Aortic Cross-Sectional Area/Height Ratio and Outcomes in Patients With Bicuspid Aortic Valve and a Dilated Ascending Aorta

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Background—In patients with bicuspid aortic valve and dilated proximal ascending aorta, we sought to assess (1) factors associated with increased longer-term cardiovascular mortality and (2) incremental prognostic use of indexing aortic root to patient height.

Methods and Results—We studied 969 consecutive bicuspid aortic valve patients (50±13 years; 87% men) with proximal aorta ≥4 cm, who also had a gated contrast-enhanced thoracic computed tomography or magnetic resonance angiography. A ratio of ascending aortic area/height was calculated on tomography, and ≥10 cm^2/m was considered abnormal, as previously reported. Society of Thoracic Surgeons score and cardiovascular death were recorded. Greater than or equal to III+ aortic regurgitation and severe aortic stenosis were seen in 37% and 10%, respectively. Society of Thoracic Surgeons score and right ventricular systolic pressure were 2±3 and 15±16 mm Hg, respectively. Abnormal ascending aortic area/height ratio was noted in 33%; 44% underwent ascending aortic surgery at 34 days. At 10.8 years (interquartile range, 9.6–12.3), 82 (9%) died (0.4% in-hospital postoperative mortality). On multivariable Cox survival analysis, ascending aortic area/height ratio (hazard ratio, 2; 95% confidence interval, 1.20–3.35) was associated with cardiovascular death, whereas aortic surgery (hazard ratio, 0.46; confidence interval, 0.26–0.80) was associated with improved survival (both *P*<0.01). Of the 405 patients with ascending aortic diameter of 4.5 to 5.5 cm, 64% had an abnormal ascending aortic area/height ratio, and 70% deaths occurred in patients with an abnormal ratio.

Conclusions—In bicuspid aortic valve patients with dilated proximal ascending aorta, ascending aortic area/height ratio was independently associated with cardiovascular death. **(*Circ Cardiovasc Imaging*. 2017;10:e006249. DOI: 10.1161/CIRCIMAGING.116.006249.)**

Key Words: aneurysm ■ aorta ■ blood pressure ■ heart valve diseases ■ magnetic resonance angiography

Bicuspid aortic valve (BAV) is a common congenital cardiac abnormality in adults, affecting ≈1% to 2% adults.[1] In previous studies, using surface echocardiography, a high prevalence (20%–80%) of concomitant aortopathy has also been reported.[2–10] The major risk associated with aortopathy relates to progressive aortic dilation with subsequent dissection or rupture. Despite improvements in diagnostic and surgical techniques, the mortality of type A aortic dissection remains high, ranging from 14% to 30%.[11–13] Another issue is that patients with a catastrophic aortic rupture may die suddenly before medical aid can be administered. Indeed, there is a potential for significant ascertainment bias in such patients in whom cause of death may or may not be appropriately attributed to aortic rupture, if it were to happen suddenly. Hence, pre-emptive aortic surgery is recommended in BAV patients whose aortic dimensions reach a certain threshold. Indeed, as recently demonstrated in patients with appropriately timed aortic surgery, the incidence of long-term events (aortic rupture and dissection) tends to be low, with a significantly improved survival in those who underwent aortic surgery versus those who did not, similar to an age- and sex-matched normal population.[10]

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However, there remains controversy as to the most appropriate threshold of aortic measurement at which prophylactic surgical intervention on the aorta is indicated.[14–16] The 2010 American College of Cardiology/American Heart Association thoracic aortic guidelines suggest aortic surgery at a threshold of 5 cm; however, the 2014 American College of Cardiology/American Heart Association valve guidelines recommended increasing the threshold for isolated replacement of the aorta to 5.5 cm, with the justification that the rate of dissection in

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previous studies was low.[9,14,17] On the contrary, prior data have suggested that ≈40% patients (including patients with BAV aortopathy) have an aortic diameter <5 cm at the time of presentation with type A dissection.[18] Furthermore, absolute aortic diameter cutoffs have inherent limitations, including failure to account for size/height, sex,[19,20] and irregular elliptical shape of the aorta (frequently observed in BAV[1,10]). Therefore, previous reports have suggested indexing aortic dimensions using either body surface area (BSA) or height.[21–25] Specifically, a cutoff of aortic area/height >10 cm^2/m has been shown in previous reports to be associated with aortic dissection in patients with bicuspid aortopathy and Marfan syndrome[21,22,24] and has been included in the most recent guidelines as an indication for elective aortic repair.[15] In a recent study, we have demonstrated its incremental prognostic use in patients with a trileaflet aortic valve and dilated proximal aorta.[26] However, in BAV patients with a dilated aortic root or ascending aorta, there are no large-scale data evaluating the incremental prognostic use of this index for actual mortality. Thus, in a large group of contemporary BAV patients with a dilated proximal ascending aorta, we sought to assess (1) the factors associated with increased longer-term mortality and (2) the incremental prognostic use of indexing ascending aorta (or aortic root) to the patient's height.

Methods

This was an observational cohort study of 969 consecutive adult patients (≥18 years of age) with BAV and a dilated ascending aorta with an initial evaluation at our tertiary care center between 2003 and 2007. Patients were included if (1) a dilated (≥4 cm) aortic root or ascending aorta was identified on an initial transthoracic echocardiogram in the setting of a BAV and (2) either a contrast-enhanced computed tomographic angiogram or a contrast-enhanced magnetic resonance angiogram of the chest confirmed the initial echo measurement. We excluded patients whose initial presentation to our institution with type A dissection and those with known Turner syndrome. Appropriate approval was obtained from the institutional review board with waiver of individual informed consent. Clinical data were manually extracted from electronic medical records, where it was entered prospectively at the time of initial encounter. History of various cardiovascular risk factors was recorded based on patient history and confirmed on guideline-based documentation or relevant therapies. Obstructive coronary artery disease was defined as a history (including a prior myocardial infarction) or documented as ≥70% (or ≥50% left main) stenosis on coronary angiography. Based on available data, Society of Thoracic Surgeons score was calculated.

Echocardiography

All patients underwent a comprehensive echocardiogram using commercially available instruments (Philips, WA; General Electric, WI; and Siemens, PA) as part of standard clinical diagnostic evaluation. Cardiac measurements were obtained according to the American Society of Echocardiography Recommendations.[27,28] Left ventricular ejection fraction was calculated using the Simpson biplane method. A semiquantitative 5-point scale (none, mild, moderate, moderate–severe, and severe) was used to stratify valvular regurgitation. Aortic regurgitation was measured according to guidelines, using multiple criteria, including ratio of aortic regurgitant jet/left ventricular outflow tract width ratio on parasternal views, density on spectral Doppler, color Doppler, and diastolic flow reversal in the thoracic aorta.

Diagnosis of BAV was based on multiple views during systole demonstrating 2 atrioventricular cusps and noting a raphe when present.[27] For quantification of aortic stenosis, left ventricular outflow tract diameter was measured on parasternal long-axis views.[27] Pulsed-wave and continuous-wave Doppler were used to record velocities across the left ventricular outflow tract and atrioventricular, respectively, from multiple windows. The atrioventricular area was calculated using the continuity equation. Severe aortic stenosis was defined as AVA ≤1 cm2 and mean atrioventricular gradient ≥40 mm Hg. A BAV risk score (between 0 and 3) was also calculated as follows: age >30 years, ≥III+aortic regurgitation, or >moderate aortic stenosis.[9] Aortic root (at the sinus of Valsalva) and ascending aortic diameters were recorded in the parasternal long-axis view, using the leading-edge to leading-edge technique, at end diastole.[28] Using aortic root dimensions, a *Z* score for adults was calculated using the following formula[25]: (measured diameter [cm]−predicted aortic root diameter [cm])/SD of 0.261. Predicted diameter was derived from the following formula: 2.423+(age in years×0.009)+(BSA×0.461)−(sex×0.267), with 1 for male and 2 for female. BSA (m^2) was calculated using the DuBois formula[29]: 0.007184×height (cm)$^{0.725}$×weight (kg)$^{0.425}$.

