Incidence of Aortic Complications in Patients With Bicuspid Aortic Valves

Hector I. Michelena, MD
Amber D. Khanna, MD
Douglas Mahoney, MS
Edit Margaryan, MD
Yan Topilsky, MD
Rakesh M. Suri, MD, PhD
Ben Eidem, MD
William D. Edwards, MD
Thoralf M. Sundt III, MD
Maurice Enriquez-Sarano, MD

Context Bicuspid aortic valve (BAV), the most common congenital heart defect, has been thought to cause frequent and severe aortic complications; however, long-term, population-based data are lacking.

Objective To determine the incidence of aortic complications in patients with BAV in a community cohort and in the general population.

Design, Setting, and Participants In this retrospective cohort study, we conducted comprehensive assessment of aortic complications of patients with BAV living in a population-based setting in Olmsted County, Minnesota. We analyzed long-term follow-up of a cohort of all Olmsted County residents diagnosed with definite BAV by echocardiography from 1980 to 1999 and searched for aortic complications of patients whose bicuspid valves had gone undiagnosed. The last year of follow-up was 2008-2009.

Main Outcome Measure Thoracic aortic dissection, ascending aortic aneurysm, and aortic surgery.

Results The cohort included 416 consecutive patients with definite BAV diagnosed by echocardiography, mean (SD) follow-up of 16 (7) years (6530 patient-years). Aortic dissection occurred in 2 of 416 patients; incidence of 3.1 (95% CI, 0.5-9.5) cases per 10 000 patient-years, age-adjusted relative-risk 8.4 (95% CI, 2.1-33.5; $P=.003$) compared with the county's general population. Aortic dissection incidences for patients 50 years or older at baseline and bearers of aortic aneurysms at baseline were 17.4 (95% CI, 2.9-53.6) and 44.9 (95% CI, 7.5-138.5) cases per 10 000 patient-years, respectively. Comprehensive search for aortic dissections in undiagnosed bicuspid valves revealed 2 additional patients, allowing estimation of aortic dissection incidence in bicuspid valve patients irrespective of diagnosis status (1.5; 95% CI, 0.4-3.8 cases per 10 000 patient-years), which was similar to the diagnosed cohort. Of 384 patients without baseline aneurysms, 49 developed aneurysms at follow-up, incidence of 84.9 (95% CI, 63.3-110.9) cases per 10 000 patient-years and an age-adjusted relative risk 86.2 (95% CI, 65.1-114; $P<.001$ compared with the general population). The 25-year rate of aortic surgery was 25% (95% CI, 17.2%-32.8%).

Conclusions In the population of patients with BAV, the incidence of aortic dissection over a mean of 16 years of follow-up was low but significantly higher than in the general population.

JAMA. 2011;306(10):1104-1113 www.jama.com

Bicuspid aortic valve is the most common congenital heart defect,[1] affecting 1.3% of the population.[2] Its most common complication is valve dysfunction.[3,4] However, BAV has also been suggested to cause aortopathy,[5-7] a process touted as similar to that of Marfan syndrome with independent aortic dilatation.[3-5,7,8] Aortic dissection is the most serious complication due to its high mortality.[9] Necropsy studies suggest that these patients are at considerable risk of aortic dissection[10,11] and high attributable risk of dissection is noted for BAV.[6,12] Thus, it is estimated that BAV is responsible for more deaths than all other congenital heart defects combined.[13] Consequently, carriers live under the threat of sudden death.[14] These associations are now challenged by 2 recent studies in which few dissections were observed[3,4]; we reported outcomes in a community-cohort limited to healthy patients with normally functioning BAV[3] and others reported on a tertiary-referral-center cohort with relatively short follow-up.[4] Thus, aortic dissections occurring late after diagnosis or in patients with significant BAV dysfunction may have eluded ascertainment. Furthermore, aortic dissection may occur in patients with undiagnosed BAV or uncertain bicuspid diagnosis. Hence, a population-based study with comprehensive ascertainment of aortic events among patients with BAV is lacking. Olmsted County, Minnesota, provides a geographically defined population with few clinicians or hospitals delivering health care in the community[15]: all echocardiograms are reviewed by one laboratory, and all cardiovascular surgeries are performed at the same center. Our objective was to determine the incidence of aortic complications among patients with the con-

Author Affiliations: Divisions of Cardiovascular Diseases (Drs Michelena, Khanna, Margaryan, Topilsky, Eidem, and Enriquez-Sarano), Biomedical Statistics and Informatics (Mr Mahoney), Cardiovascular Surgery (Dr Suri), and Anatomic Pathology (Dr Edwards), Mayo Clinic, Rochester, Minnesota; and Division of Cardiac Surgery, Massachusetts General Hospital, Boston (Dr Sundt).
Corresponding Author: Hector I. Michelena, MD, Division of Cardiovascular Disease, Mayo Clinic, 200 First St SW, Rochester, MN, 55905 (michelena.hector@mayo.edu).

©2011 American Medical Association. All rights reserved.

Downloaded From: http://jama.jamanetwork.com/ on 08/31/2014

dition in the community as well those in the general BAV population.

METHODS

The approach to the present study was to use a systematically comprehensive means of identifying aortic complications of BAV in a population-based setting. The main process was to analyze among Olmsted County residents a community cohort of all patients with definite BAV diagnosed by echocardiography with specific attention to obtaining long-term follow-up and complete ascertainment of aortic complications. To verify the results of this main process, we analyzed the outcome of patients with possible BAV but uncertain aortic cusp number and searched all possible sources for the occurrence of aortic dissections in undiagnosed carriers of BAV. The protocol was approved by the Mayo Clinic institutional review board.

