps is more frequently observed in Asians. In terms of aortic dimensions, Asians showed larger indexed dimensions at all the levels of the aorta as compared with Europeans. These findings may have important implications for prosthesis type and size selection for TAVR.

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