Tomographic Imaging

Patients underwent either a chest contrast-enhanced computed tomographic angiogram or contrast-enhanced magnetic resonance angiogram, at the discretion of the treating physician. For multidetector contrast-enhanced computed tomographic angiogram, patients were scanned using standard available scanners (Brilliance 64-slice; Philips Medical Systems, Best, The Netherlands, or Siemens 64-slice; Siemens Medical Solutions, Erlangen, Germany) after administration of low osmolar-iodinated contrast (80–100 mL of Ultravist 370) at 4 to 5 mL/s followed by 30 to 50 mL of normal saline. Bolus tracking technique using a region of interest in the ascending aorta was used, and scanning (from the carina to the diaphragm) was initiated in the craniocaudal direction during a single inspiratory breath-hold. Prospectively triggered axial or retrospectively gated spiral data were acquired. Tube voltage ranged from 100 to 120 kVp; tube current adjusted per patient weight; and beam pitch of 0.2 to 0.5 was used. In retrospective scans, ECG-based tube current modulation was used for all patients, with maximum current turned on during systole. In patients undergoing aortic contrast-enhanced magnetic resonance angiogram, it was performed on a commercially available 1.5 Tesla scanner (Achieva; Philips Medical Systems, or Avanto; Siemens Medical Solutions). After initial scout images, administration of 30 to 40 mL of gadolinium chelate and using bolus tracking technique, 3-dimensional thoracic aortic magnetic resonance angiography was performed in sagittal double-oblique plane using a breath-hold (representative parameters included field of view 360×320 mm, repetition time 5.2 ms, echo time 1.6 ms, and matrix 360×260 mm). Subsequently, using standard clinically available software (TeraRecon, Inc, Redwood City, CA), advanced offline 3-dimensional post processing of contrast-enhanced computed tomographic angiogram and aortic contrast-enhanced magnetic resonance angiogram images was performed using multiplanar and maximum intensity projections. Diameter and cross-sectional area of the ascending aorta was measured at the aortic root (maximum cusp to commissure diameter at the midpoint of the aortic sinus of Valsalva; Figure 1) and the mid portion of the ascending aorta (at the level of pulmonary artery bifurcation), using double-oblique reconstructions. Internal luminal measurements were made perpendicular to the axis of blood flow and indexed to patients' height.[15,21,22,24]

Classification of Aortopathy

Aortic root and ascending aortic diameters were classified as follows: normal (<4 cm), mild dilation (4–4.4 cm), moderate dilation (4.5–4.9 cm), mildly aneurysmal (5–5.4 cm), and severely aneurysmal (≥5.5 cm). Additionally, a ratio of ascending aorta (or aortic root area) to height ≥10 cm^2/m was considered as abnormal.[21]

Surgery During Follow-Up

Surgical procedures were recorded as follows: (1) isolated ascending aortic grafting, (2) ascending aortic grafting+atrioventricular repair/replacement, (3) ascending aortic grafting+coronary artery bypass grafting (CABG), and (4) ascending aortic grafting+atrioventricular

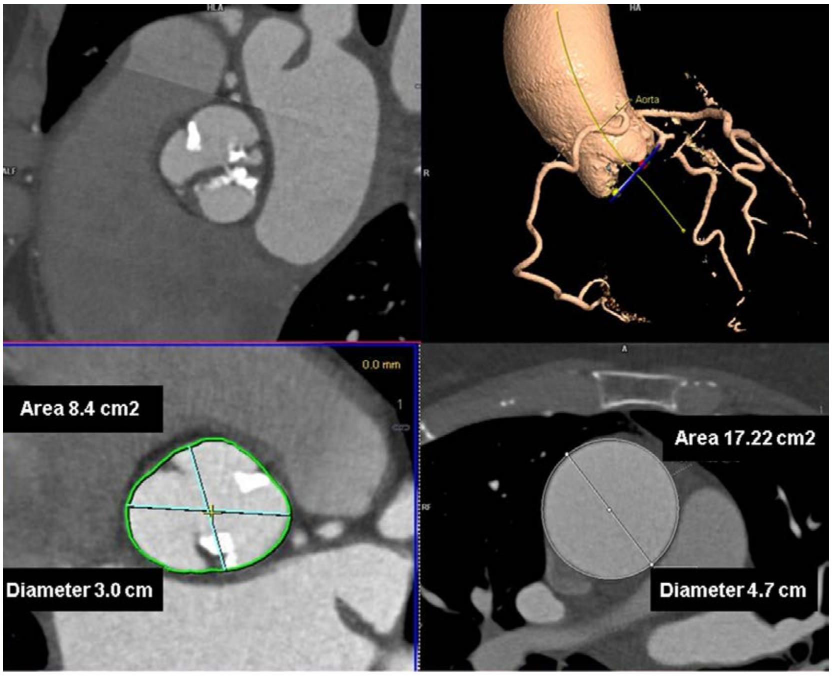

Figure 1. A contrast-enhanced computed tomographic scan in a female patient (height, 1.65 m) with a bicuspid aortic valve and dilated ascending aorta. **Top left** represents a multiplanar reformatted short-axis view of the bicuspid aortic valve. **Bottom left** represents multiplanar reformatted short-axis view of the aortic root with diameter and area measurements. **Top right** represents volume-rendered image with centerline reconstruction (yellow line) demonstrating the thoracic aorta, with a dilated ascending aorta. **Bottom right** represents multiplanar reformatted short-axis view of ascending aorta with diameter and area measurements. The ratio of aortic area/height is 10.42 cm^2/m.

repair/replacement+CABG. Time to surgery was recorded. All patients underwent a comprehensive evaluation, and the surgical decision was based on existing valvular and aortic guidelines.[14–16] Final operative technique was decided by the attending cardiothoracic surgeon. None of the patients had a comorbidity precluding undergoing cardiovascular surgery.

Outcomes

Mortality data were obtained from review of medical records, observation of death certificate, or state and nationally available databases, with subsequent confirmation with a family member. We categorized death as cardiovascular, noncardiac (eg, malignancy, cirrhosis of liver, and primary pulmonary/neurologic pathogenesis), or unknown. The primary outcome was cardiovascular death. If the cause of death could not be discerned, this was also categorized as cardiovascular in pathogenesis (and included as part of the primary outcome) unless the patient's proximal history strongly suggested a noncardiovascular cause.[30] The follow-up of the patients with a documented noncardiac death was censored at the time of event. In addition, we also recorded any type A dissection, occurring after the initial evaluation. Follow-up was defined as the time from initial echocardiogram to death or censoring (last query, August 2016).

Statistical Analysis

Continuous variables are expressed as mean±SD or median with interquartile range and compared using Student *t* test or Mann–Whitney *U* test, as appropriate. Distribution of continuous variables was tested for skewness using Kolmogorov–Smirnov test. Categorical data are expressed as percentage and compared using χ^2. To assess for primary outcomes, univariable and multivariable Cox proportional hazards analysis was used. For univariable analysis, individual associations of relevant predictors, known to be associated with primary outcome in this population, were tested. Subsequently, we created a parsimonious multivariable model incorporating various relevant variables that are typically associated with primary outcomes in such patients. Even though Society of Thoracic Surgeons score has only been validated to predict 30-day postoperative mortality, we used it in the survival analysis, because it is a composite of many factors that are known to be associated with adverse longer-term events.[31] An interaction term of cardiovascular surgery and root (or ascending aorta) ≥10 cm^2/m was entered in the multivariable model. Hazard ratios (HRs) with 95% confidence intervals (CIs) were calculated. Additionally, Kaplan–Meier survival curves were generated to determine the proportion of patients with primary events as a function over time and compared using log-rank statistic. We assessed the classification of risk using categorical net reclassification improvement. In addition, discriminative ability of various survival models to predict primary outcomes was compared using the C statistic.[32] Statistical analysis was performed using SPSS, version 11.5 (SPSS, Inc, Chicago, IL) and R 3.0.3 (R foundation for Statistical Computing, Vienna, Austria). A *P* value of <0.05 was considered significant.

Results

The baseline characteristics are shown in Tables 1 and 2. Only 10% patients had severe aortic valve stenosis, whereas 37% patients had >moderate aortic regurgitation. In the entire sample, 13% and 33% patients had a high (≥10 cm^2/m) aortic root/height and ascending aortic area/height ratio, respectively. Ascending aortic area/height and aortic root area/height ratios were not distributed normally (*P*<0.001 for both variables; Figure 2A and 2B).