Cohort

Eligible participants were residents of Olmsted County of all ages in whom a definite BAV of any type was diagnosed by echocardiography from January 1, 1980, to December 31, 1999. This included the limited patient cohort focused on valvular outcomes from our previous report.[3] In patients with questionable cusp number, echocardiograms were re-reviewed independently by 2 experienced echocardiographers (H.I.M. and M.E.S,) with subsequent consensus review to classify patients as definite BAV (included in the cohort), or tricuspid aortic valve. If uncertainty on cusp number remained after this review, patients were not included in the BAV cohort but their outcome was assessed under the undiagnosed or uncertain BAV analysis. Prisoners of the Federal Medical Center of Olmsted County were not considered county dwellers. All patients underwent baseline clinical evaluation performed by their personal physician and comprehensive 2-dimensional and Doppler transthoracic echocardiographic evaluation with state-of-the-art technology at diagnosis.[16,17] Left ventricular ejection fraction was assessed with 2-dimensional echocardiography[18] and by visual estimation if orthogonal measurements could not be obtained.[19] Diagnosis of BAV was based on short-axis imaging of the aortic valve demonstrating the existence of only 2 commissures delimiting only 2 aortic valve cusps[3,4] (FIGURE 1, an interactive video of the short-axis echocardiogram is available at http://www.jama.com). Multiple views were obtained with immediate physician review and, if necessary, repeat imaging to confirm the BAV. Bicuspid valves were classified as typical (right-left coronary cusp fusion) if the commissures were at 4 to 10, 5 to 11, or 3 to 9 o'clock (anterior-posterior cusps) and atypical (right noncoronary cusp fusion) if the commissures were at 1 to 7 or 12 to 6 o'clock (right-left cusps).[6,20,21] Doppler was used to measure blood velocity, with pulsed Doppler, color Doppler, or both assessing subaortic flow and degree of aortic regurgitation,[22] with assessment of flow reversal in the aortic arch, and with continuous-wave Doppler measurement of maximal jet velocity.[23] In patients diagnosed before Doppler became available (before 1983), wide valvular opening ascertained the absence of valve stenosis,[3] and mitral valve M-mode and clinical auscultation ascertained the presence of aortic regurgitation. Aortic stenosis was defined as Doppler peak velocity 2.5 m/s or higher, a mean systolic gradient 20 mm Hg or higher, or decreased systolic cusp excursion with prominent valve calcification for patients diagnosed before 1983.[3] Two-dimensional ascending aorta measurements were obtained in the parasternal long-axis view (Figure 1, see interactive video of the long-axis echocardiogram available at http://www.jama.com) with the patient in a left lateral decubitus position. Sinuses of Valsalva (root) and ascending aorta diameters were measured by the leading-edge to leading-edge technique, at end diastole or at its widest dimension where best visualized regardless of the cardiac cycle.[24] The largest diameter between the root and ascending aorta for each patient was used for analysis.

The follow-up of this cohort was conducted by their personal physicians and obtained by review of medical records. For patients who moved from Olmsted County, mailed surveys and telephone interviews were conducted (survey available at http://www.jama.com). Cause of death was determined by review of medical records, death certificates, and autopsy reports. If applicable, such records were tracked by state for those patients who had moved out of state and were obtained with permission of the next of kin, if necessary.

Undiagnosed or Uncertain BAV

We used the same follow-up strategies for patients in all of Olmsted County with uncertain cusp number after echocardiographic consensus review as we used with patients who had definite BAV. To ascertain patients who may have had aortic dissection without echocardiographic diagnosis of BAV, the Mayo clinic medical and surgical records databases, surgical procedures database, pathology-autopsy database, and county coroner records were searched for aortic dissections and BAV from 1980 to 2009. In addition, the Olmsted County coroner's database of refused autopsies and death certificates was searched for clinically suspected or overt diagnosis of aortic dissection and BAV. Therefore, it was possible to gather all patients with documented aortic dissection and BAV, whether it was diagnosed before the aortic complication or not.

End Points

Primary end point events were development of thoracic aorta dissection classified as type A (involving the ascending aorta) or B (nonascending thoracic aorta),[25,26] ascending aortic aneurysm, and surgery of the aorta. Secondary end points were mortality and aortic valve replacement. In current guidelines, dilatation of the ascending aorta is considered clinically significant and affects BAV management at a diameter of 45 mm or greater,[27] which we used as threshold for definition of aneurysm. Rarely, aneurysm was diagnosed by the

©2011 American Medical Association. All rights reserved.

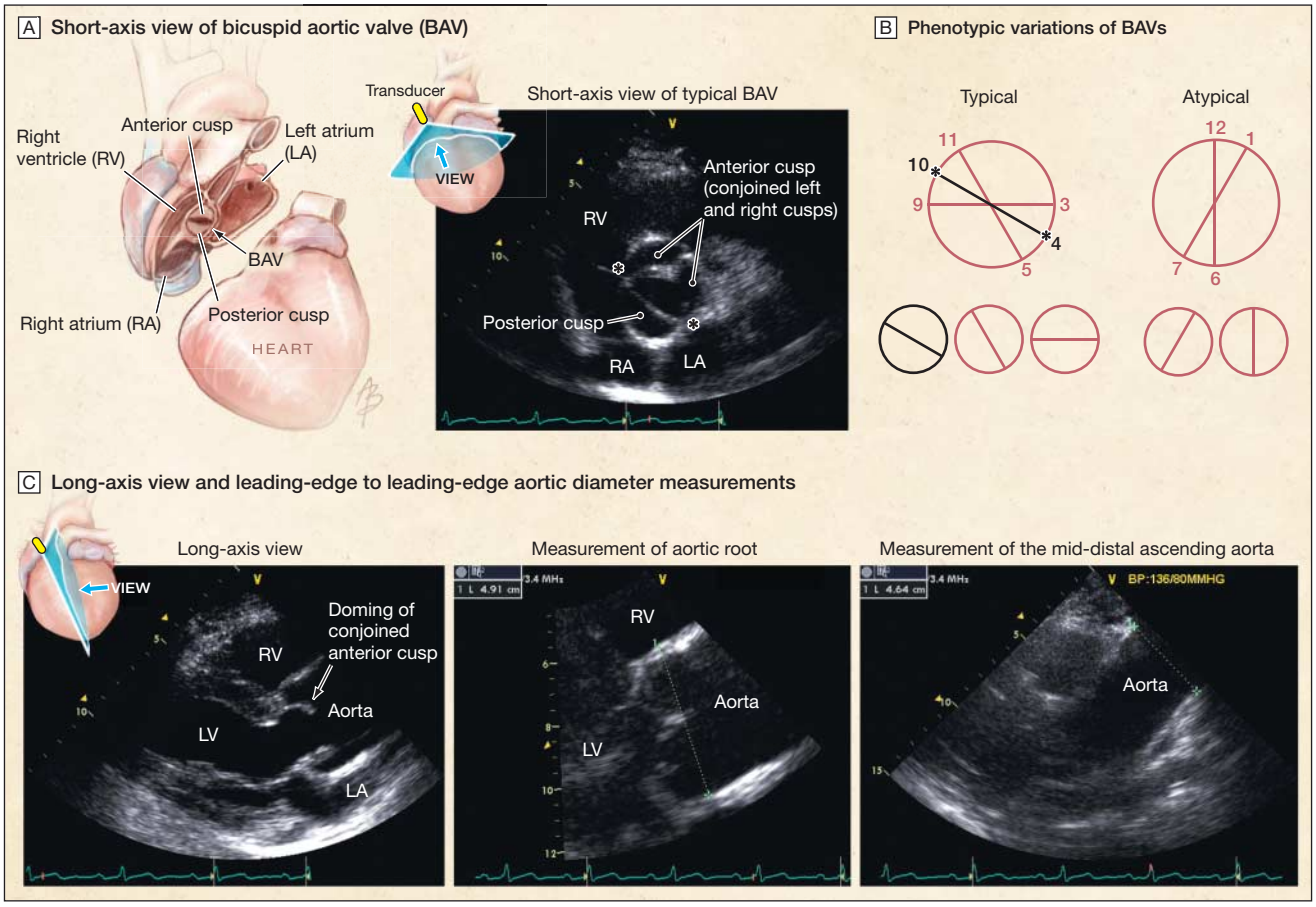
Downloaded From: http://jama.jamanetwork.com/ on 08/31/2014

responsible physician based on nonechocardiographic imaging techniques and absolute echocardiographic dimension was not available but these were considered appropriate end points.

Statistical Analysis

Continuous variables are expressed as mean (SD) and percentage for categorical variables. Paired *t* test was used for comparison between continuous data, and the Fisher and and χ^2 test, for categorical data. Survival and event rates were determined with the Kaplan-Meier method and compared groups with the 2-sample log-rank test. Association of baseline characteristics with the incidence of events was analyzed with the Cox proportional hazards method. Survival of patients was compared with that of the Minnesota white population matched for age and sex as defined by the US Census Bureau life tables and tested with a 1-sample log-rank test. Incidence of aortic dissection relative to the prevalence of the BAV population within Olmsted County was calculated by first estimating the total person-years of Olmsted County through 1980 through 1999 using US Census Bureau tables. Age and sex specific person-years for BAV were then estimated by multiplying the total population by the prevalence of 1.3%[2] giving the denominator of the incident rate calculation. The expected number of aortic dissections in the BAV cohort was estimated by applying the county age- and sex-specific incidence rates of Bickerstaff et al.[28] The expected number of aortic aneurysms in the BAV cohort was estimated by applying the county age- and sex-specific incidence rates of Clouse et al.[29] The minimum relative risk with 80% power that could be detected in this study with 2 incident aortic dissection cases was 7 assuming a 2-sided significance level of .05. The minimum relative-risk with 80% power that could be

Figure 1. Transthoracic Echocardiogram of a Study Patient With Typical Bicuspid Aortic Valve



A, Parasternal short-axis still image demonstrates a typical bicuspid valve (BAV) with a football-shaped systolic opening, right and left cusps forming a large anterior conjoined cusp and commissures at 10 and 4 o'clock (asterisks). B, Numbers indicate location of commissures according to the face of a clock. The study patient's valve configuration is shown in black. C, Left, parasternal long-axis still image demonstrates anterior conjoined cusp doming in systole. Middle, parasternal long-axis zoomed still image shows leading-edge to leading-edge measurement of the sinuses of valsalva (aortic root) at 49 mm. Right, parasternal long-axis still image 1 intercostal space higher shows measurement of the mid-distal ascending aorta at 46 mm. See interactive videos of the parasternal short- and long-axis echocardiogram at www.jama.com.

©2011 American Medical Association. All rights reserved.

Downloaded From: http://jama.jamanetwork.com/ on 08/31/2014

detected in this study with 49 incident aneurysm cases was 1.5 assuming a 2-sided significance level of .05. Event rates are summarized as events per 10 000 person-years and 95% confidence intervals were calculated assuming that the event rate followed a Poisson distribution. Analyses were performed with SAS version 9.2 (SAS Institute Inc, Cary, North Carolina). $P < .05$ was considered statistically significant.

RESULTS

BAV Community Cohort

From January 1980 to December 1999, there were 322 230 individual-patient echocardiograms performed or interpreted at the Mayo Clinic, Rochester. Of these, 41 687 corresponded exclusively to Olmsted County, of which 486 (1% of Olmsted County echocardiograms) reported a diagnosis of definite or possible BAV. Seven patients were federal inmates, leaving 479 legitimate Olmsted County residents of whom 416 had definite BAV and 63 an uncertain cusp number. Of these 63 patients, 41 were later confirmed to have a tricuspid aortic valve, leaving 22 patients with uncertain cusp number.

The 416 patients with definite BAV constituted our community cohort (TABLE 1). Two hundred eighty-eight (69%) were men, the mean (SD) age at diagnosis was 35 (21) years (median, 35 years; range, <1-89 years), and 332 (80%) were 18 years or older diagnosis. At follow-up, 401 (96%) were 18 years or older. Indications for echocardiogram were abnormal auscultatory findings (click, systolic, or diastolic murmur) in 295 (71%). Other indications included assessment of left ventricular function, suspected thoracic aorta disease, cardiac and noncardiac symptoms, and follow-up of congenital heart disease. The mean (SD) left ventricular ejection fraction was 62% (7%). A typical bicuspid-valve was present in 350 patients (84%). Any degree of aortic regurgitation was present in 247 patients (59%). Aortic stenosis was present in 94 patients (23%). The mean (SD) maximum aortic root or ascending aorta diameter was 34 (9) mm at diagnosis. Thirty patients (7%) had previously known aortic coarctation and 54 patients (13%) had associated congenital heart defects.

BAV Community Cohort Follow-up

Follow-up was complete (until 2008-2009, death, or 20-year follow-up) for 393 patients (95%). The mean (SD) follow-up time was 16 (7) years (≤29 years) amounting to 6530 patient-years. The mean (SD) age at last follow-up was 51(19) years. For the 23 patients without complete follow-up, 15 had follow-up of 9 (5) years (up to 19 years) and 8 (2% of the cohort) were lost to follow-up with fewer than 2 years of follow-up. At follow-up, echocardiograms were available in 344 patients (83%).

Aortic Dissection in the BAV Community Cohort

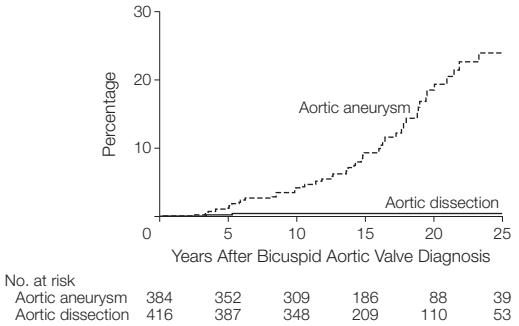
Of the 416 patients in the Olmsted County BAV cohort, 2 men with typical BAV and no aortic coarctation had acute aortic dissection during follow-up, type A in one and type B in the other. Valve status was postaortic valve replacement in one and moderate aortic stenosis in the other. Baseline aortic diameters at diagnosis were 46

Table 1. Baseline Cohort Characteristics by Total Aortic Events[a]