Surgical Data

After a clinical evaluation, 429 (44%) patients underwent cardiovascular surgery involving the aortic root or ascending aorta during follow-up, at a median time of 34 days (interquartile range, 5–624 days); 193 (45%) patients within 1 month, and 291 (68%) patients within 1 year. There were no significant differences in baseline demographics between patients who underwent aortic surgery versus those who did not, except for higher proportion of betablocker use, aortic *Z* score, and aortic root (or ascending aorta)/height ratio in the surgical group (Tables 1 and 2).

The distribution of various surgeries was as follows: 28 (7%) isolated aortic replacement, 350 (82%) ascending aortic replacement+atrioventricular repair/replacement, 5

Table 1. Baseline Characteristics of the Study Population (n=969)

	Total Population (n=969)	No Aortic Surgery During Follow-Up (n=540)	Aortic Surgery During Follow-Up (n=429)	*P* Value
Age, y	50±13	50±13	51±13	0.13
Men, n (%)	811 (84)	465 (86)	346 (81)	0.01
BSA, m^2	2±0.2	2±0.2	2±0.2	0.52
NYHA class, n (%)				
I	755 (78)	431 (80)	324 (76)	0.30
II	188 (19)	93 (17)	95 (22)	
III/IV	26 (3)	16 (3)	10 (2)	
Hypertension, n (%)	717 (75)	397 (74)	320 (75)	0.38
Hyperlipidemia, n (%)	422 (44)	241 (45)	181 (42)	0.24
Diabetes mellitus, n (%)	77 (8)	48 (9)	29 (7)	0.14
COPD, n (%)	53 (6)	33 (6)	20 (5)	0.20
Obstructive CAD, n (%)	117 (12)	66 (12)	51 (12)	0.46
Atrial fibrillation, n (%)	207 (21)	106 (20)	101 (24)	0.08
Peripheral arterial disease, n (%)	17 (2)	12 (2)	5 (1)	0.16
Prior cardiac surgery, n (%)	87 (9)	49 (9)	38 (9)	0.53
ICD, n (%)	17 (2)	9 (2)	8 (2)	0.50
Pacemaker, n (%)	37 (4)	18 (3)	19 (4)	0.25
Family history of BAV aortopathy, n (%)	27 (3)	5 (1)	22 (5)	0.04
History of endocarditis, n (%)	26 (3)	11 (3)	15 (3)	0.50
History of coarctation, n (%)	30 (3)	19 (4)	11 (3)	0.26
STS score	2±3	1.9±2	2±3	0.32
Betablockers, n (%)	771 (80)	385 (71)	386 (90)	<0.001
Calcium channel blockers, n (%)	246 (25)	139 (26)	107 (25)	0.42
ACE inhibitors, n (%)	430 (44)	240 (44)	190 (44)	0.51
Statins, n (%)	482 (50)	264 (49)	218 (51)	0.30
Aldosterone receptor blocker, n (%)	192 (20)	107 (20)	85 (20)	0.53
Hemoglobin, mg/dL	15±2	15±2	15±3	0.45
GFR, mL/min/1.73 m^2	85±20	85±20	83±19	0.11
Low-density lipoprotein, mg/dL	106±32	106±32	106±32	0.91
High-density lipoprotein, mg/dL	53±13	53±13	54±17	0.21

ACE indicates angiotensin-converting enzyme; BAV, bicuspid aortic valve; BSA, body surface area; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; GFR, glomerular filtration rate; ICD, internal cardioverter defibrillator; NYHA, New York Heart Association; and STS, society of thoracic surgeons.

(1%) ascending aortic replacement+CABG, and 46 (11%) ascending aortic replacement+atrioventricular repair/replacement+CABG. Further surgical classification was as follows: 81 (18%) valve sparing aortic root replacement, 50 (12%) composite valve+ascending aorta replacement (27 isolated, rest with concomitant CABG), and 5 homografts (1%). Of the atrioventricular surgeries, there were 13 atrioventricular repairs, whereas the rest were replacements (11 using mechanical valves). At the last follow-up, there were 4 patients in the entire study sample (1%) presenting with endocarditis and 6 patients (1.5%) requiring redo cardiovascular (including ascending aorta) surgery.

Outcomes Analysis

Total follow-up time for the entire study sample was 10 229 patient-years with 93% patients having at least 8 years of follow-up at our institution. During a mean of 10.3±2.6 years (median, 10.8 years; interquartile range, 9.6–12.3), there were 82 (9%) primary events, with 0% lost to follow-up. There were additional 13 deaths because of noncardiac pathogeneses, whose follow-up was censored at the time of the event. Within the surgical group, 30-day/in-hospital postoperative mortality occurred in 2 (0.4%) patients. Also, there were 8 patients (0.8%) with a stroke during follow-up (of which 6 occurred in the surgical group within 30 days postoperatively).

Table 2. Baseline Imaging Characteristics of the Study Population (n=969)

	Total Population (n=969)	No Aortic Surgery During Follow-Up (n=540)	Aortic Surgery During Follow-Up (n=429)	*P* Value
LV ejection fraction, %	55±8	55±6	55±8	0.19
Indexed LV end systolic dimension, cm/m²	1.6±0.5	1.6±0.5	1.6±0.5	0.44
Indexed left atrial dimension, cm/m²	1.8±0.3	1.8±0.4	1.8±0.4	0.27
Indexed LV mass, g/m²	126±46	124±47	127±44	0.27
LVOT diameter, cm	2±0.2	2±0.2	2±0.2	0.55
Aortic valve gradient				
Peak, mm Hg	25±27	21±27	29±30	<0.001
Mean, mm Hg	14±17	12±16	16±17	<0.001
Mean aortic valve gradient ≥40 mm Hg, n (%)	97 (10)	47 (9)	50 (12)	0.08
Calculated aortic valve area	1.2±0.5	1.3±0.6	1.2±0.5	0.08
Aortic valve cusp orientation				
Right-left fusion, n (%)	814 (84)	463 (86)	351 (82)	0.23
Right and noncusp fusion, n (%)	129 (13)	64 (12)	65 (15)	
Left and noncusp fusion, n (%)	23 (4)	11 (3)	12 (5)	
Aortic regurgitation ≥III+, n (%)	356 (37)	195 (36)	161 (38)	0.35
Bicuspid aortic valve risk score, n (%)				
0	32 (3)	22 (4)	10 (2)	0.02
1	496 (51)	292 (54)	202 (47)	
2	402 (42)	207 (38)	195 (46)	
3	39 (4)	17 (3)	22 (5)	
Mitral regurgitation ≥moderate, n (%)	66 (7)	40 (7)	26 (6)	0.41
Tricuspid regurgitation ≥moderate, n (%)	53 (5)	32 (6)	21 (5)	0.48
Right ventricular systolic pressure, mm Hg	15±16	15±17	15±16	0.75
Aortic root dimension, cm	4.1±0.6	4±0.5	4.3±0.6	<0.001
Aortic root *Z* score	2.3±2.2	1.9±2.2	2.8±2.3	<0.001
Aortic root cross-sectional area/height ratio, cm²/m	7.8±0.9	7.4±0.9	8.3±0.8	<0.001
Aortic root cross-sectional area/height ratio ≥10 cm²/m, n (%)	126 (13)	38 (7)	88 (21)	<0.001
Aortic root, cm, n (%)				
<4	300 (31)	184 (34)	116 (27)	<0.001
4–4.4	397 (41)	241 (45)	156 (36)	
4.5–4.9	192 (20)	93 (17)	99 (23)	
5–5.4	64 (7)	12 (2)	52 (12)	
≥5	16 (2)	0	16 (4)	
Ascending aortic dimension, cm	4.4±0.7	4.1±0.6	4.8±0.6	<0.001
Ascending aortic cross-sectional area/height ratio, cm²/m	9±0.8	7.8±0.7	10.5±0.9	<0.001
Ascending aortic cross-sectional area/height ratio ≥10 cm²/m, n (%)	321 (33)	74 (14)	247 (58)	<0.001
Ascending aorta, cm, n (%)				
<4	180 (19)	151 (28)	29 (7)	<0.001
4–4.4	324 (33)	248 (46)	76 (18)	
4.5–4.9	245 (25)	108 (20)	137 (32)	
5–5.4	160 (17)	33 (6)	127 (30)	
>5.4	60 (6)	0	60 (14)	

LV indicates left ventricular; and LVOT, left ventricular outflow tract.