Variable	No. (%) of Patients: Total (N = 416)	Aortic Events (n = 74)	No Aortic Events (n = 342)	*P* Value
Age, mean (SD), y	35 (21)	34 (19)	36 (21)	.45
Men	288 (69)	57 (77)	231 (68)	.12
Hypertension	93 (22)	18 (24)	75 (22)	.64
Smoking	132 (32)	22 (30)	110 (32)	.78
Diabetes	15 (4)	2 (3)	13 (4)	>.99
Atherosclerotic disease[b]	21 (5)	2 (3)	19 (6)	.39
Cardiac symptoms[c]	74 (18)	12 (16)	62 (18)	.86
Coarctation	30 (7)	12 (16)	18 (5)	.009
Ejection fraction %, mean (SD)	62 (7)	62 (6)	63 (7)	.25
Maximum root or ascending aorta diameter, mean (SD), mm	34 (9)	37 (11)	33 (8)	<.001
Typical bicuspid valve	350 (84)	64 (86)	286 (84)	.60
Aortic regurgitation	247 (59)	42 (57)	205 (60)	.71
Aortic stenosis	94 (23)	23 (31)	71 (21)	.06

[a] Aortic events include aneurysm, dissection, and aortic surgery.
[b] History of stroke, transient ischemic attack, or myocardial infarction at baseline.
[c] Any or combinations of cardiac symptoms (syncope, palpitations, dyspnea, typical chest pain) at baseline.

Figure 2. Risk of Aneurysm Formation and Aortic Dissection After Definite Bicuspid Aortic Valve Diagnosis



Kaplan-Meier risk of aortic aneurysm 25 years after echocardiographic diagnosis in 384 patients (32 patients with baseline aneurysm excluded). Kaplan-Meier risk of aortic dissection 25 years after echocardiographic bicuspid aortic valve diagnosis in 416 patients.

©2011 American Medical Association. All rights reserved.

Downloaded From: http://jama.jamanetwork.com/ on 08/31/2014

mm and 47 mm with their respective last measurements before dissection as 52 mm and 50 mm.. Thus, the 25-year cohort risk of aortic dissection after echocardiographic diagnosis was 0.5% (95% CI, 0%-1.28%; FIGURE 2); incidence of 3.1 (95% CI, 0.5-9.5) cases per 10 000 patient-years (TABLE 2). The general population incidence of aortic dissection has been reported from 0.2 to 0.31 per 10 000 person-years by 3 independent longitudinal population-based studies.[28,30,31] In Olmsted County,[28] this incidence was reported at 0.31 per 10 000 person-years allowing calculation of the age-adjusted relative risk of aortic dissection in BAV at 8.4 (95% CI, 2.1-33.5) compared with the county's general population (P = .003). Aortic dissection incidence was 17.4 (95% CI, 2.9-53.6) for patients 50 years or older and 44.9 (95% CI, 7.5-138.5) for patients with aneurysms at the baseline echocardiogram (Table 2). There were no dissections in patients with baseline aortic diameter less than 45 mm or with normally functioning aortic valves.

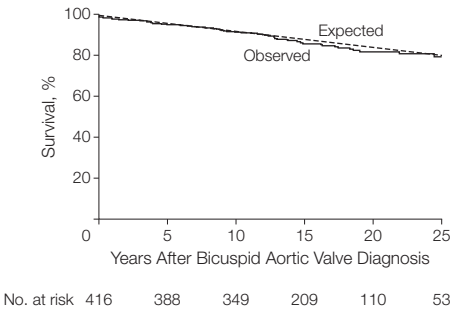
Table 2. Incidence of Aortic Dissection per 10 000 Patient-Years

Category	Incidence (95% CI)
Cohort	
Overall	3.1 (0.5-9.5)
Age, y[a]	
≥50	17.4 (2.9-53.6)
<50	0 (N/A)
Sex	
Men	4.5 (0.7-13.8)
Women	0 (N/A)
Baseline aorta diameter ≥45 mm	44.9 (7.5-138.5)
Olmsted County population	
Overall	1.5 (0.4-3.8)
Age, y[a]	
≥50	4.9 (1.0-14.2)
<50	0.5 (0.01-2.6)
Sex	
Men	2.3 (0.5-6.7)
Women	0.7 (0.01-3.9)

Abbreviation: N/A, nonapplicable.
[a] Age refers to age at bicuspid aortic valve diagnosis.

Ascertainment of possibly undetected dissections in the BAV cohort involved analysis of mortality and cause of death. Of the 59 deaths, 31 were noncardiac; 15 were due to ischemic heart disease, congestive heart failure, or both; 3 were due to severe aortic valve dysfunction; 2 were due to aortic valve endocarditis; 1 was due to associated congenital heart disease; and 2 were during cardiac surgery. The 5 sudden cardiac deaths were not related to aortic dissection: for 1 patient, a primary cardiac arrhythmia was suspected and autopsy confirmed a known aortic aneurysm but no dissection. The other 4 occurred in the setting of coronary artery disease and heart failure (no autopsies performed) and myocardial infarctions or arrhythmias were strongly suspected as causes of death (1 patient's last aortic diameter was 54 mm, and <45 mm for the other 3). No other unexplained death could be linked to an undetected aortic dissection. The survival rate for the entire cohort was 80% (95% CI, 74.2%-85.8%) 25 years after diagnosis and was identical to the expected survival of the general county population matched for age and sex (P = .98; FIGURE 3).

Figure 3. Mortality of the Bicuspid Aortic Valve Cohort



Kaplan-Meier 25-year risk of death is identical to expected.

Aortic Aneurysm in the BAV Community Cohort

Aneurysm at Diagnosis. At BAV echocardiographic diagnosis, 32 patients met aneurysm criteria with a mean (SD) aortic diameter of 48 (6) mm. The mean (SD) age at aneurysm diagnosis was 55 (17) years (range, 25-82 years), and they were followed up for 15 (6) years (≤29 years). Thirteen had elective surgery for aneurysm (1 developed type B dissection later), and 1 had emergency surgery for type A dissection. Thus, after aneurysm diagnosis, the 15-year risks of aortic surgery and aortic dissection were 46% (95% CI, 24.5%-67.5%) and 7% (95% CI, 0%-14.8%), respectively. Of the 18 patients who did not undergo aorta surgery, 6 died at follow-up with verified causes of death unrelated to dissection, and 12 were alive without dissection at last follow-up.

For patients younger than 18 years at baseline echocardiogram (mean [SD] age, 7 [6] years), the *z* scores were calculated[32]: mean (SD) baseline *z* score was 1.6 (2.3), similar to previous pediatric BAV cohorts of similar age.[33] *z* Scores of 4 or higher were considered to represent significant aortic dilation and were present in 13% of these patients, with likelihood ratios of subsequent aneurysm development and elective aneurysm surgery of 4.6 and 7.0 (P < .02), respectively, as expected.