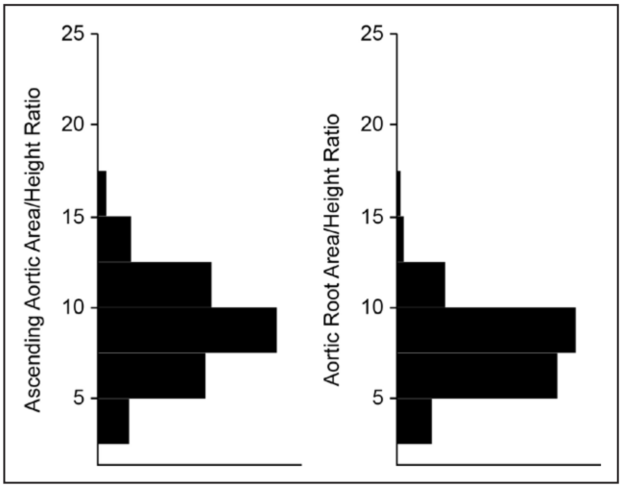

Figure 2. Histograms demonstrating the skewed distribution of ascending aortic area/height ratio (**left**) and aortic root area/height ratio (**right**) in the study sample.

Also, of the total longer-term primary events, only 6 (7%) and 17 (21%) occurred in patients with aortic root and ascending aortic dimensions ≥5 cm, respectively. After an initial clinical/imaging evaluation at our institution, 2 patients presented for repair of a documented type A dissection. These 2 patients were both women, 35 and 49 years of age who presented 253 and 1218 days after their initial evaluation with type A dissection. At the time of presentation with dissection, the aortic root dimensions were 3.7 and 4.5 cm, whereas the ascending aortic dimensions were 4.5 and 5.5 cm, respectively. Both underwent emergent AVR+ascending aortic replacement and are alive.

For the longer-term primary outcome in the entire study sample, the results of univariable and multivariable Cox proportional hazards survival analysis are shown in Tables 3 and 4. As shown in Table 4, model A, increasing Society of Thoracic Surgeons score (HR, 2.14; 95% CI, 1.35–3.39), ascending aortic area/height ratio ≥10 cm^2/m (HR, 2; 95% CI, 1.20–3.35), and higher right ventricular systolic pressure (HR, 1.31; 95% CI, 1.11–1.65) were associated with a higher proportion of primary events, whereas cardiovascular (including ascending aortic) surgery (HR, 0.46; 95% CI, 0.26–0.80) was associated with significantly improved longer-term freedom from primary events (all $P<0.01$). An interaction term between cardiovascular surgery and ascending aortic area/height ratio ≥10 cm^2/m was also significant when concomitantly entered into the model. The results were similar for aortic root area/height ratio ≥10 cm^2/m (Table 4, model B). Absolute diameter cutoffs (either aortic root or ascending aorta) ≥5 cm were not associated with primary events (Table 3).

The proportion of primary events was significantly lower in the group that underwent cardiovascular surgery during follow-up versus the group that did not (26/429 [6%] versus 56/540 [10%]; $P=0.02$). Kaplan–Meier curves, separated on the basis of cardiovascular surgery versus not, are shown in Figure 3. Because of significant interaction between ascending aortic area (or aortic root area)/height ratio and cardiovascular surgery, we performed additional analyses within the entire study sample. In the first analysis, the longer-term

Table 3. Univariable Cox Proportional Hazard Analysis for the Primary End Point of Longer-Term Death in the Entire Study Sample (n=969)

Variable	Hazard Ratio With 95% Confidence Interval	*P* Value
Clinical		
Age (for every 10-y increase)	2.14 (1.82–2.51)	<0.001
Women	1.59 (0.78–3.21)	0.19
Hypertension	1.23 (0.72–2.11)	0.43
Hyperlipidemia	1.02 (0.66–1.58)	0.94
Diabetes mellitus	1.15 (0.63–1.99)	0.49
Chronic obstructive pulmonary disease	1.49 (0.36–3.14)	0.46
Atrial fibrillation	1.21 (0.73–2.01)	0.45
Carotid artery disease	1.21 (0.67–2.25)	0.47
≥1-vessel obstructive coronary artery disease	1.13 (1.03–1.40)	0.03
Redo cardiac surgery	2.05 (1.13–3.74)	0.01
Society of Thoracic Surgeons score (for every 1% increase)	2.51 (1.62–3.90)	<0.001
New York Heart Association class ≥II	1.64 (1.14–2.39)	0.005
Betablockers	0.94 (0.55–1.61)	0.81
Angiotensin-converting enzyme inhibitors	0.89 (0.57–1.39)	0.61
Angiotensin receptor blockers	0.73 (0.44–1.23)	0.23
Glomerular filtration rate (for 10 mL/min/1.73 m^2 decrease)	1.22 (1.08–1.38)	0.01
Aortic surgery during follow-up	0.58 (0.36–0.84)	<0.01
Echocardiographic data		
Left ventricular ejection fraction (for every 10% increase)	0.67 (0.56–0.80)	<0.001
≥II+ aortic regurgitation	1.57 (0.95–2.59)	0.07
Severe aortic stenosis vs not	1.14 (0.57–2.29)	0.71
Right ventricular systolic pressure (for 10 mm Hg increase)	1.34 (1.14–1.71)	<0.001
Aortic root *Z* score	1.03 (0.93–1.14)	0.51
Tomographic data		
Absolute aortic root dimensions (continuous variable)	1.19 (0.81–1.73)	0.36
Absolute aortic root dimensions ≥5 cm	1.17 (0.51–2.73)	0.84
Aortic root area/height ratio ≥10 cm^2/m	3.06 (1.90–4.96)	<0.001
Absolute ascending aortic dimensions (continuous variable)	1.14 (0.85–1.60)	0.38
Absolute ascending aortic dimensions ≥5 cm	1.11 (0.64–1.91)	0.91
Ascending aortic area/height ratio ≥10 cm^2/m	1.89 (1.19–2.93)	<0.01

primary events of 4 subgroups, separated on basis of cardiovascular surgery (versus not) and ascending aortic area/height ratio cutoff of 10 cm^2/m were as follows: (1) no cardiovascular

Table 4. Multivariable Cox Proportional Hazard Analysis for the Primary End Point of Longer-Term Death in the Entire Study Sample (n=969)

Variable	Hazard Ratio With 95% Confidence Intervals	*P* Value
Model A: with ascending aortic area/height ratio ≥10 cm²/m in the model		
Ascending aortic area/height ratio ≥10 cm²/m	2 (1.20–3.35)	0.007
Aortic surgery during follow-up	0.46 (0.26–0.80)	0.005
Right ventricular systolic pressure (for 10 mm Hg increase)	1.31 (1.11–1.65)	<0.001
Society of Thoracic Surgeons score (for every 1% increase)	2.14 (1.35–3.39)	0.001
Interaction between aortic surgery during follow-up and ascending aortic area/height ratio ≥10 cm²/m	0.65 (0.36–0.91)	0.03
Model B: with aortic root area/height ratio ≥10 cm²/m in the model		
Aortic root area/height ratio ≥10 cm²/m	4.06 (2.45–6.70)	<0.001
Right ventricular systolic pressure (for 10 mm Hg increase)	1.29 (1.10–1.70)	<0.001
Society of Thoracic Surgeons score (for every 1% increase)	1.95 (1.21–3.16)	0.001
Aortic surgery during follow-up	0.48 (0.29–0.80)	0.004
Interaction between aortic surgery during follow-up and aortic root area/height ratio ≥10 cm²/m	0.56 (0.28–0.94)	0.04

The following additional potential predictors were considered for multivariable analysis: betablockers, angiotensin-converting enzyme inhibitors, aortic regurgitation ≥III+, and severe aortic stenosis. Variables that constitute STS score were not considered for individual analysis. STS score and right ventricular systolic pressure were entered as continuous variables, whereas the rest were entered as categorical variables. STS indicates Society of Thoracic Surgeons.

surgery and ascending aortic area/height ratio <10 cm²/m (40/466 [9%]), (2) cardiovascular surgery and ascending aortic area/height ratio <10 cm²/m (9/182 [5%]), (3) cardiovascular surgery and ascending aortic area/height ratio ≥10 cm²/m (17/247 [7%]), and (4) no cardiovascular surgery and ascending aortic area/height ratio ≥10 cm²/m (16/74 [22%]; *P*<0.001). Kaplan–Meier survival curves of these 4 subgroups are shown in Figure 4A. Similarly, the longer-term primary events of 4 subgroups, separated on basis of cardiovascular surgery (versus not) and aortic root area/height ratio cutoff of 10 cm²/m, were as follows: (1) no cardiovascular surgery and aortic root area/height ratio <10 cm²/m (40/502 [8%]), (2) cardiovascular surgery and aortic root area/height ratio <10 cm²/m (17/341 [5%]), (3) cardiovascular surgery and aortic root area/height ratio ≥10 cm²/m (9/88 [10%]), and (4) no cardiovascular surgery and aortic root area/height ratio ≥10 cm²/m (16/38 [42%]). Kaplan–Meier survival curves of these 4 subgroups are shown in Figure 4B. Data on similar subgroup analyses as above, incorporating absolute diameter cutoffs (either aortic root or ascending aorta) ≥5 cm, are shown in the online-only Data Supplement.

For the primary outcome, addition of ascending aortic or aortic root absolute diameter cutoffs ≥5 cm to a standard clinical model (Society of Thoracic Surgeons score, angiotensin-converting enzyme inhibitors, angiotensin receptor blocker therapy, ≥III+ aortic regurgitation, ≥severe aortic stenosis, and right ventricular systolic pressure) did not provide incremental prognostic use, as shown in Table 5, models A and C. However, addition of ascending aortic or aortic root area/height ratio ≥10 cm²/m and cardiovascular surgery to the same clinical model provided incremental prognostic use (both C statistic and net reclassification improvement; Table 5, models B and D.

We further analyzed the data on 405 patients (42%) who had an intermediate ascending aortic diameter between 4.5 and 5.5 cm and did not reach the guideline-based cutoff of 5.5 cm[14] (number of longer-term primary events=33). However, 258 (64%) had an ascending aortic area/height ratio ≥10 cm²/m, and 23 (70%) primary events occurred in patients with an ascending aortic area/height ratio ≥10 cm²/m. We further divided these 405 patients into 4 subgroups, based on ascending aortic area/height ratio using a cutoff of 10 cm²/m and whether they had cardiovascular surgery versus not. The longer-term primary events for the 4 subgroups were as follows: (1) no cardiovascular surgery and ascending aortic area/height ratio <10 cm²/m (5/72 [7%]), (2) cardiovascular surgery and ascending aortic area/height ratio <10 cm²/m (5/75 [7%]), (3) cardiovascular surgery and ascending aortic area/height ratio ≥10 cm²/m (8/189 [4%]), and (4) no cardiovascular surgery and ascending aortic area/height ratio ≥10 cm²/m (15/69 [22%]). The Kaplan–Meier survival curves of these 4 subgroups are shown in Figure 5A. Similarly, we also analyzed the data of 256 (26%) patients who had an intermediate aortic root diameter between 4.5 and 5.5 cm (number of longer-term primary events=31). In this subgroup, 109 (43%) such patients had an aortic root area/height ratio ≥10 cm²/m, and 24 (77%) primary events occurred in patients with an aortic root area/height ratio ≥10 cm²/m. We further divided these 256 patients into 4 subgroups, based on aortic root area/height ratio using a cutoff of 10 cm²/m and whether they had cardiovascular surgery versus not. The longer-term outcomes (number of primary events=31) for the 4 subgroups were as follows: (1) no cardiovascular surgery and aortic root area/height ratio <10 cm²/m (4/72 [6%]), (2) cardiovascular surgery and aortic root area/height ratio <10 cm²/m (3/75 [4%]),

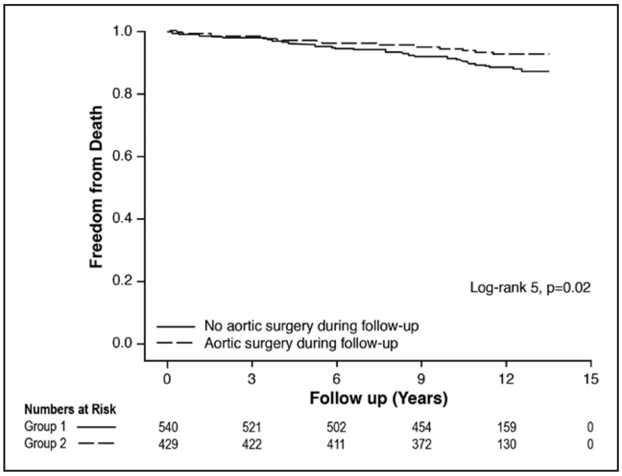

Figure 3. Kaplan–Meier survival curves of the entire study sample separated on basis of aortic surgery vs not.

(3) cardiovascular surgery and aortic root area/height ratio ≥10 cm^2/m (8/76 [11%]), and (4) no cardiovascular surgery and aortic root area/height ratio ≥10 cm^2/m (16/33 [49%]). The Kaplan–Meier survival curves are shown in Figure 5B.

Discussion

In this large contemporary group of 969 patients with BAV aortopathy undergoing multimodality imaging evaluation, we demonstrate that ≈33% and 13% of patients had an abnormal ascending aortic and aortic root/height ratio (≥10 cm^2/m), respectively. The study population was significantly older (mean, 50 years) than the previous reports, and we specifically examined the predictive contribution of aortic size on long-term mortality.[9,17,33] An abnormal ascending aortic area/height ratio (or a similarly increased aortic root area/height ratio) was independently associated with higher long-term cardiovascular mortality, whereas cardiovascular (including ascending aortic replacement in all patients) surgery was associated with improved longer-term survival. We further demonstrate that addition of an abnormal ascending aortic area (or aortic root)/height ratio (and not absolute aortic dimensions) and cardiovascular surgery to known clinical predictors provided incremental prognostic use and provided improved reclassification of risk of longer-term primary events. However, the improvement in C statistic was only modest. In patients with ascending aortic dimensions between 4.5 and 5.5 cm (the group below the threshold where pre-emptive surgery is generally recommended), 42% patients had an abnormal ascending aortic area/height ratio, but accounted for 70% longer-term deaths, with a much higher proportion in the subgroup that did not undergo surgery. The findings were similar when aortic root measurements were considered. We also demonstrate significant differences in primary outcomes of nonoperated patients with different aortopathy phenotypes, with the root phenotype demonstrating higher event rates versus the ascending phenotype.

There is significant controversy on the threshold above which pre-emptive aortic replacement surgery is recommended in BAV patients. The 2010 American College of Cardiology/American Heart Association aortic guidelines suggest aortic surgery at a threshold of 5 cm, but the 2014 American Heart Association/American College of Cardiology valve guidelines recommend increasing the threshold for isolated replacement of the aorta to 5.5 cm, with the justification that the rate of dissection in the previous reports was low.[9,14,17] However, in 1 series, 38 of 642 BAV patients had ascending aortic interventions, but there is no data at what threshold these interventions were performed, which may mask the absolute risk of complications, especially because few patients had aorta ≥5.5 cm in that series.[9] In another recent study, 49 of 416 patients underwent prophylactic surgery for