No Aneurysm at Diagnosis. Of the 384 cohort patients without aneurysm at BAV diagnosis, 49 developed aneurysm criteria a mean (SD) of 14 (6) years after their bicuspid-valve diagnosis (45 patients with ascending aorta ≥45 mm; mean 48 [3] mm and 4 defined by nonechocardiographic imaging). Age at aneurysm diagnosis was 47 (17) years (range, 13-76 years) and during follow-up (5 [4] years, ≤13 years) after aneurysm diagnosis, almost half underwent elective ascending aortic surgery (5-year risk, 47%; 95% CI, 31.4%-62.6%) and no aortic dissections occurred. Thus, in the BAV cohort without aneurysm at baseline, the 25-year risk of aneurysm formation was 26% (95% CI, 18.2%-33.8%; Figure 2); incidence of 84.9 (95% CI, 63.3-110.9) per 10 000

©2011 American Medical Association. All rights reserved.

Downloaded From: http://jama.jamanetwork.com/ on 08/31/2014

patient-years. In Olmsted County,[29] the general population incidence of thoracic aortic aneurysms between 1980 and 1994 was reported at 1.04 per 10 000 person-years. Thus, the age-adjusted relative-risk of aneurysm formation in BAV is 86.2 (95% CI, 65.1-114) compared with the county's general population ($P<.001$). If a cutoff of 50 mm or more is used for aneurysm definition, the cohort incidence of aneurysm would be 28.8 (95% CI, 17.5-44.2) per 10 000 patient-years and the relative risk would remain high at 26.4 (95% CI, 16.6-41.9; $P<001$ compared with the county's general population.

Baseline characteristics were tested as univariate predictors of aneurysm formation (TABLE 3). Baseline aortic stenosis and aortic dimension 40 mm or more at baseline were univariate predictors of aneurysm formation. After controlling for age, sex, hypertension, and presence of aortic regurgitation, baseline aortic stenosis and aortic dimension of 40 mm or more at baseline predicted aneurysm formation independently (Table 3).

Table 3. Predictors of Aortic Aneurysm Formation

Variable	No. of Events	Denominator	Univariate Analysis, Hazard Ratio (95% CI)	*P* Value
Age, y[a]	N/A	416	1.0 (0.98-1.02)	.05
Sex				
Men	288	416	1.7 (0.9-3.5)	.10
Hypertension	93	416	1.2 (0.5-2.4)	.69
Smoking	132	416	1.3 (0.7-2.4)	.34
Diabetes	15	416	1.3 (0.2-13.9)	.81
Atherosclerotic disease[b]	21	416	0.7 (0.03-3.1)	.68
Total cholesterol, mg/dL[a]	N/A	255	1.0 (0.99-1.01)	.44
Typical bicuspid aortic valve	350	416	0.98 (0.5-2.3)	.98
Any aortic regurgitation	247	416	1.8 (0.99-3.4)	.05
Baseline aorta diameter ≥40 mm	90	416	3.4 (1.7-6.4)	.001
Baseline aortic stenosis	94	416	2.9 (1.6-5.2)	<.001
			Multivariate, Hazard Ratio (95% CI)	
Age, y			1.0 (0.98-1.02)	.76
Sex				
Male			1.2 (0.6-2.5)	.68
Hypertension			0.95 (0.4-2.1)	.91
Any aortic regurgitation			1.5 (0.8-2.9)	.17
Baseline aorta diameter ≥40 mm			3.3 (1.5-7.2)	.004
Baseline aortic stenosis			3.4 (1.8-6.3)	<.001

Abbreviation: N/A, nonapplicable (measurements).
SI conversion factor: to convert total cholesterol from mg/dL to mmol/L, multiply by 0.0259.
[a] Hazards ratios of continuous variables represent risk increase per unit of the regressor variable. For age, it is for each 1-year increase; total cholesterol, for each 1 mg/dL increase.
[b] History of stroke, transient ischemic attack, or myocardial infarction at baseline.

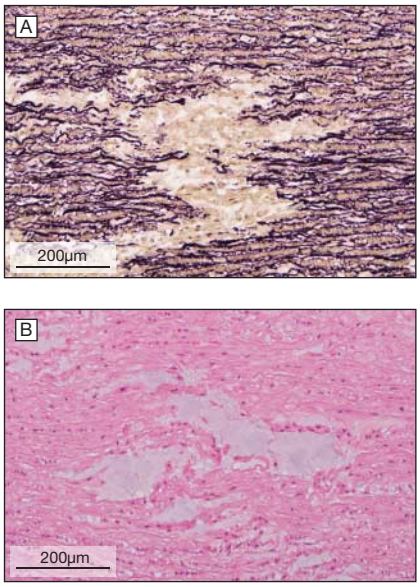
Aortic Surgery in the BAV Community Cohort

Of the 416 cohort patients, 49 patients underwent surgery of the thoracic aorta, including 36 for elective aneurysm repair. Light microscopy analysis with Verhoeff-Van Gieson staining was available for 25 of these, with evidence of medial degeneration (cystic medial necrosis or laminar medial necrosis) in 13 (52%) of them (FIGURE 4). Independent predictors of elective aneurysm repair were a baseline aortic diameter of 40 mm or more (hazard ratio [HR] 2.4, 95% CI, 1.1-5.0; $P=.03$) and undergoing aortic valve replacement (HR, 17; 95% CI, 4.9-107; $P<.001$). Another 11 patients underwent surgery for aortic coarctation or recoarctation and 2 for ascending aortic dissection. Thus, the 25-year risk of aortic surgery after BAV diagnosis was 25% (95% CI, 17.2%-32.8%); FIGURE 5). In contrast, 133 underwent aortic valve replacement for severe aortic valve dysfunction with 25-year risk of 53% (95% CI, 43.2%-62.8%).

Aortic Dissection With BAV in the Population (Diagnosed and Undiagnosed)

To ascertain potential aortic dissections in patients with undiagnosed BAV, we examined the 47 pathologically proven aortic dissections with BAV at the Mayo Clinic, Rochester, Minnesota, between 1980 and 2009. Of these, 4 were from Olmsted County. Two patients were part of the BAV community cohort. Two other dissections occurred in patients with undiagnosed BAV: a 47-year-old man who presented with chest pain, was diagnosed by echocardiogram with type A aortic dissection, had severely regurgitant BAV and an ascending aorta of 70 mm; and a 73-year-old woman with undiagnosed BAV who had undergone valve replacement for severe aortic stenosis with pathologic confirmation of congenital BAV. She presented with type A aortic dissection (last ascending aorta measure-

Figure 4. Light Microscopy Showing Aortic Medial Degeneration in a Study Patient

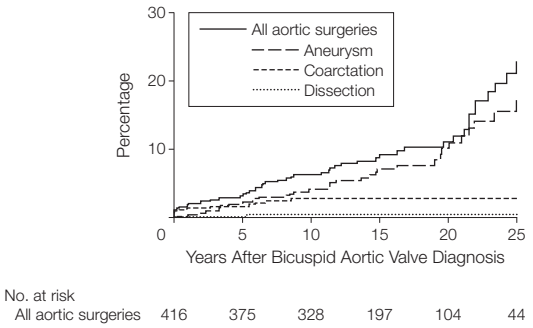


A, Medial degeneration of the ascending aorta, characterized by fragmentation and disruption of the medial elastic layers and, B, by a pool of blue-gray extracellular matrix that is rich in acid mucopolysaccharides. A, Verhoeff-van Gieson stain, original magnification ×50. B, hematoxylin-eosin stain, original magnification ×50.