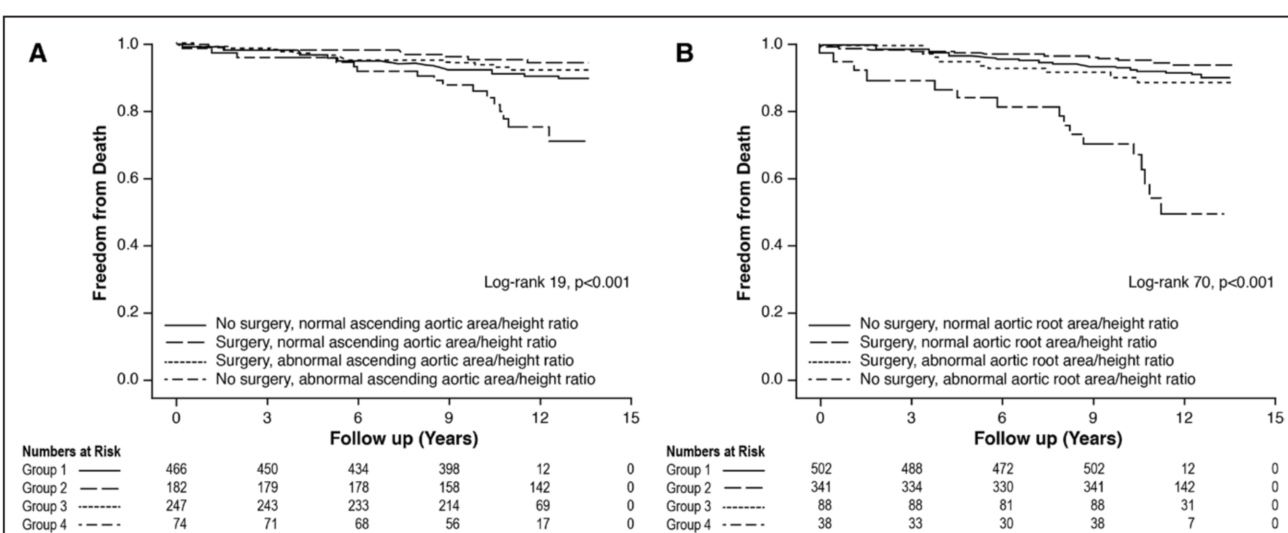

Figure 4. **A**, Kaplan–Meier survival curves of the entire study sample, divided into 4 subgroups as follows: group 1, no aortic surgery and normal ascending aortic area/height ratio <10 cm^2/m; group 2, aortic surgery and normal ascending aortic area/height ratio <10 cm^2/m; group 3, surgery and abnormal ascending aortic area/height ratio ≥10 cm^2/m; and group 4, no surgery and abnormal ascending aortic area/height ratio ≥10 cm^2/m. **B**, Kaplan–Meier survival curves of the entire study sample, divided into 4 subgroups as follows: group 1, no aortic surgery and normal aortic root area/height ratio <10 cm^2/m; group 2, surgery and normal aortic root area/height ratio <10 cm^2/m; group 3, surgery and abnormal aortic root area/height ratio ≥10 cm^2/m; and group 4, no surgery and abnormal aortic root area/height ratio ≥10 cm^2/m.

Table 5. Incremental Prognostic Use of Aortic Area/Height Ratio and Aortic Surgery for the Primary Outcome of Death in the Entire Study Sample (n=969)

Model A: with ascending aortic diameter ≥5 cm					
	Model 1: clinical model	Model 2: clinical model+ascending aortic diameter ≥5 cm	P value for difference between model 1 and 2	Model 3: clinical model+diameter ≥5 cm+CV surgery	*P* value for difference between model 2 and 3
C statistic	0.60 (0.51–0.77)	0.61 (0.47–0.77)	0.19	0.68 (0.59–0.87)	0.03
Categorical NRI	0.19 (0.04–0.34)	0.03 (−0.10 to 0.44)	0.21	0.23 (0.04–0.39)	0.01
Model B: with ascending aortic area/height ratio ≥10 cm²/m					
	Model 1: clinical model	Model 2: clinical model+ascending aortic area/height ratio ≥10 cm²/m	*P* value for difference between model 1 and 2	Model 3: clinical model+aortic root are ascending aortic area/height ratio ≥10 cm²/m+CV surgery	*P* value for difference between model 2 and 3
C statistic	0.60 (0.51–0.77)	0.66 (0.52–0.76)	0.03	0.72 (0.61–0.86)	0.02
Categorical NRI	0.19 (0.04–0.34)	0.25 (0.06–0.41)	<0.01	0.27 (0.05–0.37)	<0.01
Model C: with aortic root diameter ≥5 cm					
	Model 1: clinical model	Model 2: clinical model aortic root diameter ≥5 cm	*P* value for difference between model 1 and 2	Model 3: clinical model+aortic root diameter ≥5 cm+CV surgery	*P* value for difference between model 2 and 3
C statistic	0.61 (0.52–0.78)	0.61 (0.49–0.83)	0.34	0.69 (0.58–0.85)	0.03
Categorical NRI	0.19 (0.04–0.34)	0.02 (−0.12 to 0.39)	0.39	0.21 (0.06–0.34)	0.01
Model D: with aortic root area/height ratio ≥10 cm²/m					
	Model 1: clinical model	Model 2: clinical model aortic root area/height ratio ≥10 cm²/m	*P* value for difference between model 1 and 2	Model 3: clinical model+aortic root area/height ratio ≥10 cm²/m+CV surgery	*P* value for difference between model 2 and 3
C statistic	0.61 (0.52–0.78)	0.68 (0.53–0.81)	0.02	0.74 (0.60–0.84)	0.01
Categorical NRI	0.19 (0.04–0.34)	0.24 (0.06–0.36)	0.01	0.22 (0.07–0.33)	<0.01

Clinical model included the following predictors: Society of Thoracic Surgeons score, angiotensin-converting enzyme inhibitors, angiotensin receptor blocker therapy, ≥III+ aortic regurgitation, ≥severe aortic stenosis and right ventricular systolic pressure. All patients had aortic surgery, whereas some had additional procedures also. Please refer to text for details.

CV indicates cardiovascular; and NRI, net reclassification improvement.

a dilated ascending aorta, but again the threshold used for surgical intervention was unclear.[17] On the contrary, in the international registry of acute aortic dissection (where a proportion of patients had a BAV),[18] of 591 type A dissections, 40% and 59% had aortic diameter <5 cm and <5.5 cm, respectively.[18] Also, older data have suggested that 15% of patients presenting with acute aortic dissection had BAV.[1] Indeed, in a recent report of 4654 patients with nonsyndromic ascending aortic dilation (of which 12.6% had BAV), there was a low rate of acute aortic pathology (dissection or rupture) at diameters <5 cm, when timely aortic repair was performed. However, the authors did not report the association between aortic surgery and death, nor did they index aortic size to height or BSA.[34]

Indeed, it seems that risk stratification of aortopathies in patients with borderline aortic diameters, especially in females and relatively shorter men could potentially be improved.[19,20] Previous reports have suggested that indexing ascending aorta sizes to BSA or height might help identify patients who are at a higher risk for development of an adverse event, including cardiovascular death or an acute aortic pathology, despite their aortas not reaching the published thresholds where surgical repair is recommended.[21–23,25] In a previous report, a ratio of aortic diameter and BSA (aortic root *Z* score) was a significant predictor of rupture alone along with the combined end point of rupture, death, or dissection.[23] However, there are many shortcomings of aortic *Z* scores[25]: (1) *Z* scores are derived from transthoracic echocardiography using diameters as opposed to planimetered area measured on 3-dimensional tomographic imaging, (2) BAV patients often have eccentric dilation of the ascending aorta and aortic root, which would make the use of diameter alone prone to misclassification, (3) for adults, *Z* scores are available only for the aortic root and not the ascending aorta, and (4) BSA is significantly affected by obesity and as such, patients would potentially have a larger aorta before surgical repair is indicated. Indeed, in a recent report on Marfan patients, a *Z* score correcting aortic root diameter to height was demonstrated to perform better than a score using BSA.[35] As a result, for the current study, we indexed aortic area to height, as previously described.[21,22] Additionally, to improve the accuracy of aortic area measurement, we planimetered the aortic root and ascending aorta on tomographic images, using double-oblique techniques. Indeed, based on the work by Vasan et al,[19] it seems that normal aorta size relates best to height. Multiple previous studies have suggested that an ascending aortic or aortic