©2011 American Medical Association. All rights reserved.

Downloaded From: http://jama.jamanetwork.com/ on 08/31/2014

Figure 5. Risk of Aortic Surgery After Definite Bicuspid Aortic Valve Diagnosis



Kaplan-Meier risk of aortic surgery 25 years after echocardiographic bicuspid aortic valve in 416 patients.

ment 47 mm) at later follow-up. Both patients had a typical BAV without aortic coarctation. There was no other case identified despite a comprehensive search. Therefore, the estimated incidence of aortic dissection for the Olmsted County bicuspid valve population was 1.5 (95% CI, 0.4-3.8) cases per 10 000 patient-years based on the currently accepted BAV prevalence of 1.3%[2] (Table 2). The incidence per 10 000 patient-years was 0 for the 0- to 39-year age group, 1.7 (95% CI, 0.04-9.2) for the 40- to 59-year age group, and 8.1 (95% CI, 1.7-23.7) for patients older than 60 years.

Of the 22 Olmsted County residents with questionable cusp number, 17 had complete follow-up (mean, 13; SD, 10 years) and 5 patients had follow-up in less than 2 years, with no aortic dissections found.

COMMENT

To our knowledge, this study reports for the first time the BAV incidence of aortic dissection in a population-based setting, using a community cohort with definite BAV diagnosis and comprehensive methods to assess aortic events in undiagnosed BAV in the population. Our study shows that patients with BAV develop a clinical aortopathy that affects outcome. The risk of aortic dissection in our cohort (BAV prevalence 100%) is approximately 8 times higher than in the general population (BAV prevalence, 1.3%), but despite this high relative risk, the absolute incidence of aortic dissection remains very low. By virtue of searching for dissection in diagnosed and undiagnosed patients with bicuspid valves, we corroborate this low rate of dissection in the general BAV population with overlapping 95% confidence intervals. As further confirmation, we observed no excess mortality during 25 years of follow-up within the largest BAV community cohort up to date. Hence, the low rate of aortic dissection does not appear to be underestimated by misallocated deaths. The low aortic dissection incidence and lack of association with a detectable reduction in survival is reassuring. Due to purported similarities between BAV and Marfan aortas,[5,7] aortic outcomes in BAV have been assumed as equivalent to Marfan.[14,34] Although BAV aortopathy may share biological similarities with Marfan syndrome and aneurysms are common in both conditions, our study provides evidence that their clinical outcome is not comparable because aortic dissection is a major cardiovascular criterion for Marfan syndrome[35] and patients with Marfan syndrome who have not undergone surgery have poor survival, with aortic complications being responsible for 80% of cardiac deaths.[36] In our study, proactive guideline-based[27] elective aortic surgery for ascending aortic aneurysms likely limited the possibility of dissection, such that the low incidence of aortic dissection is that of a treated population and not a historical rate in an untreated BAV population that would not be relevant to current clinical practice. Our study also reveals higher risk BAV subsets, those 50 years or older and those with aortic aneurysms at diagnosis incur higher dissection risk. Also, dissections were only observed with dysfunctional BAV,[3] and the presence of aortic stenosis (but not regurgitation) was an independent predictor of aneurysm formation. These observations support current recommendations[27] of electively repairing ascending aortic aneurysms and have implications for clinical and echocardiographic surveillance of these patient subsets.

Despite a low incidence of dissection, patients with BAV incur significant morbidity, with 25-year risks of aortic surgery of 25% (95% CI, 17.2%-32.8%), aneurysm formation 26% (95% CI, 18.2-33.8%), and valve replacement 53% (95% CI, 43.2%-62.8%; Figure 2 and Figure 5). Our study confirms that aortic valve replacement remains the most common complication of patients with BAV. This highlights the importance of early recognition of BAV by careful cardiac auscultation in order to prevent heart failure due to late valvular surgery referrals, as well as potentially to prevent dissection by elective aorta surgical repair.

Our study shows light-microscopy pathologic evidence of ongoing aortopathy in the aneurysmal aortas of patients undergoing surgery, confirming the existence of this degenerative process.[3-8] However, we observed an independent association between aortic stenosis and aneurysm formation, suggesting a hemodynamic mechanism that coexists with the aortopathy mechanism in the genesis of aneurysms. Our study reveals aneurysm formation to be independent of baseline atherosclerotic disease, coarctation, age, sex, hypertension, or type of BAV. The high aneurysm incidence results in high rates of elective aortic surgery, and patients with aneurysm at baseline incur higher dissection incidence. Thus, research should focus on identifying biological pathways leading to aneurysm formation amenable to

©2011 American Medical Association. All rights reserved.

Downloaded From: http://jama.jamanetwork.com/ on 08/31/2014

medical intervention aimed at preventing and stabilizing aortic enlargement in BAV. The observed disproportion between aneurysm and dissection rates (Figure 2) suggests that the occurrence of aortic dissection in BAV patients may not exclusively be a matter of absolute aortic size.[37] This observation argues for research in the development of nonsize markers to help refine the risk stratification for aortic dissection in patients with BAV. Finally, despite a notable risk of elective aortic surgery in patients with coarctation (Figure 5), we found no increased ascending aorta complications in coarctation patients, a subject of controversy in previous tertiary-referral-based studies.[38,39]

Limitations

Despite the large size of our series and long follow-up, we observed a limited number of dissections; thus, our purpose is not to define predictors of dissection but rather to analyze its incidence in absolute terms and relative to the general population for the first time. In addition, our study was not designed to analyze the progression of aortic dilatation, but rather the incidence of clinical aortic complications. The retrospective community cohort study design that we used constitutes the only feasible method to address our aims. Although all patients with BAV seen at the Mayo Clinic would provide a larger sample, a cohort of all community patients with documented definite BAV has the advantage of eliminating many referral biases that have plagued previous BAV studies. The highly morbid nature of aortic dissection makes it highly unlikely to have been overlooked, but the link to BAV dissection may be overlooked; thus, we carried out the comprehensive ascertainment of aortic events described. Prospective, long-term follow-up of an entire BAV population identified by echocardiogram at birth might provide complete data on the natural history of aortic complications in BAV, but this is unrealistic due to the massive echocardiographic screening required and the long duration over multiple decades for such a study. Because follow-up echocardiograms were available for 83% (not 100%) of the cohort, the incidence of aneurysm formation could have been underestimated. Nevertheless, aneurysm diagnoses by nonechocardiographic methods were also considered end points, and high aneurysm incidence is obvious from our study, irrespective of its definition. The frequency of subsequent follow-up echocardiograms in this cohort was determined not only by the BAV condition but by the patient's personal physician and the patients' other cardiac and noncardiac comorbidities, potentially resulting in earlier or later diagnosis of aortic aneurysms, which in turn could influence the incidence of aortic complications. However, this is representative of current community practice. The 95% confidence intervals of the calculated incidences of aortic dissection are wide, reflecting the rarity of aortic dissections in BAV. More precise estimates would be obtained in a larger population. Nevertheless, considering the maximum 95% confidence intervals, aortic dissection occurred in fewer than 1 in 1000 patients with BAV per year. Conversely, aneurysm developed in at least 1 of every 100 BAV patients per year.