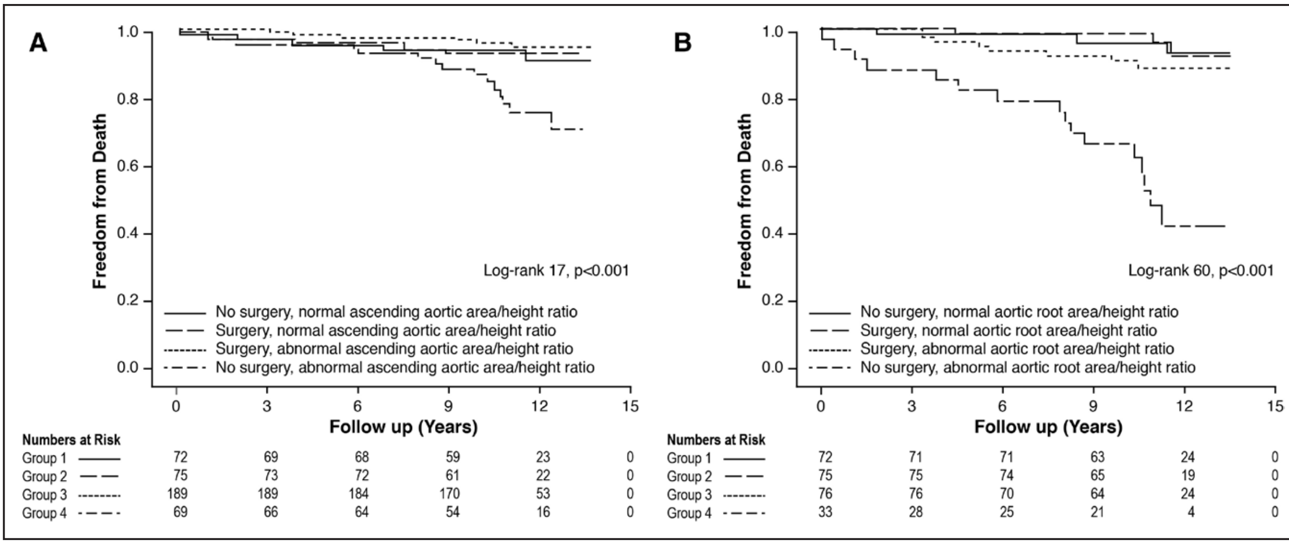

Figure 5. **A**, Kaplan–Meier survival curves of the subgroup with ascending aorta between 4.5 to 5.5 cm, divided into 4 subgroups as follows: group 1, no aortic surgery and normal ascending aortic area/height ratio <10 cm^2/m; group 2, aortic surgery and normal ascending aortic area/height ratio <10 cm^2/m; group 3, surgery and abnormal ascending aortic area/height ratio ≥10 cm^2/m; and group 4, no surgery and abnormal ascending aortic area/height ratio ≥10 cm^2/m. **B**, Kaplan–Meier survival curves of the subgroup with aortic root between 4.5 to 5.5 cm, divided into 4 subgroups as follows: group 1, no aortic surgery and normal aortic root area/height ratio <10 cm^2/m; group 2, surgery and normal aortic root area/height ratio <10 cm^2/m; group 3, surgery and abnormal aortic root area/height ratio ≥10 cm^2/m; and group 4, no surgery and abnormal aortic root area/height ratio ≥10 cm^2/m.

root/height ratio >10 cm^2/m be used for prophylactic repair in patients with Marfan syndrome or those with BAV-related aortopathy.[21,22,24] In a recent study, we have also demonstrated its incremental prognostic use in patients with a trileaflet aortic valve and dilated proximal aorta.[26] The current study focuses on a large sample of BAV patients, with a much longer follow-up along with using tomographic imaging to measure aortic area, rather than relying on echocardiography, which is prone to errors related to the inability to adequately image the largest aortic dimension. It is conceivable that the aortic area/height ratio >10 cm^2/m may not have similar prognostic use in different disease conditions (ie, BAV, Marfan, trileaflet aortic valve, etc). However, the purpose of the current study was to test the incremental prognostic value of the ratio that is recommended in the current guidelines. To develop disease-specific ascending aorta/height ratios, a large-scale multicenter study (likely prospective) would be needed.

The low rate of dissections noted in the current study likely reflects higher (44%) use of prophylactic concomitant ascending aortic replacement surgery. This confirms prior reports that showed a high rate of surgical intervention in BAV patients during their lifetime either secondary to valvular dysfunction or associated aortopathies.[9,17,33] Multiple previous reports have described long-term outcomes in BAV patients,[9,17,33,34] with low rates of dissections/ruptures in follow-up. In a natural history of 212 normally functioning or minimally dysfunctional BAV patients, the authors demonstrate a 90% survival at 20 years, but a 33% rate of composite cardiovascular events and 27% need for cardiovascular surgery in that time frame.[33] In another report, of 642 consecutive patients with BAV, the mortality and dissection rates were low (4% and 2%, respectively) during almost 9 years of follow-up; however, 22% patients needed cardiovascular surgery during that time frame.[9] In a follow-up study by Michelena et al,[17] the rate of aortic dissection at 16 years of follow-up was low but significantly higher than the general population. However, only 9% patients had a concomitant aortopathy. Also, in a recent report, there was a low rate of acute aortic pathology (dissection or rupture) at diameters <5 cm, when timely aortic repair was performed.[34]

Based on the results of the current study, it seems that aortic surgery could be offered to certain BAV patients who have an aortic area/height ratio >10 cm^2/m, before they reach the absolute recommended aortic diameter threshold of 5.5 cm.[15] However, such a consideration should be balanced against the potential for increased short-term mortality and morbidity associated with surgery in lesser experienced centers. Indeed, as demonstrated by the results of the current study and others pertaining to complex aortic root and ascending aortic surgeries, the most appropriate option would be to offer this only at high-volume experienced centers that have demonstrated excellent surgical outcomes, after shared decision making.[10,36–41] These findings need prospective validation, especially in patients with an isolated BAV aortopathy.

Limitations

Because this was an observational study from a single center that was retrospectively analyzed, there is a potential for referral and selection bias. However, the data entry and surgical decision making occurred prospectively. We did not include surgery as an end point in survival analysis because of relatively short time duration between initial evaluation and surgery. Also, cardiovascular surgery is determined by physician/patient choice, and it becomes difficult to tease apart whether the surgery itself or the selection of patients appropriate for surgery leads to better outcomes. However, this answer can only be answered by a well-powered prospective study. The study cohort does not represent otherwise healthy patients with an isolated aneurysm of the proximal aorta, who die only of aortic-related causes. This relatively older male population might have significant silent coronary artery disease that presents as sudden cardiac death during the follow-up (including BAV patients with dilated proximal aorta and an abnormal aortic area/height ratio). This likely reflects the tertiary referral nature of our practice, where a significant proportion of patients that are followed longitudinally elsewhere are sent specifically for definitive surgical care, including ascending aortic surgery (±coronary bypass or valvular surgery in many cases). The current study demonstrates associations, not causality. We report mortality as the primary end point, as opposed to aortic dissection. We feel that is more objective because not all patients who died suddenly underwent a postmortem autopsy to confirm or exclude aortic dissection/rupture as a cause of death. Also, it has been demonstrated previously that all-cause mortality is less biased than attempting to specifically discern a cause of death.[42,43] There is a possibility that there were some patients who presented with type A dissection locally and survived; thus, not accounted for in the survival analysis.

Conclusions

In BAV patients with dilated aortic root or proximal ascending aorta, all of whom underwent a dedicated clinical and multimodality imaging evaluation, ascending aortic/height ratio (or an aortic root area area/height ratio) of ≥10 cm^2/m was associated with a higher risk of longer-term cardiovascular mortality, whereas cardiovascular surgery was associated with significantly improved long-term survival.

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Disclosures

Dr Griffin holds the Brown Family Endowed Chair in Cardiovascular Medicine. Dr Roselli is a consultant for Medtronic, Sorin, and St. Jude. Dr Johnston is a consultant for Edwards, St. Judes, KEF, and Interactive Visual Health Record. The other authors report no conflicts.

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CLINICAL PERSPECTIVE

This study of 969 patients with bicuspid aortic valve and concomitant aortopathy showed that there is incremental prognostic value of indexing ascending aorta (or aortic root) area to height, rather than using unindexed aortic diameter. Incorporation of the ratio significantly reclassified risk for death. An abnormal ratio was independently associated with higher long-term mortality, whereas cardiovascular surgery was associated with improved survival. Of the 405 patients with ascending aortic diameter of 4.5 to 5.5 cm, 64% had an abnormal ascending aortic area/height ratio, and 70% deaths occurred in patients with an abnormal ratio. The findings were similar when aortic root measurements were considered. The clinical implication of these observations is that an ascending aortic area/height ratio >10 cm^2/m has significant and independent prognostic use and may be used to risk stratify patients with bicuspid aortic valve and dilated aorta and can contribute to clinical decision making. However, such a consideration should be balanced against the potential for increased short-term mortality and morbidity in lesser experienced surgical centers.

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Aortic Cross-Sectional Area/Height Ratio and Outcomes in Patients With Bicuspid Aortic Valve and a Dilated Ascending Aorta

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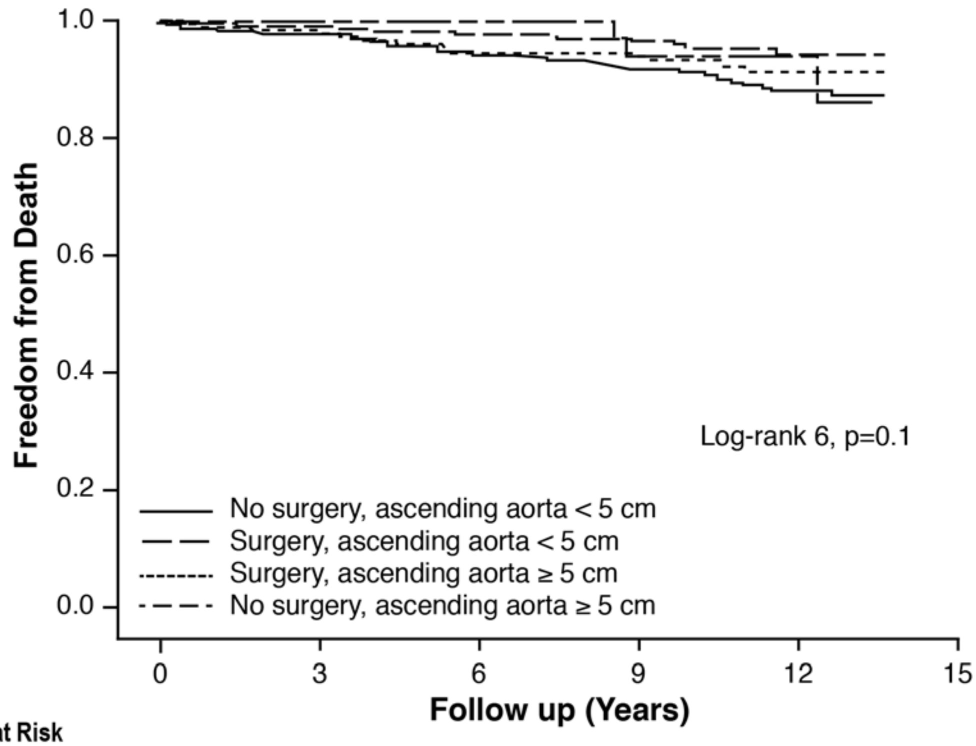
Supplemental Material

As shown in table 2, in the entire study sample, there were 80 and 220 patients, respectively who had aortic root and ascending aortic dimensions ≥ 5 cm, respectively. In order to understand the association between cardiovascular (CV) surgery, these respective dimensions and longer-term primary events, we performed the following subgroup analyses.

In the first analysis, the longer-term primary events of 4 subgroups, separated on basis of CV surgery (vs. not) and ascending aortic dimension cutoff of 5 cm were as follows: 1) no CV surgery and ascending aortic dimension < 5 cm (53/503 [11%]) 2) CV surgery and ascending aortic dimension < 5 cm (12/246 [5%]) 3) CV surgery and ascending aortic dimension ≥ 5 cm (14/187 [7%]) and 4) no aortic surgery and ascending aortic dimension ≥ 5 cm (3/33 [9%], p=0.1). Kaplan-Meier survival curves of these 4 subgroups, are shown in Supplemental Figure 1a. Similarly, the longer-term primary events of 4 subgroups, separated on basis of CV surgery (vs. not) and aortic root dimension cutoff of 5 cm were as follows: 1) no CV surgery and aortic root dimension < 5 cm (54/523 [10%]) 2) CV surgery and aortic root dimension < 5 cm (22/366 [6%]) 3) CV surgery and aortic root dimension ≥ 5 cm (4/68 [6%]) and 4) no CV surgery and aortic root dimension ≥ 5 cm (2/12 [17%], p=0.2). Kaplan-Meier survival curves of these 4 subgroups, are shown in Supplemental Figure 1b.

In addition, because of small but potentially significant differences in outcomes based on surgery (vs. not) in the subgroup of patients with a normal ascending aortic (or aortic root) ratio of < 10 cm2/m, we also analyzed the association between absolute ascending aortic (and aortic root) dimensions, and survival. In the subgroup of patients with ascending aortic area/height ratio of < 10 (n=648), the mean ascending aortic dimensions in survivors (n=599) vs. nonsurvivors (n=49) were 4.1±0.4 cm vs. 4.0±0.5 cm, p=0.54. Similarly, in the subgroup of patients with aortic root area/height ratio of < 10 (n=843), the mean ascending aortic dimensions in survivors (n=786) vs. nonsurvivors (n=57) were 4.0±0.5 cm vs. 3.9±0.5 cm, p=0.16.

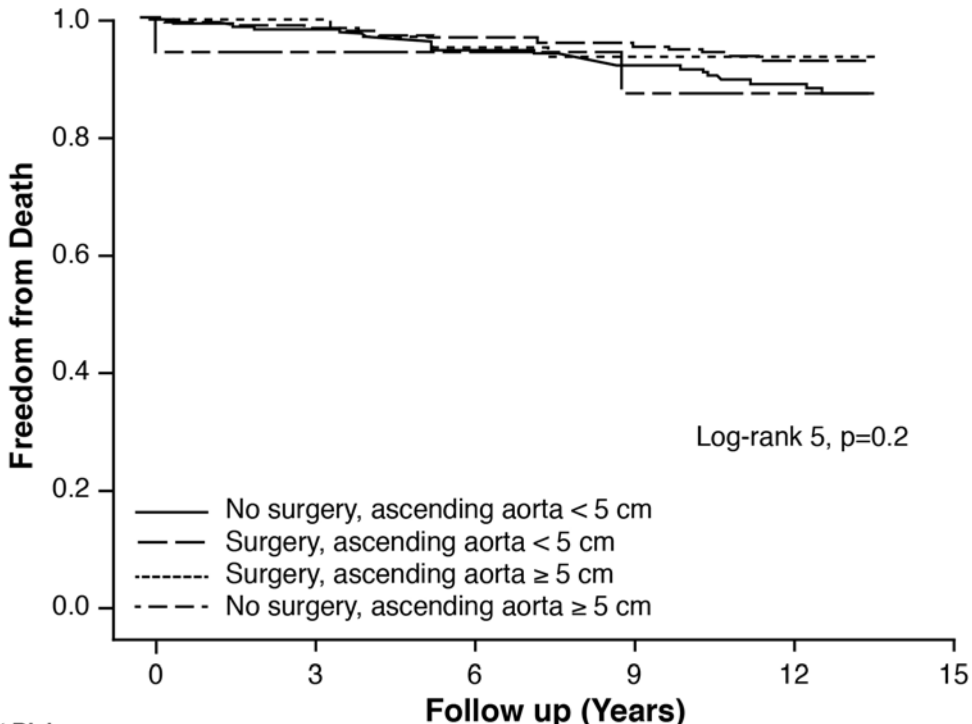
Supplemental Figure 1a:



Numbers at Risk

Group 1 ——	503	484	465	426	147	0
Group 2 — —	246	243	240	216	79	0
Group 3 --------	187	179	171	156	51	0
Group 4 - — — -	33	33	33	28	12	0

Supplemental Figure 1b:



Numbers at Risk

	0	3	6	9	12	15
Group 1 ———	523	506	487	441	153	0
Group 2 — —	366	359	352	317	103	0
Group 3 --------	68	63	59	55	27	0
Group 4 - — — -	12	12	12	11	6	0