Selection of the largest diameter between the aortic root and ascending aorta prevents underestimation of the size of the aorta, particularly in light of current guidelines not differentiating between the root or ascending aorta proper.[25-27] Furthermore, patients may present with both types of ascending aorta dilatation.[40]

Our echocardiographic definition of aortic aneurysm (≥45 mm) is based on a clinically significant guideline-derived cutoff,[27] nevertheless, if a higher cutoff is chosen (≥50 mm), the high incidence of aneurysms and significantly increased relative risk compared with the general population are persistent, confirming that the excess risk of aortopathy is independent of the cutoff chosen. Finally, our study population comprised adult patients in its majority and is predominantly white and of Northern European descent,[15] and results could differ in other settings.

In conclusion, our study provides new data on long-term BAV outcomes that is both reassuring and a cause for careful monitoring of these patients. There is a clinical aortopathy associated to BAV, with excess risk of aneurysm formation and aortic dissection. However, the incidence of dissection is low and had no detectable association with survival for the follow-up period of this study. The dissection incidence was higher in patients older than 50 years and higher in those with baseline aortic aneurysms, highlighting the importance of close monitoring and current guideline implementation in these subgroups. One quarter of patients needed surgery of the aorta at 25 years, driven primarily by elective aneurysm repair, with aortic stenosis being an independent predictor of aneurysm formation. Research efforts should concentrate on elucidating biological pathways of BAV aortopathy amenable to medical treatment, as well as identifying nonsize markers for refining risk prediction of aortic dissection in these patients.

Author Contributions: Dr Michelena had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Michelena, Mahoney, Edwards, Sundt, Enriquez-Sarano.
Acquisition of data: Michelena, Khanna, Mahoney, Margaryan, Topilsky, Edwards, Enriquez-Sarano.
Analysis and interpretation of data: Michelena, Khanna, Mahoney, Suri, Eidem, Edwards, Sundt, Enriquez-Sarano.
Drafting of the manuscript: Michelena, Khanna, Mahoney, Edwards, Enriquez-Sarano.
Critical revision of the manuscript for important intellectual content: Michelena, Mahoney, Margaryan, Topilsky, Suri, Eidem, Edwards, Sundt, Enriquez-Sarano.
Statistical analysis: Michelena, Mahoney, Enriquez-Sarano.
Obtained funding: Michelena, Enriquez-Sarano.
Administrative, technical, or material support: Michelena, Khanna, Topilsky, Eidem, Edwards, Enriquez-Sarano.
Study supervision: Michelena, Suri, Eidem, Sundt, Enriquez-Sarano.
Conflict of Interest Disclosures: All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Dr Suri reported institutional support from Sorin RC on minimally invasive aortic valve replacement. Dr Enriquez-Sarano reported serving on the advisory board of Valtech; otherwise no other disclosures were reported.
Funding/Support: Partially funded by a faculty devel-

©2011 American Medical Association. All rights reserved.

Downloaded From: http://jama.jamanetwork.com/ on 08/31/2014

opment grant awarded to Dr Michelena by the Department of Internal Medicine of the Mayo Clinic, Rochester, Minnesot. The Division of Cardiovascular Diseases of the Mayo Clinic supported the costs of survey creation and mailings, as well as statistical analysis costs.

Online-Only Material: The eSurvey and Interactive videos of the long- and short-axis echocardiograms are available at http://www.jama.com.

Additional Contributions: The authors wish to thank David J. Huschka, BS, cardiovascular department, Mayo Clinic, for his contributions in electronic research application solutions, for which he was not compensated beyond his usual pay.

REFERENCES

1. Hoffman JI, Kaplan S. The incidence of congenital heart disease. *J Am Coll Cardiol*. 2002;39(12):1890-1900.

2. Roger VL, Go AS, Lloyd-Jones DM, et al; American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics—2011 update: a report from the American Heart Association. *Circulation*. 2011;123(4):e18-e209.

3. Michelena HI, Desjardins VA, Avierinos JF, et al. Natural history of asymptomatic patients with normally functioning or minimally dysfunctional bicuspid aortic valve in the community. *Circulation*. 2008;117(21):2776-2784.

4. Tzemos N, Therrien J, Yip J, et al. Outcomes in adults with bicuspid aortic valves. *JAMA*. 2008;300(11):1317-1325.

5. Fedak PW, de Sa MP, Verma S, et al. Vascular matrix remodeling in patients with bicuspid aortic valve malformations: implications for aortic dilatation. *J Thorac Cardiovasc Surg*. 2003;126(3):797-806.

6. Sabet HY, Edwards WD, Tazelaar HD, Daly RC. Congenitally bicuspid aortic valves: a surgical pathology study of 542 cases (1991 through 1996) and a literature review of 2,715 additional cases. *Mayo Clin Proc*. 1999;74(1):14-26.

7. Fedak PW, Verma S, David TE, Leask RL, Weisel RD, Butany J. Clinical and pathophysiological implications of a bicuspid aortic valve. *Circulation*. 2002;106(8):900-904.

8. Nkomo VT, Enriquez-Sarano M, Ammash NM, et al. Bicuspid aortic valve associated with aortic dilatation: a community-based study. *Arterioscler Thromb Vasc Biol*. 2003;23(2):351-356.

9. Hagan PG, Nienaber CA, Isselbacher EM, et al. The International Registry of Acute Aortic Dissection (IRAD): new insights into an old disease. *JAMA*. 2000;283(7):897-903.

10. Roberts CS, Roberts WC. Dissection of the aorta associated with congenital malformation of the aortic valve. *J Am Coll Cardiol*. 1991;17(3):712-716.

11. Larson EW, Edwards WD. Risk factors for aortic dissection: a necropsy study of 161 cases. *Am J Cardiol*. 1984;53(6):849-855.

12. Edwards WD, Leaf DS, Edwards JE. Dissecting aortic aneurysm associated with congenital bicuspid aortic valve. *Circulation*. 1978;57(5):1022-1025.

13. Ward C. Clinical significance of the bicuspid aortic valve. *Heart*. 2000;83(1):81-85.

14. Coady MA, Stockwell PH, Robich MP, Poppas A, Sellke FW. Should aortas in patients with bicuspid aortic valve really be resected at an earlier stage than tricuspid? CON. *Cardiol Clin*. 2010;28(2):299-314.

15. Melton LJ III. History of the Rochester epidemiology project. *Mayo Clin Proc*. 1996;71(3):266-274.

16. Tajik AJ, Seward JB, Hagler DJ, Mair DD, Lie JT. Two-dimensional real-time ultrasonic imaging of the heart and great vessels: technique, image orientation, structure identification, and validation. *Mayo Clin Proc*. 1978;53(5):271-303.

17. Nishimura RA, Miller FA Jr, Callahan MJ, Benassi RC, Seward JB, Tajik AJ. Doppler echocardiography: theory, instrumentation, technique, and application. *Mayo Clin Proc*. 1985;60(5):321-343.

18. Quinones MA, Waggoner AD, Reduto LA, et al. A new, simplified and accurate method for determining ejection fraction with two-dimensional echocardiography. *Circulation*. 1981;64(4):744-753.

19. Rich S, Sheikh A, Gallastegui J, Kondos GT, Mason T, Lam W. Determination of left ventricular ejection fraction by visual estimation during real-time two-dimensional echocardiography. *Am Heart J*. 1982;104(3):603-606.

20. Duran AC, Frescura C, Sans-Coma V, Angelini A, Basso C, Thiene G. Bicuspid aortic valves in hearts with other congenital heart disease. *J Heart Valve Dis*. 1995;4(6):581-590.

21. Fernandes SM, Sanders SP, Khairy P, et al. Morphology of bicuspid aortic valve in children and adolescents. *J Am Coll Cardiol*. 2004;44(8):1648-1651.

22. Perry GJ, Helmcke F, Nanda NC, Byard C, Soto B. Evaluation of aortic insufficiency by Doppler color flow mapping. *J Am Coll Cardiol*. 1987;9(4):952-959.

23. Currie PJ, Seward JB, Reeder GS, et al. Continuous-wave Doppler echocardiographic assessment of severity of calcific aortic stenosis: a simultaneous Doppler-catheter correlative study in 100 adult patients. *Circulation*. 1985;71(6):1162-1169.

24. Lang RM, Bierig M, Devereux RB, et al; Chamber Quantification Writing Group; American Society of Echocardiography's Guidelines and Standards Committee; European Association of Echocardiography. Recommendations for chamber quantification: a report from the American Society of Echocardiography's Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. *J Am Soc Echocardiogr*. 2005;18(12):1440-1463.

25. Coady MA, Rizzo JA, Hammond GL, et al. What is the appropriate size criterion for resection of thoracic aortic aneurysms? *J Thorac Cardiovasc Surg*. 1997;113(3):476-491.

26. Coady MA, Rizzo JA, Hammond GL, Kopf GS, Elefteriades JA. Surgical intervention criteria for thoracic aortic aneurysms: a study of growth rates and complications. *Ann Thorac Surg*. 1999;67(6):1922-1926.

27. Bonow RO, Carabello BA, Kanu C, et al; American College of Cardiology/American Heart Association Task Force on Practice Guidelines; Society of Cardiovascular Anesthesiologists; Society for Cardiovascular Angiography and Interventions; Society of Thoracic Surgeons. ACC/AHA 2006 guidelines for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (writing committee to revise the 1998 Guidelines for the Management of Patients With Valvular Heart Disease): developed in collaboration with the Society of Cardiovascular Anesthesiologists: endorsed by the Society for Cardiovascular Angiography and Interventions and the Society of Thoracic Surgeons. *Circulation*. 2006;114(5):e84-e231.

28. Bickerstaff LK, Pairolero PC, Hollier LH, et al. Thoracic aortic aneurysms: a population-based study. *Surgery*. 1982;92(6):1103-1108.

29. Clouse WD, Hallett JW Jr, Schaff HV, Gayari MM, Ilstrup DM, Melton LJ III. Improved prognosis of thoracic aortic aneurysms: a population-based study. *JAMA*. 1998;280(22):1926-1929.

30. Pate JW, Richardson RL, Eastridge CE. Acute aortic dissections. *Am Surg*. 1976;42(6):395-404.

31. Mészáros I, Mórocz J, Szlávi J, et al. Epidemiology and clinicopathology of aortic dissection. *Chest*. 2000;117(5):1271-1278.

32. Roman MJ, Devereux RB, Kramer-Fox R, O'Loughlin J. Two-dimensional echocardiographic aortic root dimensions in normal children and adults. *Am J Cardiol*. 1989;64(8):507-512.

33. Warren AE, Boyd ML, O'Connell C, Dodds L. Dilatation of the ascending aorta in paediatric patients with bicuspid aortic valve: frequency, rate of progression and risk factors. *Heart*. 2006;92(10):1496-1500.

34. Guntheroth WG. A critical review of the American College of Cardiology/American Heart Association practice guidelines on bicuspid aortic valve with dilated ascending aorta. *Am J Cardiol*. 2008;102(1):107-110.

35. De Paepe A, Devereux RB, Dietz HC, Hennekam RC, Pyeritz RE. Revised diagnostic criteria for the Marfan syndrome. *Am J Med Genet*. 1996;62(4):417-426.

36. Murdoch JL, Walker BA, Halpern BL, Kuzma JW, McKusick VA. Life expectancy and causes of death in the Marfan syndrome. *N Engl J Med*. 1972;286(15):804-808.

37. Pape LA, Tsai TT, Isselbacher EM, et al; International Registry of Acute Aortic Dissection (IRAD) Investigators. Aortic diameter >or=5.5 cm is not a good predictor of type A aortic dissection: observations from the International Registry of Acute Aortic Dissection (IRAD). *Circulation*. 2007;116(10):1120-1127.

38. Oliver JM, Alonso-Gonzalez R, Gonzalez AE, et al. Risk of aortic root or ascending aorta complications in patients with bicuspid aortic valve with and without coarctation of the aorta. *Am J Cardiol*. 2009;104(7):1001-1006.

39. Beaton AZ, Nguyen T, Lai WW, et al. Relation of coarctation of the aorta to the occurrence of ascending aortic dilation in children and young adults with bicuspid aortic valves. *Am J Cardiol*. 2009;103(2):266-270.

40. Schaefer BM, Lewin MB, Stout KK, et al. The bicuspid aortic valve: an integrated phenotypic classification of leaflet morphology and aortic root shape. *Heart*. 2008;94(12):1634-1638.

©2011 American Medical Association. All rights reserved.

Downloaded From: http://jama.jamanetwork.com/ on 08/31/2014